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TISSUE CONTACT SENSING USING A MEDICAL DEVICE

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Abstract of WO2016134264 (A1)

Medical devices and methods for making and using medical devices are disclosed. An example system for sensing tissue contact is disclosed. The system comprises a catheter shaft including a distal end portion. The distal end portion includes a sensing assembly having a plurality of electrodes. The plurality of electrodes includes a current-carrying electrode, a first sensing electrode and a second sensing electrode. The first sensing electrode is positioned a first distance from the current-carrying electrode. The second sensing electrode is positioned a second distance from the current-carrying

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electrode and the first distance is different from the second distance. The system also includes a controller coupled to the plurality of mapping electrodes. The controller is capable of calculating a parameter based at least in part on the first and the second distances.

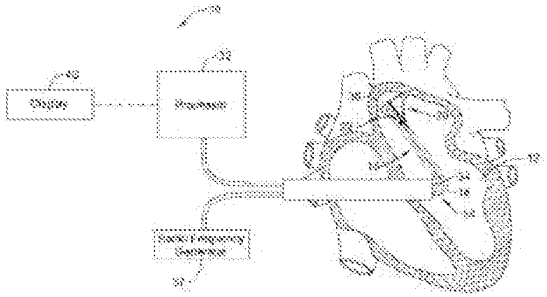


FIG. 1

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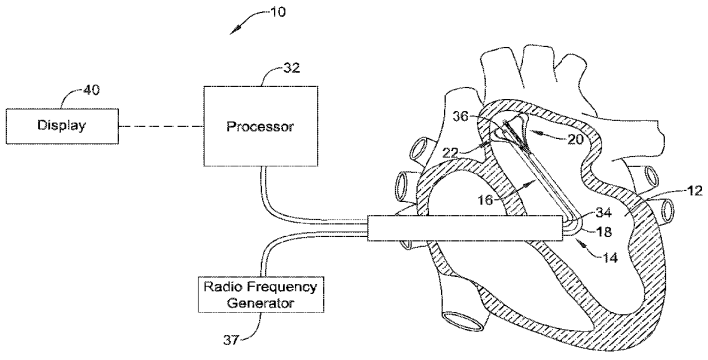


FIG. 1

(57) **Abstract**: Medical devices and methods for making and using medical devices are disclosed. An example system for sensing tissue contact is disclosed. The system comprises a catheter shaft including a distal end portion. The distal end portion includes a sensing assembly having a plurality of electrodes. The plurality of electrodes includes a current-carrying electrode, a first sensing electrode and a second sensing electrode. The first sensing electrode is positioned a first distance from the current-carrying electrode. The second sensing electrode is positioned a second distance from the current-carrying electrode and the first distance is different from the second distance. The system also includes a controller coupled to the plurality of mapping electrodes. The controller is capable of calculating a parameter based at least in part on the first and the second distances.

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TISSUE CONTACT SENSING USING A MEDICAL DEVICE

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application claims priority to Provisional Application No. 62/118,897, filed February 20, 2015, which is herein incorporated by reference in its entirety.

TECHNICAL FIELD

[0002] The present disclosure pertains to medical devices, and methods for manufacturing medical devices. More particularly, the present disclosure pertains to tissue diagnosis and/or ablation.

BACKGROUND

[0003] A wide variety of intracorporeal medical devices have been developed for medical use, for example, intravascular use. Some of these devices include guidewires, catheters, and the like. These devices are manufactured by any one of a variety of different manufacturing methods and may be used according to any one of a variety of methods. Of the known medical devices and methods, each has certain advantages and disadvantages. There is an ongoing need to provide alternative medical devices as well as alternative methods for manufacturing and using medical devices.

SUMMARY

[0004] This disclosure provides design, material, manufacturing method, and use alternatives for medical devices. An example electrophysiology medical device is disclosed. The medical device comprises:

a catheter shaft including a distal end portion, wherein the distal end portion includes a sensing assembly having a plurality of mapping electrodes;

wherein the plurality of mapping electrodes includes at least one current-carrying electrode, a first sensing electrode and a second sensing electrode;

wherein the first sensing electrode is spaced from the current-carrying electrode a first distance;

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wherein the second sensing electrode is spaced from the current-carrying electrode a second distance;

wherein the first distance is different from the second distance; and

a controller coupled to the plurality of mapping electrodes;

wherein the controller is capable of calculating a parameter based at least in part on the first and the second distances.

[0005] Alternatively or additionally, the parameter indicates the proximity of the medical device to tissue.

[0006] Alternatively or additionally, calculating the parameter includes sensing a first voltage potential between the first electrode and one or more return electrodes, and sensing a second voltage potential between the second electrode and one or more return electrodes.

[0007] Alternatively or additionally, calculating the parameter includes solving at least one linear equation, and wherein the at least one linear equation includes the first distance, the second distance, the first voltage and the second voltage.

[0008] Alternatively or additionally, the sensing assembly includes a plurality of splines, and wherein the plurality of electrodes are disposed on the plurality of splines.

[0009] Alternatively or additionally, the sensing assembly includes a plurality of splines, and wherein the plurality of splines includes an outwardly facing surface, and wherein the plurality of electrodes are disposed on the outwardly facing surface.

[0010] Alternatively or additionally, the sensing assembly includes a plurality of splines, and wherein the plurality of splines are arranged in a basket.

[0011] Alternatively or additionally, the plurality of electrodes are each designed to sequentially and/or simultaneously operate in a sensing configuration and a current-carrying configuration.

[0012] Alternatively or additionally, further comprising displaying the parameter on a display.

[0013] Alternatively or additionally, displaying the parameter includes displaying a confidence value corresponding to the parameter.

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[0014] Alternatively or additionally, the displaying the parameter on a display further includes displaying an anatomical shell and/or an electroanatomical map that indicates the proximity of one or more of the plurality of electrodes to tissue.

[0015] Another example system for sensing tissue contact comprises:

a catheter shaft including a distal end portion, wherein the distal end portion includes a sensing assembly having a plurality of electrodes;

wherein the plurality of electrodes includes a current-carrying electrode, a first sensing electrode and a second sensing electrode;

wherein the first sensing electrode is positioned a first distance from the current-carrying electrode;

wherein the second sensing electrode is positioned a second distance from the current-carrying electrode;

wherein the first distance is different from the second distance;

a processor, wherein the processor is designed to:

simultaneously detect:

(a) a first parameter based at least in part on the first and second distances, and

(b) an impedance increase across at least one of the plurality of electrodes.

[0016] Alternatively or additionally, wherein the impedance increase is defined by a change in impedance by at least 100%.

[0017] Alternatively or additionally, wherein simultaneously detecting an impedance increase indicates that at least one of the plurality of electrodes is embedded in tissue.

[0018] Alternatively or additionally, wherein simultaneously detecting a first parameter based at least in part on the first and second distances includes sensing a first voltage potential between the first electrode and one or more return electrodes, and sensing a second voltage potential between the second electrode and the one or more return electrodes.

[0019] Alternatively or additionally, wherein simultaneously detecting a first parameter includes solving at least one linear equation, and wherein the at least one

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linear equation includes the first distance, the second distance, the first voltage and the second voltage.

[0020] Alternatively or additionally, wherein simultaneously detecting an impedance increase includes measuring an impedance between a current-carrying electrode and one or more return electrodes

[0021] Another example electrophysiology medical device comprises:

a catheter shaft including a distal end portion;

a sensing assembly having a plurality of electrodes, wherein the plurality of electrodes includes four or more terminals;

wherein the four or more terminals includes one or more current-carrying electrodes and one or more sensing electrodes;

wherein the one or more current- carrying electrodes, the one or more sensing electrodes, or both includes a mapping electrode;

wherein the four or more terminals are designed to measure an electrical characteristic; and

a processor coupled to the sensing assembly.

[0022] Alternatively or additionally, wherein the electrical characteristic is a voltage, an impedance, or both.

[0023] Alternatively or additionally, wherein the electrical characteristic indicates the proximity of the medical device to tissue.

[0024] Another medical device for sensing contact with tissue comprises:

a catheter shaft, wherein the shaft includes a distal portion;

a sensing assembly coupled to the distal portion of the catheter shaft, wherein the sensing assembly includes a plurality of electrodes; and

wherein the plurality of electrodes includes at least a first mapping electrode, and wherein the first mapping electrode is designed to detect an impedance increase, and wherein the impedance increase is defined by an increase of an impedance by 100% or more.

[0025] The above summary of some embodiments is not intended to describe each disclosed embodiment or every implementation of the present disclosure. The

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Figures, and Detailed Description, which follow, more particularly exemplify these embodiments.

[0026] While multiple embodiments are disclosed, still other embodiments of the present invention will become apparent to those skilled in the art from the following detailed description, which shows and describes illustrative embodiments of the invention. Accordingly, the drawings and detailed description are to be regarded as illustrative in nature and not restrictive.

BRIEF DESCRIPTION OF THE DRAWINGS

[0027] The disclosure may be more completely understood in consideration of the following detailed description in connection with the accompanying drawings, in which:

[0028] FIG. 1 is a plan view of an example tissue diagnosis and/or ablation system;

[0029] FIG. 2 illustrates an example medical device including an electrode structure, a catheter shaft and a handle;

[0030] FIG. 3 illustrates an example basket electrode structure including sensing electrodes;

[0031] FIG. 4 illustrates an example electrode having multiple layers;

[0032] FIG. 5 illustrates an example electrode having multiple layers;

[0033] FIGS. 6-8 illustrate an example electrode structure utilized with the system of FIG. 1 moving between blood and tissue;

[0034] FIG. 9 illustrates an example electrode structure having multiple sensing electrodes spaced different distances away from a tip electrode.

[0035] While the disclosure is amenable to various modifications and alternative forms, specifics thereof have been shown by way of example in the drawings and will be described in detail. It should be understood, however, that the intention is not to limit the invention to the particular embodiments described. On the contrary, the intention is to cover all modifications, equivalents, and alternatives falling within the spirit and scope of the disclosure.

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DETAILED DESCRIPTION

[0036] For the following defined terms, these definitions shall be applied, unless a different definition is given in the claims or elsewhere in this specification.

[0037] All numeric values are herein assumed to be modified by the term "about", whether or not explicitly indicated. The term "about" generally refers to a range of numbers that one of skill in the art would consider equivalent to the recited value (e.g., having the same function or result). In many instances, the terms "about" may include numbers that are rounded to the nearest significant figure.

[0038] The recitation of numerical ranges by endpoints includes all numbers within that range (e.g. 1 to 5 includes 1, 1.5, 2, 2.75, 3, 3.80, 4, and 5).

[0039] As used in this specification and the appended claims, the singular forms "a", "an", and "the" include plural referents unless the content clearly dictates otherwise. As used in this specification and the appended claims, the term "or" is generally employed in its sense including "and/or" unless the content clearly dictates otherwise.

[0040] It is noted that references in the specification to "an embodiment", "some embodiments", "other embodiments", etc., indicate that the embodiment described may include one or more particular features, structures, and/or characteristics. However, such recitations do not necessarily mean that all embodiments include the particular features, structures, and/or characteristics. Additionally, when particular features, structures, and/or characteristics are described in connection with one embodiment, it should be understood that such features, structures, and/or characteristics may also be used connection with other embodiments whether or not explicitly described unless clearly stated to the contrary.

[0041] The following detailed description should be read with reference to the drawings in which similar elements in different drawings are numbered the same. The drawings, which are not necessarily to scale, depict illustrative embodiments and are not intended to limit the scope of the invention.

[0042] Cardiac arrhythmia and/or other cardiac pathology contributing to abnormal heart function may originate in cardiac cellular tissue. One technique that may be utilized to treat the arrhythmia and/or cardiac pathology may include ablation of tissue substrates

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contributing to the arrhythmia and/or cardiac pathology. Ablation by heat, chemicals or other means of creating a lesion in the tissue substrate may isolate diseased tissue from normal heart circuits. In some instances, electrophysiology therapy may involve locating tissue contributing to the arrhythmia and/or cardiac pathology using a mapping and/or diagnosing catheter and then using an ablation electrode to destroy and/or isolate the diseased tissue.

[0043] Prior to performing an ablation procedure, a physician and/or clinician may utilize specialized mapping and/or diagnostic catheters to precisely locate tissue contributing and/or causing an arrhythmia or other cardiac pathology. It is often desirable to precisely locate the targeted tissue prior to performing an ablation procedure in order to effectively alleviate and/or eliminate the arrhythmia and/or cardiac pathology. Further, precise targeting of the tissue may prevent or reduce the likelihood that healthy tissue (located proximate the targeted tissue) is damaged.

[0044] Several methods and/or techniques may be employed to precisely locate targeted tissue where an ablation or other therapeutic procedure may be performed. An example method may include utilizing an ablation, mapping and/or diagnostic catheter to determine how close the catheter is to targeted tissue. Further, the ablation, mapping and/or diagnostic catheter may include one or more sensing electrodes located on a distal portion of the catheter. The electrodes may sense, measure and/or provide a processor with information relating to electrical characteristics of the cardiac tissue and surrounding media. Using the sensed and/or measured information, the processor may be able to correlate the spatial location of the distal portion of the catheter to the cardiac tissue. For example, electrodes may sense the impedance, resistance, voltage potential, etc. of the cardiac tissue and/or surrounding media and determine how far a distal portion of a diagnostic and/or ablation catheter is to cardiac tissue.

[0045] In general, the size, shape and spacing of electrodes on a diagnostic (e.g. mapping) catheter may contribute to the accuracy to which a diagnostic catheter may sense and/or measure electrical characteristics. For example, some methods and/or techniques disclosed herein may emit a current from a first electrode and measure a voltage, impedance or other electrical characteristic of local tissue using other electrodes. Further, in some instances the size of an electrode may directly influence

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the magnitude of the measured response by a processor. For example, as will be discussed in detail later, impedance measurements corresponding to tissue contact may be magnified by using small, flat electrodes as compared to other sensing electrode configurations. Small, flat electrodes may increase the likelihood that a given electrode may become fully embedded and/or surrounded in cardiac tissue. Fully embedding a sensing electrode within cardiac tissue may directly correspond to determining whether the electrode is in contact with the cardiac tissue.

[0046] In addition, larger electrodes may be more susceptible (as compared to smaller electrodes) to detecting far field electrical activity. Detection of far field electrical activity may negatively affect the detection of local (e.g. targeted) electrical activity.

[0047] Therefore, in some instances it may be desirable to utilize and incorporate small, flat electrodes into the distal portion of a mapping and/or a diagnostic catheter. For example, some of the medical devices and methods disclosed herein may include sensing and measuring electrical activity using one or more relatively small, flat electrodes in conjunction with other sensing methods, electrodes, ablation electrodes, diagnostic catheters and/or other medical devices. Further, some of the medical devices and methods disclosed herein may utilize electrical characteristics collected from small, flat electrodes to assess tissue proximity and/or contact. Other methods and medical devices are also disclosed.

[0048] FIG. 1 is a schematic view of a system 10 for accessing a targeted tissue region in the body of a patient for diagnostic and/or therapeutic purposes. FIG. 1 generally shows the system 10 deployed in a region of the heart. For example, system 10 may be deployed in any chamber of the heart, such as the left atrium, left ventricle, right atrium, or right ventricle, another region of the cardiovascular system, or other anatomical region. While the illustrated embodiment shows the system 10 being used for sensing contact and/or proximity to myocardial tissue, the system 10 (and the methods described herein) may alternatively be configured for use in other tissue applications, such as procedures for sensing tissue in the prostate, brain, gall bladder, uterus, nerves, blood vessels and other regions of the body, including body regions not typically accessed by a catheter.

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[0049] System 10 includes a mapping catheter or probe 14. In some instances, system 10 may also include an ablation catheter or probe 16. Each probe 14/16 may be separately introduced into the selected heart region 12 through a vein or artery (e.g., the femoral vein or artery) using a suitable percutaneous access technique. Alternatively, mapping probe 14 and ablation probe 16 can be assembled in an integrated structure for simultaneous introduction and deployment in the heart region 12.

[0050] Mapping probe 14 may include flexible catheter body 18. The distal end of catheter body 18 carries three-dimensional multiple electrode structure 20. In the illustrated embodiment, structure 20 takes the form of a basket defining an open interior space 22 (see FIG. 2), although other multiple electrode structures could be used. Structure 20 carries a plurality of mapping electrodes 24 (not explicitly shown on FIG. 1, but shown on FIG. 2) each having an electrode location on structure 20 and a conductive member. Each mapping electrode 24 may be configured to sense electrical characteristics (e.g. voltage and/or impedance) in an adjacent anatomical region.

[0051] Electrodes 24 may be electrically coupled to processing system 32. A signal wire (not shown) may be electrically coupled to each electrode 24 on structure 20. The signal wires may extend through body 18 of probe 14 and electrically couple each electrode 24 to an input of processing system 32. Electrodes 24 may sense electrical characteristics correlated to an anatomical region adjacent to their physical location within the heart. The sensed cardiac electrical characteristic (e.g., voltage, impedance, etc.) may be processed by processing system 32 to assist a user, for example a physician, by generating processed output – e.g. an anatomical map (e.g., 3D map of heart chamber) – to identify one or more sites within the heart appropriate for a diagnostic and/or treatment procedure, such as an ablation procedure.

[0052] Processing system 32 may include dedicated circuitry (e.g., discrete logic elements and one or more microcontrollers; application-specific integrated circuits (ASICs); or specially configured programmable devices, such as, for example, programmable logic devices (PLDs) or field programmable gate arrays (FPGAs)) for receiving and/or processing the acquired physiological activity. In some examples, processing system 32 may include a general purpose microprocessor and/or a

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specialized microprocessor (e.g., a digital signal processor, or DSP, which may be optimized for processing activation signals) that executes instructions to receive, analyze and display information associated with the received physiological activity. In such examples, processing system 32 can include program instructions, which when executed, perform part of the signal processing. Program instructions can include, for example, firmware, microcode or application code that is executed by microprocessors or microcontrollers. The above-mentioned implementations are merely exemplary, and the reader will appreciate that processing system 32 can take any suitable form for receiving electrical signals and processing the received electrical signals.

[0053] Ablation probe 16 may include flexible catheter body 34 that carries one or more ablation electrodes 36. The one or more ablation electrodes 36 may be electrically connected to radio frequency (RF) generator 37 that is configured to deliver ablation energy to the one or more ablation electrodes 36. Ablation probe 16 may be movable with respect to the anatomical feature to be treated, as well as structure 20. Ablation probe 16 may be positionable between or adjacent to mapping electrodes 24 of structure 20 as the one or more ablation electrodes 36 are positioned with respect to the tissue to be treated.

[0054] Processing system 32 may output data to a suitable device, for example display device 40, which may display relevant information for a user. In some examples, device 40 is a display (e.g. a CRT, LED), or other type of display, or a printer. Device 40 may present the relevant characteristics in a format useful to the user. In addition, processing system 32 may generate position-identifying output for display on device 40 that aids the user in guiding an ablation electrode into contact with tissue at the site identified for ablation.

[0055] FIG. 2 illustrates mapping catheter 14 and shows mapping electrodes 24 at the distal end suitable for use in system 10 shown in FIG. 1. Mapping catheter 14 may include flexible catheter body 18, the distal end of which may carry three-dimensional multiple electrode structure 20 with mapping electrodes or sensors 24. Mapping electrodes 24 may sense electrical characteristics (e.g. voltage, impedance) in the myocardial tissue. The sensed cardiac electrical activity may be processed by the processing system 32 to assist a user in identifying the site or sites having a heart

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rhythm disorder or other myocardial pathology via generated and displayed relevant characteristics. This information can then be used to determine an appropriate location for applying appropriate therapy, such as ablation, to the identified sites, and to navigate the one or more ablation electrodes 36 to the identified sites.

[0056] Multiple electrode structure 20 may include base member 41 and distal tip 42 between which flexible splines 44 generally extend in a circumferentially spaced relationship. As discussed herein, structure 20 may take the form of a basket defining an open interior space 22. Structure 20 may flare distally from a constrained configuration to a more open configuration. In some examples, the splines 44 are made of a resilient inert material, such as Nitinol, other metals, silicone rubber, suitable polymers, or the like and are connected between base member 41 and distal tip 42. In some instances, splines 44 may be made of parylene. As shown in FIG. 2, splines 44 may include a substantially flat outwardly facing surface 21 and may resemble strips having a substantially reduced thickness and extending from distal tip 42 to catheter body 18. In some instances, splines 44 may have a rectangular and/or ovular cross-section. These are just examples; other cross-sectional shapes are contemplated. Other shapes, configurations and arrangements are contemplated including arrangements disclosed in U.S. Patent 8103327, the entire disclosure of which is herein incorporated by reference.

[0057] In some embodiments described herein, distal tip 42 may include an ablation electrode. Further, in some instances distal tip 42 may include an ablation electrode coupled to RF generator 37. Distal tip 42 may emit ablative energy and/or an electrical current.

[0058] In some instances, splines 44 are positioned in a resilient, pretensioned condition, to bend and conform to the tissue surface they contact. In the example illustrated in FIG. 2, eight splines 44 form three-dimensional multiple electrode structure 20. Additional or fewer splines 44 could be used in other examples. As illustrated, each spline 44 carries eight mapping electrodes 24. Additional or fewer mapping electrodes 24 could be disposed on each spline 44 in other examples of three dimensional multiple electrode structure 20. Slidable sheath 50 may be movable along the major axis of catheter body 18. Moving sheath 50 distally relative to catheter body 18 may cause

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sheath 50 to move over structure 20, thereby collapsing structure 20 into a compact, low profile condition suitable for introduction into and/or removal from an interior space of an anatomical structure, such as, for example, the heart. In contrast, moving sheath 50 proximally relative to the catheter body may expose structure 20, allowing structure 20 to elastically expand and assume the pre-tensioned position illustrated in FIG. 2.

[0059] In other examples, slidable sheath 50 (or other deployment shaft) may be connected to distal tip 42. Further, deployment of structure 20 may include manipulating a slidable sheath 50 (or other deployment shaft) coupled to distal tip 42. For example, deployment of structure 20 may be accomplished by pulling slidable sheath 50 (or other deployment shaft) in a proximal direction. The proximal movement of slidable sheath 50 (or other deployment shaft) may result in distal tip 42 moving in a proximal direction. As distal tip 42 moves proximally, it may force splines 44 to flare out and assume the shape of structure 20 shown in Fig. 2, for example.

[0060] A signal wire (not shown) may be electrically coupled to each mapping electrode 24. The signal wires may extend through body 18 of mapping catheter 14 (or otherwise through and/or along body 18) into handle 54, in which they are coupled to external connector 56, which may be a multiple pin connector. Connector 56 may electrically couple mapping electrodes 24 to processing system 32. It should be understood that these descriptions are just examples. Some addition details regarding these and other example mapping systems and methods for processing signals generated by a mapping catheter can be found in U.S. Patent Nos. 6,070,094, 6,233,491, and 6,735,465, the disclosures of which are hereby expressly incorporated herein by reference.

[0061] To illustrate the operation of system 10, FIG. 3 is a schematic side view of example basket structure 20 including a plurality of mapping electrodes 24. In the illustrated example, the basket structure includes 64 mapping electrodes 24. Mapping electrodes 24 are disposed in groups of eight electrodes (labeled 1, 2, 3, 4, 5, 6, 7, and 8) on each of eight splines (labeled A, B, C, D, E, F, G, and H). While an arrangement of sixty-four mapping electrodes 24 is shown disposed on basket structure 20, mapping electrodes 24 may alternatively be arranged in different numbers (more or fewer splines and/or electrodes), on different structures, and/or in different positions. In addition,

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multiple basket structures can be deployed in the same or different anatomical structures to simultaneously obtain signals from different anatomical structures.

[0062] FIG. 4 shows example electrode 60 disposed along spline 44. Electrode 60 may be one of the plurality of mapping electrodes 24. In some instances, such as that shown in FIG. 4, electrode 60 may be affixed along a surface of spline 44. However, it is contemplated that electrode 60 may be coupled to spline 44 using a variety of methodologies. As discussed herein, electrode 60 may be described as being "affixed," "on" and/or otherwise embedded and/or encased on any structure contemplated herein. This is not intended to be limiting. Positioning/locating electrode 60 along spline 44 may include embedding, partially embedding, encasing, partially encasing, isolating, attaching, affixing, fastening, bonding to the outer surface, embedding within the wall, or the like. Additionally, as shown and described with respect to FIGS. 1-3, it is contemplated that more than one electrode 60 may be affixed to spline 44.

[0063] In some instances, electrode 60 may include base layer 62 and top layer 64. Top layer 64 may be a layer of material applied over base layer 62. For example, in some instances base layer 62 may be made from gold, while top layer 64 may be made of iridium oxide. A masked layer of parylene may be applied over base layer 62 such that only top layer 64 is exposed. In some applications, base layer 62 may be applied as a plated layer. For example, electrode structure 20 may be constructed from a method of manufacturing that may bear some resemblance to an analogous processes utilized in the manufacturing of semiconductors. In other words, the manufacturing process may include "printing" or "layering" top layer 64 along, atop, within, embedded with, etc. bottom layer 62. Further, the example method of manufacturing may include forming bottom layer 62 of material (e.g. gold) upon which top layer 64 (e.g. iridium oxide) may be "printed," "layered," "plated," "sputtered," or the like. The manufacturing method may further include layering one or more additional layers on top and/or within the either top layer 64 and/or bottom layer 62. Additional layers of material may include traces, circuit components, or the like. In some instances, a portion of a layer may be removed to expose an underlying layer. These are just examples, other materials and manufacturing techniques are contemplated.

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Further, while the following discussion is directed toward the electrode structure previously described, it is contemplated that a variety of electrode designs, including those without multiple layers, may be utilized with any of the medical devices, systems or methodologies disclosed herein.

[0064] FIG. 5 shows a plan view of electrode 60 including spline 44, bottom layer 62 and top layer 64. FIG. 5 shows bottom layer 62 beneath top layer 64 and having a length substantially aligned with the length of spline 44. The length of top layer 64 is depicted by the letter "X." Further, FIG. 5 shows top layer 64 having a width perpendicular to the longitudinal axis of spline 44 and depicted by the letter "Y." In some instances, top layer 64 may have an exposed length of .25 – 1.5 mm, .5 – 1.25 mm, .75 – 1.0 mm, or the like. In some instances, the length of top layer 64 may be .95 mm.

[0065] As shown in FIGS. 4 & 5, electrode 60 may have a substantially low profile. This reduced profile may allow electrode 60 to be embedded within spline 44, set "flush" with the exterior surface 21 of spline 44, sit slightly "proud" of the top surface of spline 44 or sit significantly proud of spline 44. In instances where electrode 60 is embedded within spline 44, surfaces of electrode 60 other than top layer 64 may not be exposed to surfaces in contact with the outermost surface of spline 44. In other words, in some cases the only exposed surfaces of electrode 60 include top layer 64.

[0066] FIGS. 4 & 5 depict electrode 60 (including bottom layer 62 and top layer 64) as having generally rectangular shapes. This is merely an example. It is contemplated that electrode 60 (and any portion thereof) may be circular, trapezoidal, square, oval, triangular, or the like.

[0067] As stated above, basket structure 20 may be advanced into an anatomical structure and positioned adjacent to the anatomical structure to be treated (e.g. left atrium, left ventricle, right atrium, or right ventricle of the heart). Additionally, processing system 32 may be configured to record selected electrical characteristics (e.g. voltage, impedance, etc.) from each mapping electrode 24. In some instances, these electrical characteristics may provide diagnostic information corresponding to the relationship between the basket structure 20 and the anatomical structure.

[0068] An example method for assessing tissue contact may include determining a parameter of a model and observing changes in the parameter as the distal end of

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catheter 14 moves between different mediums (e.g. as between blood and tissue). It can be appreciated that catheter 14 may move between blood and tissue as catheter 14 is manipulated within a cardiac chamber.

[0069] A scaling factor may be a parameter in a model used for this purpose. The model may relate to one or more potential differences between one or more sensing electrodes and a reference electrode. A reference electrode may be an electrode placed a distance away from the potential measuring electrodes. For example, a reference electrode may be placed on the back of a patient. Sensing electrodes may be one of several combinations of electrodes 24 on basket structure 20.

[0070] Additionally or alternatively, the model may also relate to the distance in space between a current–carrying electrode and one or more sensing electrodes. The current–carrying electrode may take a variety of forms. For example, the current–carrying electrode may be any one of mapping electrodes 24 on basket structure 20 and/or a distal ablation tip electrode located on distal tip 42.

[0071] In some configurations, the potential measurement between a sensing electrode and a reference electrode may be modeled as being inversely proportional to the distance between a current–carrying electrode and a sensing electrode. For example, the relationship may be modeled as:

$$\varphi_{SEi} = \frac{K}{\|r_{CCE1} - r_{SEi}\|} + C$$

[0072] In this example, the parameter K may be used to assess tissue contact. The above equation is just an example. Other models and parameters are contemplated. In some instances, the parameter K may be referred to as a "K-factor."

[0073] As stated above, the model may relate to both the potential differences between one or more sensing electrodes and the distance between a current-carrying electrode and sensing electrodes. For example, FIG. 9 illustrates an example distal tip 42 including a current-carrying electrode 70 and four sensing electrodes 63, 65, 67 and 68. FIG. 9 is just an example. It is understood that combinations and configurations of any

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of mapping electrodes 24 on electrode structure 20 may be utilized for any embodiment described herein. For example, any one of mapping electrodes 24 may be configured as either a sensing and/or current-carrying electrode.

[0074] In some instances, the relationship between the above electrodes and potential values may be represented by the following equation:

$$\begin{bmatrix} \varphi_{SE1} \\ \varphi_{SE2} \\ \varphi_{SE3} \\ \varphi_{SE4} \end{bmatrix} = \begin{bmatrix} \frac{1}{\|r_{CCE1} - r_{SE1}\|} & 1 \\ \frac{1}{\|r_{CCE1} - r_{SE2}\|} & 1 \\ \frac{1}{\|r_{CCE1} - r_{SE3}\|} & 1 \\ \frac{1}{\|r_{CCE1} - r_{SE4}\|} & 1 \end{bmatrix} [K\ C]$$

[0075] It can be appreciated that the variables $\begin{bmatrix} \varphi_{SE1} \\ \varphi_{SE2} \\ \varphi_{SE3} \\ \varphi_{SE4} \end{bmatrix}$ represent the measured potential difference between the four sensing electrodes (e.g. 63, 65, 67, 68 in FIG. 9) and a reference electrode (not shown in FIG. 9). Additionally, the potential differences may be determined by system 10. Further, it can be appreciated that $\|r_{CCE1} - r_{SE1}\|, \|r_{CCE1} - r_{SE2}\|, \|r_{CCE1} - r_{SE3}\|$ and $\|r_{CCE1} - r_{SE4}\|$ represent the absolute value of the distance (in space) between the current-carrying electrode (e.g. 70 in FIG. 9) and the four sensing electrodes (e.g. 63, 65, 67, 68 in FIG. 9), respectively. It is further understood that these distances may be determined as the position (and distance) for every sensing electrode in relation to the current-carrying electrode is known. For example, because the electrodes are fixed along the spline, the distance between electrodes on the spline is known. Furthermore, it is contemplated that when the spline is in a non-linear configuration (e.g. expanded), the distance between electrodes can be determined using curvilinear and/or straight line calculation. In other

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words, the position, and therefore, the distances, between example sensing electrodes 63, 65, 67, 68 and current-carrying electrode 70 are known on electrode structure 20.

[0076] The parameters K and C in the above system of linear equations can be estimated using a number of well-known techniques for optimization or linear regression. For example, least squares can be used to estimate K and C. Other methods are contemplated. Furthermore, it can be appreciated that the above system of linear equations may be arranged in other ways. For example, the linear equations may be combined such that the parameter C vanishes and only K remains to be estimated.

[0077] Scaling factor K may be inversely proportional to the conductivity of a given medium. In other words, the scaling factor K will be different for two mediums having different conductivities. For example, the conductivity of blood is greater than that of cardiac tissue, and therefore, the scaling factor K will be lower for blood as compared to cardiac tissue.

[0078] Knowing the potential differences and absolute distance values, it may be possible to solve the linear equation set (above) for the scaling factor, K. Is should be noted that in order to solve the disclosed linear equation set, sensing electrodes must be located at different distances away from the current injecting electrode. If, for example, the distances were all identical, then the matrix on the right-hand side of the equation would be singular and result in an infinite number of equally valid solutions. Referring to Fig. 9, it can be seen that sensing electrodes 63, 65, 67, 68 are located at different distances from current injecting electrode 70.

[0079] Fig. 9 illustrates the sensing electrodes 63, 65, 67, 68 positioned longitudinally along spline 44. However, it is contemplated that the sensing electrodes 63, 65, 67, 68 may be positioned in a configuration other than along the longitudinal axis and yet still maintain variable distances between the sensing electrodes and the current-carrying electrode 70. Additionally, in some instances it may be possible to reduce the number of sensing electrodes to two or three and solve the corresponding linear equation set for scaling factor K. In other instances, it may be desirable to increase the number of sensing electrodes; the parameter K can still be estimated using well-known techniques such as least squares.

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[0080] It can be appreciated from the above discussion that it may be possible to utilize known variables to solve the disclosed linear equation for the scaling factor K. Therefore, system 10 may determine and compare different scaling factor values as the distal end portion of catheter 14 is moved between different mediums (e.g. blood, tissue). The difference in the scaling factors may be utilized as a diagnostic indicator of tissue contact.

[0081] Furthermore, because each individual mapping electrode 24 may be configured as either a sensing and/or current-carrying electrode, more than one electrode may be utilized to indicate tissue contact through the use of multiplexed measurements. Multiplexing may include any of a number of known techniques such as time-division, frequency-division, or code-division multiplexing. For example, in one frequency or time "slot", electrode 63 may be the current-carrying electrode, while electrodes 65, 67, and 68 may be sensing electrodes. In a second frequency or time slot, electrode 65 may be the current-carrying electrode, while electrodes 63, 67, and 68 may be sensing electrodes. It is understood than any combination of electrodes on structure 20 may be current-carrying and/or the sensing electrodes. Further, because most of the impedance "seen" by the current-carrying electrode is due to the conductive medium nearest the electrode, any given electrode may be indicative of the contact of a different part of the electrode structure 20 with tissue. Multiple electrodes may therefore be combined to provide two or more spatially-distinct contact indicators.

[0082] It can be appreciated from the above discussion that the size and arrangement of the mapping electrodes 24 disclosed herein may be more desirable for detecting a localized scaling factor K as compared to other electrode structures. The small, flat electrode geometry may make the applied current distribution more localized to nearby tissue than would be achieved with a larger, non-flat electrode. The close spacing of the mapping electrodes 24 may result in a more localized estimate of the scaling factor than would be achieved with larger electrode spacing.

[0083] Using the scaling factor K to assess tissue contact may be highly reliable. However, in some instances, the positioning and/or configuration of system 10 may alter the scaling K-factor results. In these instances, it may be desirable to utilize a supplemental method for assessing tissue contact. A variety of supplemental methods

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for assessing tissue contact are contemplated. For example, a supplemental method for assessing tissue contact may include comparing the amplitude of measured cardiac activation, or a spatial or temporal derivative thereof, to a threshold value. Another example supplemental method for assessing tissue contact may include determining a threshold impedance value that positively identifies tissue contact. More specifically, in some instances system 10 may be capable of sensing and/or measuring an impedance increase and correlating the impedance increase to a visual, audible, etc. indication of tissue contact.

[0084] For example, system 10 may be capable of utilizing threshold impedance measurements to sense contact between mapping electrodes 24 and adjacent tissue. In general, the impedance of a given medium may be measured by applying a known voltage or current to a given medium and measuring the resulting voltage or current. In other words, impedance measurements of a given medium can be obtained by injecting current between two electrodes and measuring the resulting voltage between the same electrodes through which the current was injected. The ratio of the voltage potential provides an indication of the impedance of the medium through which the current traveled.

[0085] For example, in some instances a current may be injected between an electrode 24 and one or more return electrodes (e.g. patch electrode, mini-electrode, measuring electrode, sensing electrode, or the like). Impedance of the medium (e.g. tissue, blood) adjacent to a current-carrying electrode 24 may be measured according to the methodology disclosed above. For example, if electrode 24 is adjacent to or embedded in cardiac tissue, the impedance of the cardiac tissue may be determined by measuring the ratio of the voltage potential between electrode 24 and the one or more return electrodes. While the above discussion generally describes utilizing the current carrying electrodes and the return electrode(s) in unipolar mode, it is contemplated that electrodes 24 may be capable of operating, or configured to operate, in bipolar sensing modes.

[0086] The size and shape of electrodes 24 may influence the ability (or inability) of electrodes 24 to measure the electrical characteristics (e.g. impedance) of cellular tissue and/or a surrounding medium (e.g. blood). In some instances, the degree of

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contact that an electrode 24 maintains with the cardiac tissue may influence the magnitude of a sensed electrical response. For example, an exaggerated impedance value may be sensed when electrode 24 is completely covered and/or embedded in tissue. In some instances, this exaggerated impedance value may be described as an "impedance increase." This impedance increase may, therefore, directly correspond to tissue contact. It can be appreciated that the substantially flat, reduced-profile and relatively smaller shape of electrode 60 shown in FIG. 4 may increase the likelihood that as electrode 60 is positioned adjacent tissue it will be completely covered by tissue and thereby trigger an impedance increase. Further, this impedance increase may be sensed by processing system 32, and in some instances, output a signal to display 40 indicating that electrode 60 has made contact with tissue. The impedance increase may be 100%, 150%, 200%, 250%, 300%, 350%, 400%, 500%, 600%, 700%, 800%, 900%, 1000%, 2000%, 50,000% or more of the magnitude of a measured baseline impedance value.

[0087] FIGS. 6-8 are a series of drawings that illustrate electrode structure 20 being manipulated within an example cardiac chamber. More specifically, FIGS. 6-8 depict electrode structure 20 advancing through blood toward cardiac tissue. For example, FIG. 6 shows electrode structure 20, including mapping electrode 24, surrounded entirely by blood. FIG. 7 shows mapping electrode 24 positioned at a blood/tissue interface, while FIG. 8 shows electrode structure 20 embedded within cardiac tissue. In these examples, one or more of the plurality of mapping electrodes 24 may be continuously sensing impedance values adjacent to their respective outer surfaces as electrode structure 20 is manipulated within the cardiac chamber. Additionally, processing system 32 may be continuously operating to "sense" an impedance increase from any one of electrodes 24. For example, as mapping electrode 24 moves from a position illustrated in FIG. 6 to an embedded positioned illustrated in FIG. 8, processing system 32 may sense an impedance increase and output a corresponding indication of tissue contact to display 40.

[0088] It can be appreciated from the above discussion that the size and shape of the electrodes disclosed herein may be more desirable for detecting an impedance increase as compared to relatively larger, non-flat electrodes. In other words, the

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electrode size and shape disclosed herein may be more easily covered and/or embedded in adjacent tissue, thereby leading to a greater number of sensed impedance increases and correspondingly positive indications of tissue contact.

[0089] In addition or alternatively to any of the embodiments disclosed herein, in some instances it may be desirable to sense tissue contact by simultaneously using two or more methods discussed herein. As stated above, in some instances processing system 32 may have difficulty sensing and comparing a change in K-factor values while being manipulated in an anatomical structure (e.g. cardiac chamber). Therefore, it may be desirable for processing system 32 to sense an impedance increase while simultaneously monitoring and determining changes in the K-factor. However, in some instances processing system 32 may detect an impedance increase correlating to positive tissue contact despite not having sensed tissue contact utilizing the K-factor method. Having detected an impedance increase (in the absence of a positive tissue contact via the K-factor method), system 10 may be designed such that a positive indication of tissue contact is output to a display and/or a clinician. Likewise, processing system 10 may, at times, sense a change in the K-factor corresponding to positive tissue contact despite not having sensed an impedance increase. Furthermore, it is contemplated that in some instances system 10 may simultaneously sense a change in the K-factor and an impedance increase, both of which provide a positive indication of tissue contact.

[0090] In addition or alternatively to any of the embodiments disclosed herein, improvements in the measurements of any electrical characteristic disclosed herein (e.g. impedance) may be achieved by utilizing a four-terminal sensing configuration among any of mapping electrodes 24 on electrode structure 20 (of which any number may be operated as sensing and/or current-carrying electrodes). In general, a four-terminal sensing configuration drives current through a pair of “current-carrying” electrodes and measures the voltage across a different pair of “sensing” electrodes.

[0091] One advantage of a four-terminal sensing configuration is that the measured impedance may not be sensitive to the impedance of the electrodes themselves. In a two-terminal sensing configuration, the measured impedance includes the surrounding medium and both electrodes. In contrast, a four-terminal sensing

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configuration measures voltage across electrodes through which the current is negligible. As a result, the measured impedance is that of the surrounding medium and is largely independent of the impedance of the electrode and its interface with the surrounding medium.

[0092] Additionally, in some instances, improvements in the measurements of any electrical characteristic disclosed herein (e.g. impedance) may be improved by utilizing a three-terminal sensing configuration among any of mapping electrodes 24 on electrode structure 20 (of which any number may be operated as sensing and/or current-carrying electrodes). Some examples of three-terminal sensing may be found in U.S. Patent Application 8,449,535, the entirety of which is incorporated herein by reference. Further, in at least some instances, three-terminal sensing may be used instead of the four-terminal sensing configurations described herein, to the extent applicable.

[0093] It can be appreciated that four-terminal sensing may be incorporated and/or utilized by any combination of mapping electrodes 24 on electrode structure 20. Additionally, it is contemplated that any individual mapping electrode 24 on electrode structure 20 may operate as a sensing electrode or a current-carrying electrode. Additionally, as described above, system 10 may multiplex sensing configurations such that mapping electrodes 24 are both sensing and current carrying electrodes.

[0094] Furthermore, it is contemplated that sensing tissue contact utilizing the K-factor method, the impedance method or a combination of both can further incorporate four-terminal sensing as desired. For example, voltage values for the K-factor method may be obtained using four-terminal sensing. Likewise, impedance increase values for the impedance increase method may be obtained using four-terminal sensing. Additionally, either method may utilize four-terminal sensing in combination with any other method. For example, a “K-factor four terminal” method may be utilized simultaneously with the impedance increase method, which, in turn, may or may not incorporate four-terminal sensing. Additionally, an “impedance increase four terminal” method may be utilized simultaneously with the K-factor method, which, in turn, may or may not incorporate four-terminal sensing.

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[0095] In some examples, mapping electrodes 24 may be operatively coupled to processor 32. Further, generated output from mapping electrodes 24 may be sent to processor 32 of system 10 for processing in one or more manners discussed herein and/or for processing in other manners. As stated, an electrical characteristic (e.g. impedance) and/or an output signal from an electrode pair may at least partially form the basis of a contact assessment.

[0096] Further, system 10 may be capable of processing or may be configured to process the electrical signals from mapping electrodes 24. Based, at least in part, on the processed output from mapping electrodes 24 processor 32 may generate an output to a display (not shown) for use by a physician or other user. In instances where an output is generated to a display and/or other instances, processor 32 may be operatively coupled to or otherwise in communication with the display. Illustratively, the display may include various static and/or dynamic information related to the use of system 10. In one example, the display may include one or more of an image of the target area, an anatomical shell, a map conveying tissue proximity achieved at locations on the anatomical shell, an electroanatomical map that incorporates tissue proximity information, an image of structure 20, and/or indicators conveying information corresponding to tissue proximity, which may be analyzed by the user and/or by a processor of system 10 to determine the existence and/or location of arrhythmia substrates within the heart, to determine the location of catheter 18 within the heart, and/or to make other determinations relating to use of catheter 18 and/or other elongated members.

[0097] System 10 may include an indicator in communication with processor 32. The indicator may be capable of providing an indication related to a feature of the output signals received from one or more of the electrodes of structure 20. In one example, an indication to the clinician about a characteristic of structure 20 and/or the myocardial tissue interacted with and/or being mapped may be provided on the display. In some cases, the indicator may provide a visual and/or audible indication to provide information concerning the characteristic of structure 20 and/or the myocardial tissue interacted with and/or being mapped. For example, system 10 may determine that a measured impedance corresponds to an impedance value of cardiac tissue and

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therefore may output a color indicator (e.g. green) to a display. The color indicator may allow a physician to more easily determine whether to apply ablative therapy to a given cardiac location. This is just an example. It is contemplated that a variety of indicators may be utilized by system 10.

[0098] In some embodiments, the processed output from mapping electrodes 24 may be used by processor 32 in ways that are not directly visible to the clinician. For example, processed information for contact assessment may be incorporated into algorithms for catheter localization, generation of anatomical shells and electroanatomical maps, or registration of images.

[0099] In some embodiments, the display may include an anatomical shell or an electroanatomical map that incorporates tissue proximity information. For example, regions of an anatomical shell where impedance values of cardiac tissue are measured may be more opaque than regions where impedance values of blood are measured. In other examples, an electroanatomical map displaying features such as voltage, activation time, dominant frequency, or the like may display an indicator (e.g. color, texture, pattern, etc.) in regions where impedance values of blood are measured. In both cases, the indication of regions where tissue contact may have occurred (or has likely occurred above a given probability or acceptability threshold) may guide the physician in moving the catheter and collecting measurements. Examples of anatomical shells and electroanatomical maps may be found in U.S. Patent Application Publication 20120184863, U.S. Patent Application Publication 20120184864 and U.S. Patent Application Publication 20120184865, the entirety of which is incorporated herein by reference.

[00100] In some examples, tissue proximity data may be collected for one or more mapping electrodes 24 on the structure 20 according to any of the processes and/or methods disclosed herein. Further, the collected parameter and/or tissue proximity values may be displayed on an anatomical shell and/or electroanatomical map as discussed above.

[00101] In other examples, tissue contact information may be used to mask portions of an anatomical shell and/or an electroanatomical map. Further, displayed (or masked) portions of the shell or map may correspond to a threshold confidence levelof

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tissue contact. For example, masked portions may correspond to parameter values that are below a threshold confidence value.

[00102] As discussed above, the anatomical and/or electroanatomical map displaying (or masking) tissue contact locations may be manipulated by a clinician in order to generate more accurate diagnostic representations of an anatomical region (e.g. heart chamber).

[00103] The following documents are herein incorporated by reference: U.S. Patent Application Pub. US2008/0243214, U.S. Patent Application Pub. US2014/0058375, U.S. Patent Application Pub. US2013/0190747, U.S. Patent Application Pub. US2013/0060245, and U.S. Patent Application Pub. US2009/0171345.

[00104] Various modifications and additions can be made to the exemplary embodiments discussed without departing from the scope of the present invention. For example, while the embodiments described above refer to particular features, the scope of this invention also includes embodiments having different combinations of features and embodiments that do not include all of the described features. Accordingly, the scope of the present invention is intended to embrace all such alternatives, modifications, and variations as fall within the scope of the claims, together with all equivalents thereof.

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CLAIMS

We claim:

1. An electrophysiology medical device, comprising:
a catheter shaft including a distal end portion, wherein the distal end portion includes a sensing assembly having a plurality of mapping electrodes;
wherein the plurality of mapping electrodes includes at least one current-carrying electrode, a first sensing electrode and a second sensing electrode;
wherein the first sensing electrode is spaced from the current-carrying electrode a first distance;
wherein the second sensing electrode is spaced from the current-carrying electrode a second distance;
wherein the first distance is different from the second distance; and
a controller coupled to the plurality of mapping electrodes;
wherein the controller is capable of calculating a parameter based at least in part on the first and the second distances.

2. The medical device of claim 1, wherein the parameter indicates the proximity of the medical device to tissue.

3. The medical device of any one of claims 1-2, wherein calculating the parameter includes sensing a first voltage potential between the first electrode and one or more return electrodes, and sensing a second voltage potential between the second electrode and one or more return electrodes.

4. The medical device of claim 3, wherein calculating the parameter includes solving at least one linear equation, and wherein the at least one linear equation includes the first distance, the second distance, the first voltage and the second voltage.

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5. The medical device of any one of claims 1-4, wherein the sensing assembly includes a plurality of splines, and wherein the plurality of electrodes are disposed on the plurality of splines.

6. The medical device of any one of claims 1-4, wherein the sensing assembly includes a plurality of splines, and wherein the plurality of splines includes an outwardly facing surface, and wherein the plurality of electrodes are disposed on the outwardly facing surface.

7. The medical device of any one of claims 5-6, wherein the sensing assembly includes a plurality of splines, and wherein the plurality of splines are arranged in a basket.

8. The medical device of any one of claims 1-7, wherein the plurality of electrodes are each designed to sequentially and/or simultaneously operate in a sensing configuration and a current-carrying configuration.

9. The medical device of any one of claims 1-8, further comprising displaying the parameter on a display.

10. The medical device of claim 9, wherein displaying the parameter includes displaying a confidence value corresponding to the parameter.

11. The medical device of any one of claims 1-10, wherein the displaying the parameter on a display further includes displaying an anatomical shell and/or an electroanatomical map.

12. The medical device of claim 11, wherein the anatomical shell and/or electroanatomical map correspond to one or more parameter values, and wherein the one or more parameter values indicates the proximity of one or more electrodes to tissue.

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13. The medical device of any one of claims 11-12, further comprising masking a portion of the anatomical shell and/or the electroanatomical map.

14. The medical device of claim 13, wherein the masked portion corresponds to one or more parameter values that are below a threshold confidence value.

15. The medical device of claim 12, wherein the parameter values correspond to a color, texture, symbol and/or pattern.

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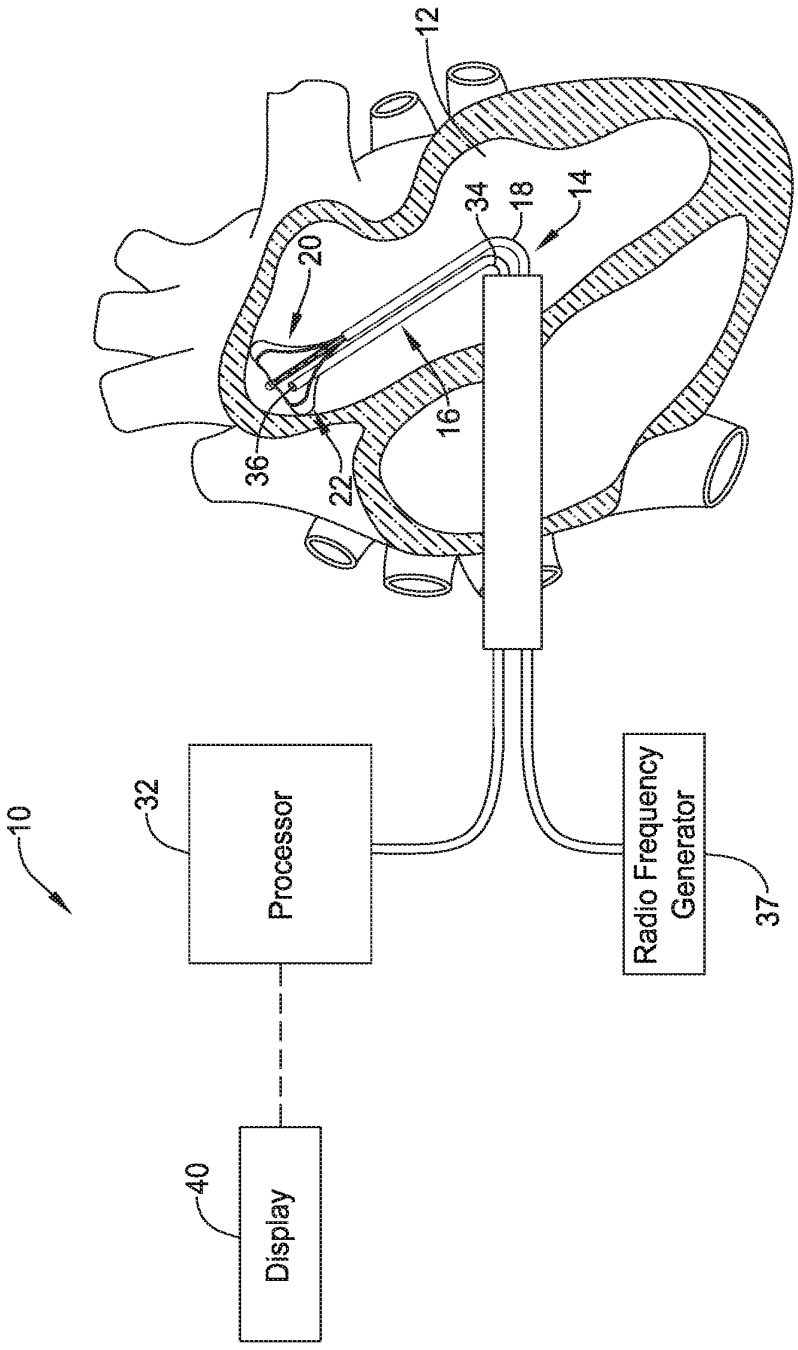

12
34
18
14
20
16
36
22
10
32
Processor
Radio Frequency Generator
37
40
Display

FIG. 1

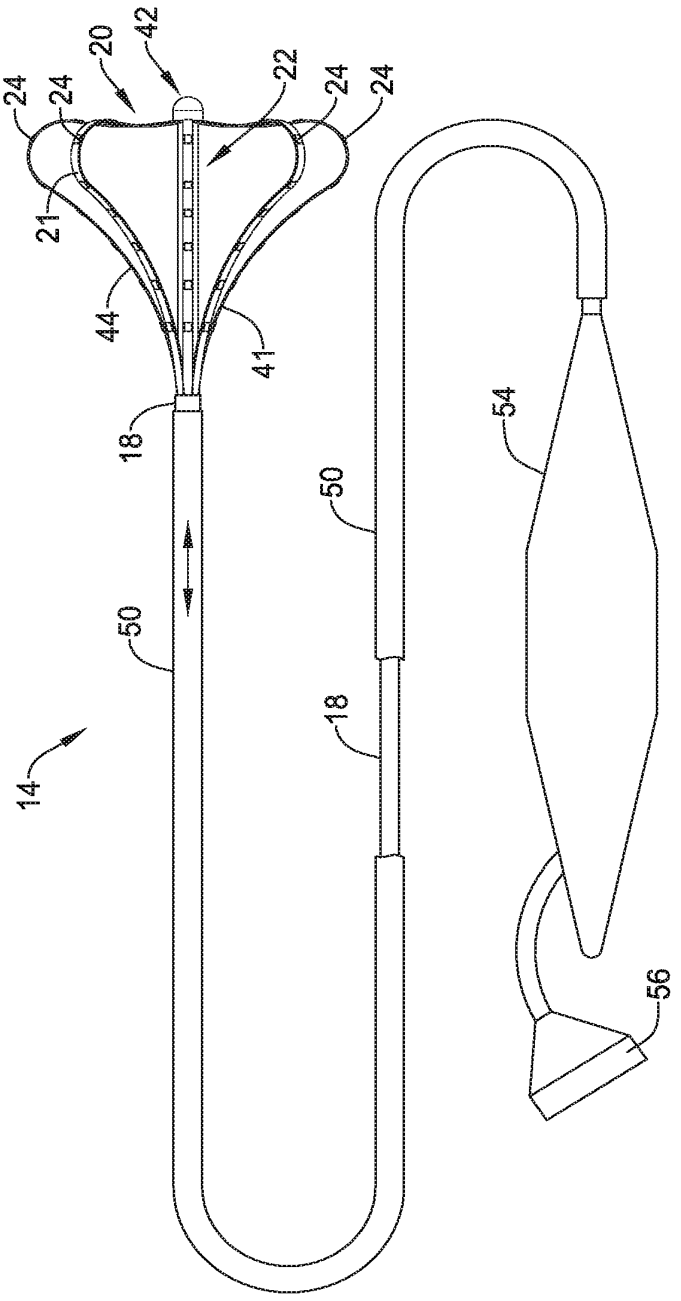


FIG. 2

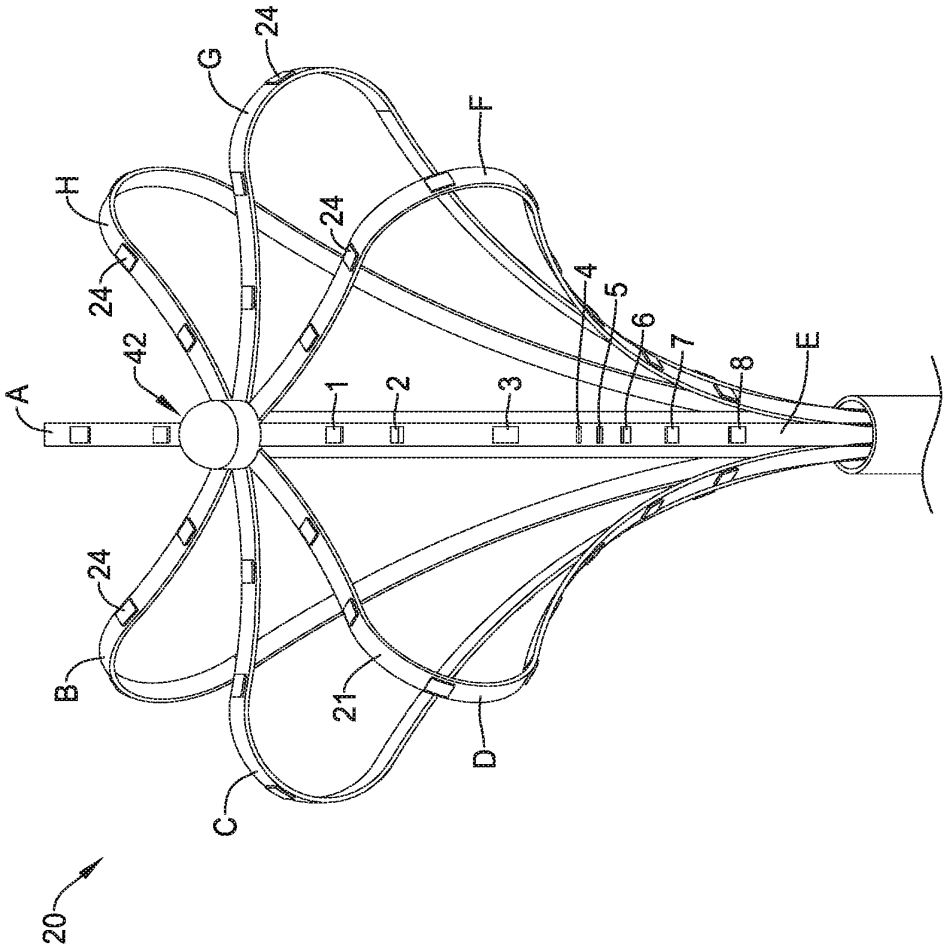


FIG. 3

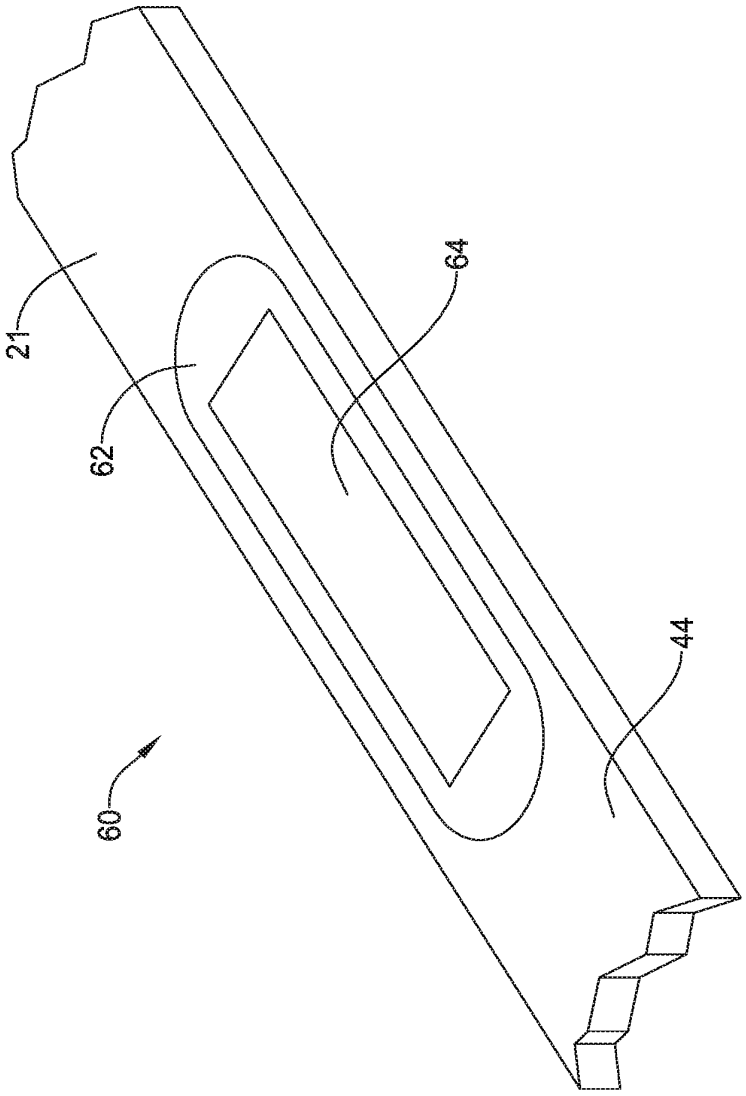


FIG. 4

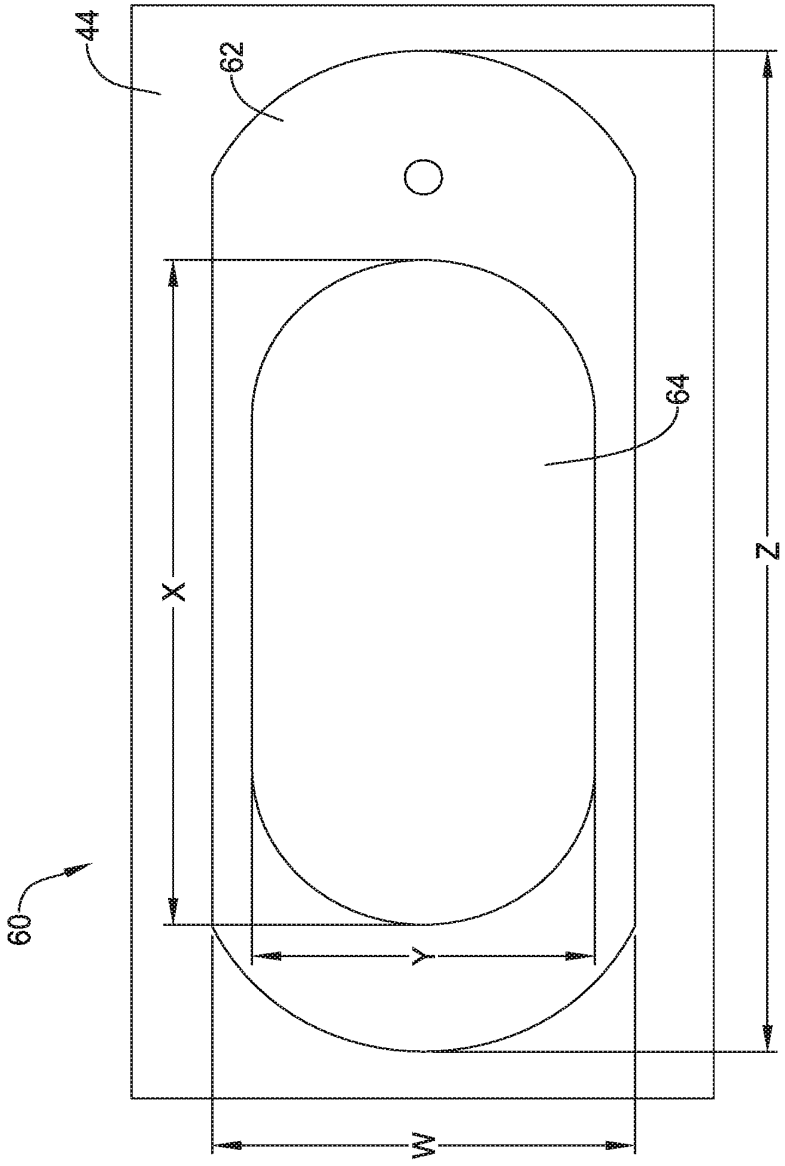


FIG. 5

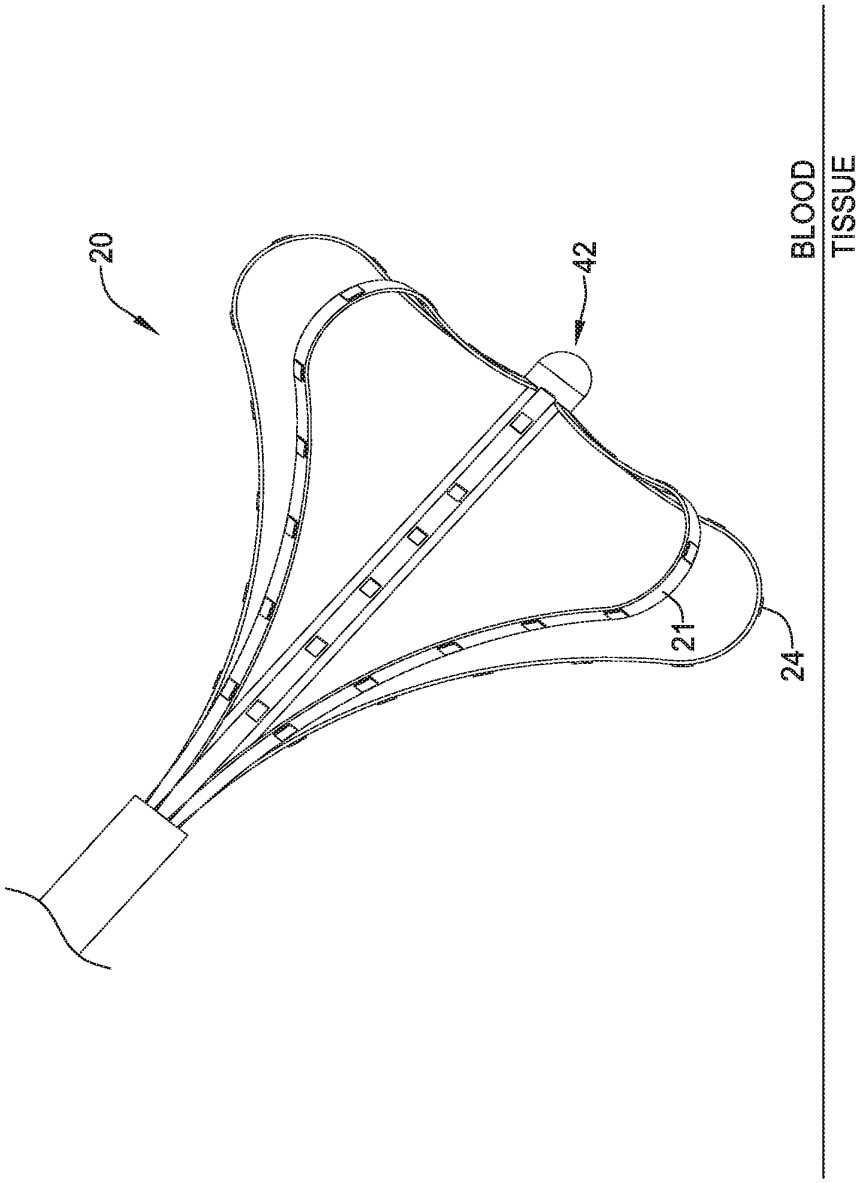


FIG. 6

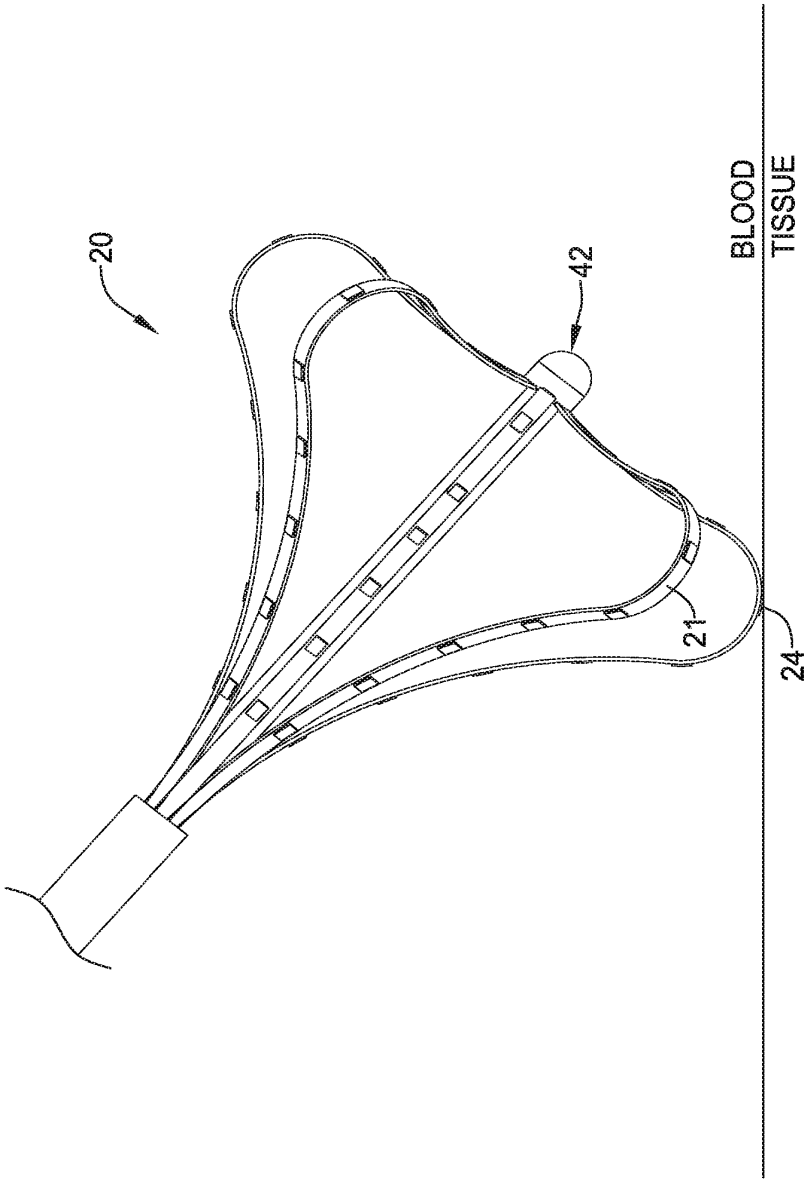


FIG. 7

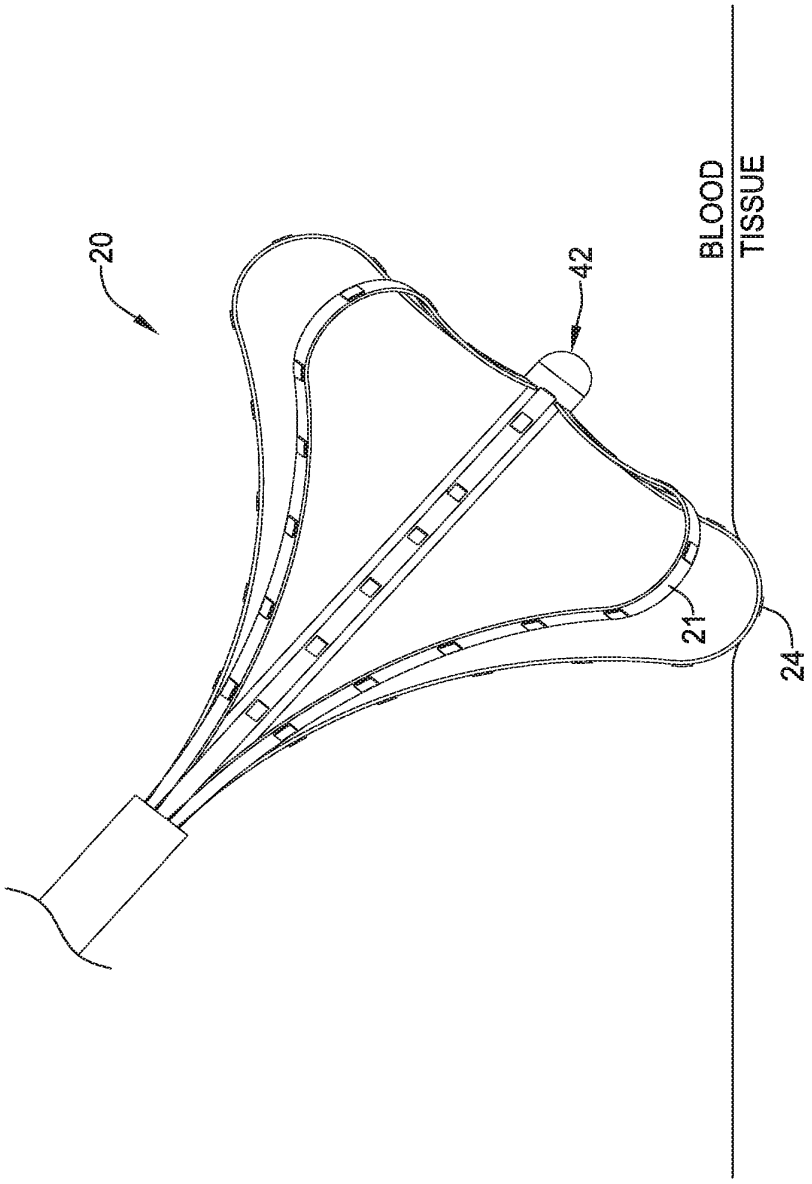


FIG. 8

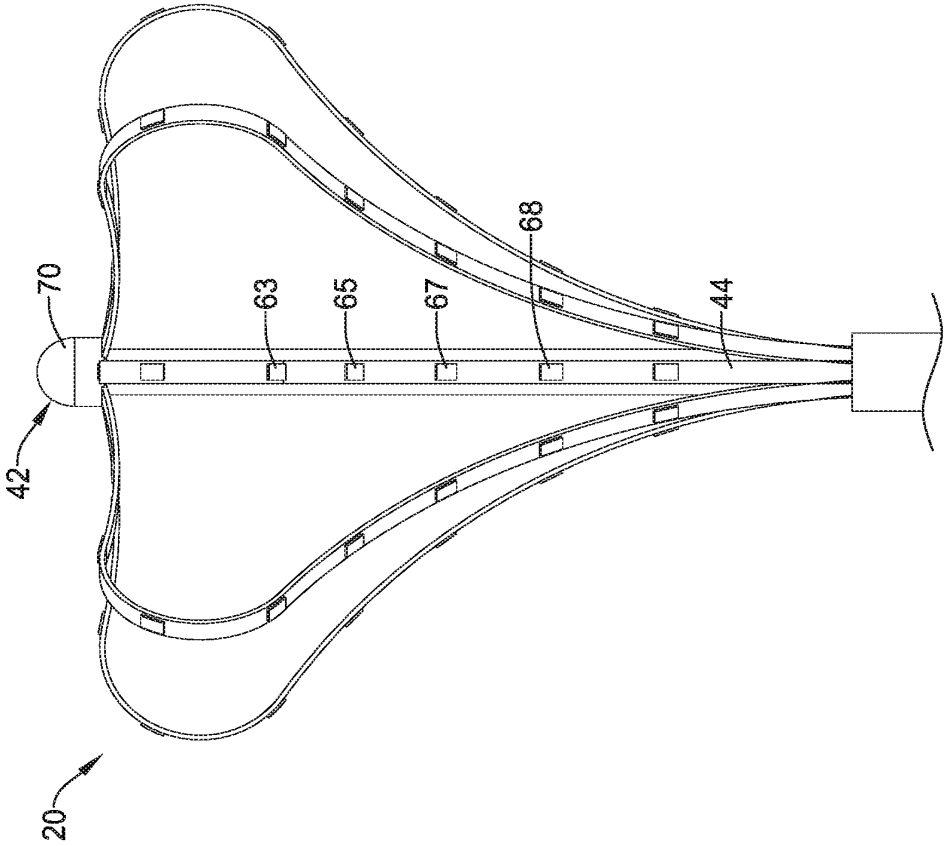


FIG. 9

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2016/018689

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61B5/00 A61B5/053 A61B5/06
ADD. A61B18/14 A61B18/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2014/036439 A2 (ACUTUS MEDICAL INC [US]) 6 March 2014 (2014-03-06) abstract; figure 1A paragraphs [0036] - [0038], [0085] - [0094], [0103] - [0104], [0118] - [0120], [0138] the whole document	1-15
X	US 2014/364715 A1 (HAUCK JOHN A [US]) 11 December 2014 (2014-12-11) abstract; figure 3 paragraphs [0024] - [0027] the whole document	1-15

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search	Date of mailing of the international search report
20 April 2016	28/04/2016

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Furlan, Stéphane

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2016/018689

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 391 024 B1 (SUN WEIMIN [US] ET AL) 21 May 2002 (2002-05-21) abstract; figures 8a-8c column 4, line 6 - line 42 the whole document -----	1-15
A	US 2009/275827 A1 (AIKEN ROBERT D [US] ET AL) 5 November 2009 (2009-11-05) abstract paragraphs [0057] - [0064]; figure 6 the whole document -----	1-15

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2016/018689

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		US 2009275827 A1	05-11-2009
		WO 2010132472 A1	18-11-2010

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DEVICES FOR THERAPEUTIC NASAL NEUROMODULATION AND ASSOCIATED METHODS AND SYSTEMS

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Applicant(s): NAT UNIV IRELAND GALWAY [IE]; QI ZHAN MICHELE [US] ± (NATIONAL UNIVERSITY OF IRELAND GALWAY, ; QI ZHAN, Michele)

Classification: **- international:** ***A61B18/00; A61B18/02; A61B18/04; A61B18/18; A61N1/05; A61N1/18; A61N1/32; A61N1/36***

- cooperative: **A61B17/00234 (US); A61B18/1492 (EP, US); A61B18/24 (EP, US); A61F7/123 (US); A61N1/0546 (EP, US); A61N1/18 (EP, US); A61N1/32 (EP, US); A61N1/36017 (EP, US); A61N1/36082 (EP, US); A61N1/40 (US); A61N7/00 (US);** A61B18/02 (EP, US); A61B18/1815 (EP, US); A61B2017/003 (US); A61B2018/00029 (EP, US); A61B2018/0016 (EP, US); A61B2018/00214 (EP, US); A61B2018/0022 (EP, US); A61B2018/00267 (EP, US); A61B2018/00327 (EP, US); A61B2018/00434 (EP, US); A61B2018/00577 (EP, US); A61B2018/00702 (EP, US); A61B2018/00797 (EP, US); A61B2018/1467 (EP, US); A61B2218/002 (EP, US); A61F2007/0006 (US); A61F2007/0054 (US); A61N1/36025 (EP, US); A61N2007/0021 (US); A61N5/022 (EP, US)

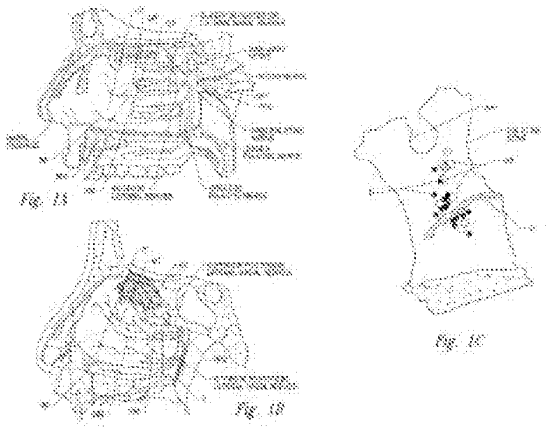
Application number: WO2016US32132 20160512 Global Dossier

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Also published as: WO2016183337 (A3) AU2016262085 (A1) CA2984207 (A1) CN107835705 (A) EP3294410 (A2) more

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IPR2025-01124

Abstract of WO2016183337 (A2)



Devices for therapeutic nasal neuromodulation and associated systems and methods are disclosed herein. A system for therapeutic neuromodulation in a nasal region configured in accordance with embodiments of the present technology can include, for example, a shaft and a therapeutic element at a distal portion of the shaft. The shaft can locate the distal portion intraluminally at a target site inferior to a patient's sphenopalatine foramen. The therapeutic element can include an energy delivery element configured to therapeutically modulate postganglionic parasympathetic nerves at microforamina of a palatine bone of the human patient for the treatment of rhinitis or other indications. In other embodiments, the therapeutic element can be configured to therapeutically modulate nerves that innervate the frontal, ethmoidal, sphenoidal, and maxillary sinuses for the treatment of chronic sinusitis.

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Aerin Medical Inc. v. Neurent Medical Ltd.
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A61B 18/02 (2006.01) *A61B 18/04* (2006.01)

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(72) Inventors: **TOWNLEY, David**; Latoon North, Newmarket-on-fergus, County Clare (IE). **SHIELDS, Brian**; 19 Ocean Drive, Oranmore, Galway (IE). **KEOGH, Ivan**; Rusheen House, Bama Road, Galway (IE). **FARREL, Conor**; Rosbeg, Wesrport, County Mayo (IE).

(74) Agents: **DUNHAM, Nicole, S.** et al.; Perkins Coie LLP, P.O. Box 1247, Seattle, WA 98111-1247 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

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(54) Title: DEVICES FOR THERAPEUTIC NASAL NEUROMODULATION AND ASSOCIATED METHODS AND SYSTEMS

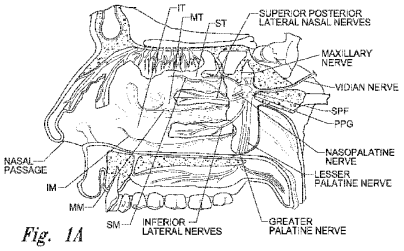


Fig. 1A

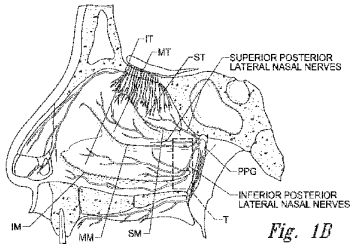


Fig. 1B

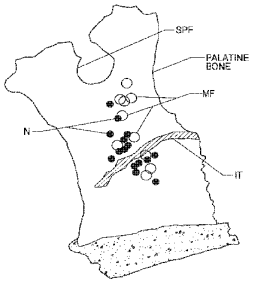


Fig. 1C

(57) Abstract: Devices for therapeutic nasal neuromodulation and associated systems and methods are disclosed herein. A system for therapeutic neuromodulation in a nasal region configured in accordance with embodiments of the present technology can include, for example, a shaft and a therapeutic element at a distal portion of the shaft. The shaft can locate the distal portion intraluminally at a target site inferior to a patient's sphenopalatine foramen. The therapeutic element can include an energy delivery element configured to therapeutically modulate postganglionic parasympathetic nerves at microforamina of a palatine bone of the human patient for the treatment of rhinitis or other indications. In other embodiments, the therapeutic element can be configured to therapeutically modulate nerves that innervate the frontal, ethmoidal, sphenoidal, and maxillary sinuses for the treatment of chronic sinusitis.

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DEVICES FOR THERAPEUTIC NASAL NEUROMODULATION AND ASSOCIATED METHODS AND SYSTEMS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] The present application claims priority to U.S. Provisional Patent Application No. 62/160,289, filed May 12, 2015, which is incorporated by reference herein in its entirety.

TECHNICAL FIELD

[0002] The present technology relates generally to devices, systems, and methods for therapeutically modulating nerves in or associated with a nasal region of a patient. In particular, various embodiments of the present technology are related to therapeutic neuromodulation systems and methods for the treating rhinitis and other indications.

BACKGROUND

[0003] Rhinosinusitis is characterized as an inflammation of the mucous membrane of the nose and refers to a group of conditions, including allergic rhinitis, non-allergic rhinitis, chronic rhinitis, chronic sinusitis, and medical resistant rhinitis. Symptoms of rhinosinusitis include nasal blockage, obstruction, congestion, nasal discharge (e.g., rhinorrhea and/or posterior nasal drip), facial pain, facial pressure, and/or reduction or loss of smell. Allergic rhinitis can include further symptoms, such as sneezing, watery rhinorrhea, nasal itching, and itchy or watery eyes. Severe rhinitis can lead to exacerbation of coexisting asthma, sleep disturbances, and impairment of daily activities. Depending on the duration and type of systems, rhinosinusitis can fall within four subtypes: acute rhinosinusitis, recurrent rhinosinusitis, chronic rhinosinusitis with nasal polyposis (i.e., soft, non-cancerous growths on the lining of the nasal passages or sinuses), and chronic rhinosinusitis without nasal polyposis. Acute rhinosinusitis refers to symptoms lasting for less than twelve weeks, whereas chronic rhinosinusitis (with and without nasal polyposis) refers to symptoms lasting longer than twelve weeks. Recurrent rhinosinusitis refers to four or more episodes of acute rhinosinusitis within a twelve-month period, with resolution of symptoms between each episode.

[0004] There are numerous environmental and biological causes of rhinosinusitis. Non-allergic rhinosinusitis, for example, can be caused by environmental irritants (e.g.,

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exhaust fumes, cleaning solutions, latex, perfume, dust, etc.), medications (e.g., NSAIDs, oral contraceptives, blood pressure medications including ACE inhibitors, antidepressants, etc.), foods (e.g., alcoholic beverages, spicy foods, etc.), hormonal changes (e.g., pregnancy and menstruation), and/or nasal septum deviation. Triggers of allergic rhinitis can include exposure to seasonal allergens (e.g., exposure to environmental allergens at similar times each year), perennial allergens that occur any time of year (e.g., dust mites, animal dander, molds, etc.), and/or occupational allergens (e.g., certain chemicals, grains, latex, etc.).

[0005] The treatment of rhinosinusitis can include a general avoidance of rhinitis triggers, nasal irrigation with a saline solution, and/or drug therapies. Pharmaceutical agents prescribed for rhinosinusitis include, for example, oral H1 antihistamines, topical nasal H1 antihistamines, topical intranasal corticosteroids, systemic glucocorticoids, injectable corticosteroids, anti-leukotrienes, nasal or oral decongestants, topical anticholinergic, chromoglycate, and/or anti-immunoglobulin E therapies. However, these pharmaceutical agents have limited efficacy (e.g., 17% higher than placebo or less) and undesirable side effects, such as sedation, irritation, impairment to taste, sore throat, dry nose, epistaxis (i.e., nose bleeds), and/or headaches. Immunotherapy, including sublingual immunotherapy ("SLIT"), has also been used to treat allergic rhinitis by desensitizing the patient to particular allergens by repeated administration of an allergen extract. However, immunotherapy requires an elongated administration period (e.g., 3-5 years for SLIT) and may result in numerous side effects, including pain and swelling at the site of the injection, urticarial (i.e., hives), angioedema, asthma, and anaphylaxis.

[0006] Surgical interventions have also been employed in an attempt to treat patients with drug therapy resistant, severe rhinitis symptoms. In the 1960's through 1980's, surgeries were performed to sever parasympathetic nerve fibers in the vidian canal to decrease parasympathetic tone in the nasal mucosa. More recent attempts at vidian neurectomies were found to be 50-88% effective for the treatment of rhinorrhea, with other ancillary benefits including improvements in symptoms of sneezing and nasal obstruction. These symptomatic improvements have also been correlated to histologic mucosal changes with reductions in stromal edema, eosinophilic cellular infiltration, mast cell levels, and histamine concentrations in denervated mucosa. However, despite the clinical and histologic efficacy of vidian neurectomy, resecting the vidian nerve failed to gain widespread acceptance largely due to the morbidities associated with its lack of anatomic and autonomic selectivity. For example, the site of neurectomy includes preganglionic secretomotor fibers to the lacrimal

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gland, and therefore the neurectomy often resulted in the loss of reflex tearing, i.e., lacrimation, which in severe cases can cause vision loss. Due to such irreversible complications, this technique was soon abandoned. Further, due passage of postganglionic pterygopalatine fibers through the retro-orbital plexus, the position of the vidian neurectomy relative to the target end organ (i.e., the nasal mucosa) may result in re-innervation via the autonomic plexus and otic ganglion projections traveling with the accessory meningeal artery.

[0007] The complications associated with vidian neurectomies are generally attributed to the nonspecific site of autonomic denervation. Consequently, surgeons have recently shifted the site of the neurectomy to postganglionic parasympathetic rami that may have the same physiologic effect as a vidian neurectomy, while avoiding collateral injury to the lacrimal and sympathetic fibers. For example, surgeons in Japan have performed transnasal inferior turbinate submucosal resections in conjunction with resections of the posterior nasal nerves ("PNN"), which are postganglionic neural pathways located further downstream than the vidian nerve. (*See*, Kobayashi T, Hyodo M, Nakamura K, Komobuchi H, Honda N, Resection of peripheral branches of the posterior nasal nerve compared to conventional posterior neurectomy in severe allergic rhinitis. *Auris Nasus Larynx.* 2012 Feb 15;39:593-596.) The PNN neurectomies are performed at the sphenopalatine foramen, where the PNN is thought to enter the nasal region. These neurectomies are highly complex and laborious because of a lack of good surgical markers for identifying the desired posterior nasal nerves and, even if the desired nerves are located, resection of the nerves is very difficult because the nerves must be separated from the surrounding vasculature (e.g., the sphenopalatine artery).

BRIEF DESCRIPTION OF THE DRAWINGS

[0008] Many aspects of the present technology can be better understood with reference to the following drawings. The components in the drawings are not necessarily to scale. Instead, emphasis is placed on illustrating clearly the principles of the present technology. For ease of reference, throughout this disclosure identical reference numbers may be used to identify identical or at least generally similar or analogous components or features.

[0009] Figure 1A is a cut-away side view illustrating the anatomy of a lateral nasal wall.

[0010] Figure 1B is an enlarged side view of the nerves of the lateral nasal wall of Figure 1A.

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[0011] Figure 1C is a front view of a left palatine bone illustrating geometry of microforamina in the left palatine bone.

[0012] Figure 2 is a partially schematic view of a therapeutic neuromodulation system for therapeutically modulating nerves in a nasal region in accordance with an embodiment of the present technology.

[0013] Figures 3A-3E are partial cut-away side views illustrating various approaches for delivering a distal portion of a therapeutic neuromodulation device to a target site within a nasal region in accordance with embodiments of the present technology.

[0014] Figure 4 is an isometric view of a distal portion of a therapeutic neuromodulation device configured in accordance with an embodiment of the present technology.

[0015] Figures 5A-5G are isometric views of electrode configurations of therapeutic neuromodulation devices for therapeutic neuromodulation in accordance with embodiments of the present technology.

[0016] Figures 6A and 6B are partially schematic diagrams illustrating electrode configurations at a distal portion of a therapeutic neuromodulation device for nerve detection configured in accordance with embodiments of the present technology.

[0017] Figure 7 is a graph illustrating threshold levels of electrical conductivity of nasal tissue with respect to temperature.

[0018] Figures 8 and 9 are isometric views of a distal portion of a therapeutic neuromodulation device configured in accordance with an embodiment of the present technology.

[0019] Figure 10A is an isometric view of a distal portion of a therapeutic neuromodulation device configured in accordance with another embodiment of the present technology, and Figure 10B is an isometric view illustrating the therapeutic neuromodulation device of Figure 10A at a treatment site.

[0020] Figures 11A-11D are isometric views illustrating a distal portion of a therapeutic neuromodulation device configured in accordance with yet another embodiment of the present technology.

[0021] Figure 12 is a side view of a distal portion of a therapeutic neuromodulation device configured in accordance with a further embodiment of the present technology.

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[0022] Figure 13 is a side view of a distal portion of a therapeutic neuromodulation device configured in accordance with a still further embodiment of the present technology.

[0023] Figure 14 is an isometric side view of a distal portion of a therapeutic neuromodulation device configured in accordance with an additional embodiment of the present technology.

[0024] Figure 15 is an isometric side view of a distal portion of a therapeutic neuromodulation device configured in accordance with an additional embodiment of the present technology.

[0025] Figure 16 is a cross-sectional side view of a distal portion of a therapeutic neuromodulation device configured in accordance with an additional embodiment of the present technology.

[0026] Figure 17 is a cross-sectional side view of a distal portion of a therapeutic neuromodulation device configured in accordance with an additional embodiment of the present technology.

[0027] Figure 18 is a cross-sectional side view of a distal portion of a therapeutic neuromodulation device configured in accordance with an additional embodiment of the present technology.

[0028] Figure 19 is a side view of a distal portion of a therapeutic neuromodulation device configured in accordance with an additional embodiment of the present technology.

[0029] Figure 20 is a partial cut-away side view illustrating target sites proximate to ostia of nasal sinuses for a therapeutic neuromodulation device configured in accordance with embodiments of the present technology.

DETAILED DESCRIPTION

[0030] The present technology is generally directed to devices for therapeutic nasal neuromodulation and associated systems and methods. The disclosed devices are configured to provide an accurate and localized non-invasive application of energy to disrupt the parasympathetic motor sensory function in the nasal region. Specific details of several embodiments of the present technology are described herein with reference to Figures 1A-20. Although many of the embodiments are described with respect to devices, systems, and methods for therapeutically modulating nerves in the nasal region for the treatment of rhinitis, other applications and other embodiments in addition to those described herein are

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within the scope of the present technology. For example, at least some embodiments of the present technology may be useful for the treatment of other indications, such as the treatment of chronic sinusitis and epitaxis. It should be noted that other embodiments in addition to those disclosed herein are within the scope of the present technology. Further, embodiments of the present technology can have different configurations, components, and/or procedures than those shown or described herein. Moreover, a person of ordinary skill in the art will understand that embodiments of the present technology can have configurations, components, and/or procedures in addition to those shown or described herein and that these and other embodiments can be without several of the configurations, components, and/or procedures shown or described herein without deviating from the present technology.

[0031] With regard to the terms "distal" and "proximal" within this description, unless otherwise specified, the terms can reference relative positions of portions of a therapeutic neuromodulation device and/or an associated delivery device with reference to an operator and/or a location within the nasal cavity. For example, in referring to a delivery catheter suitable to deliver and position various prosthetic valve devices described herein, "proximal" can refer to a position closer to the operator of the device or access point at the entrance point of a patient's nostril, and "distal" can refer to a position that is more distant from the operator of the device or further from the access point at the entrance of the patient's nostril. Additionally, posterior, anterior, inferior and superior are used in accordance with standard medical terminology.

[0032] As used herein, the terms "therapeutic modulation" of nerves and "therapeutic neuromodulation" refer to the partial or complete incapacitation or other effective disruption of neural activity, including partial or complete ablation of nerves. Therapeutic neuromodulation, for example, can include partially or completely inhibiting, reducing, and/or blocking neural communication along neural fibers.

Anatomy of the Nasal Cavity

[0033] Figure 1A is a cut-away side view illustrating the anatomy of a lateral nasal wall, and Figure 1B is an enlarged side view of the nerves of the lateral nasal wall of Figure 1A. The sphenopalatine foramen ("SPF"; Figure 1A) is an opening or conduit defined by the palatine bone and the sphenoid bone through which the sphenopalatine vessels and the posterior superior nasal nerves travel into the nasal cavity. More specifically, the orbital and sphenoidal processes of the perpendicular plate of the palatine bone define the sphenopalatine

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notch, which is converted into the SPF by the articulation with the surface of the body of the sphenoid bone.

[0034] The location of the SPF is highly variable within the posterior region of the lateral nasal cavity, which makes it difficult to visually locate the SPF. Typically, the SPF is located in the middle meatus ("MM"; Figure 1A); however, anatomical variations also result in the SPF being located in the superior meatus ("SM"; Figure 1A) or at the transition of the superior and middle meatuses. In certain individuals, for example, the inferior border of the SPF has been measured at about 19 mm above the horizontal plate of the palatine bone (i.e., the nasal sill), which is about 13 mm above the horizontal lamina of the inferior turbinate ("IT"; Figure 1A), and the average distance from the nasal sill to the SPF is about 64.4 mm, resulting in an angle of approach from the nasal sill to the SPA of about 11.4°. However, studies to measure the precise location of the SPF are of limited practical application due to the wide variation of its location.

[0035] The anatomical variations of the SPF are expected to correspond to alterations of the autonomic and vascular pathways traversing into the nasal cavity. In general, it is thought that the posterior nasal nerves (also referred to as lateral posterior superior nasal nerves) branch from the pterygopalatine ganglion ("PPG"; also referred to as the sphenopalatine ganglion; Figure 1A) through the SPF to enter the lateral nasal wall of the nasal cavity, and the sphenopalatine artery passes from the pterygopalatine fossa through the SPF on the lateral nasal wall. The sphenopalatine artery branches into two main portions: the posterior lateral nasal branch and the posterior septal branch. The main branch of the posterior lateral nasal artery travels inferiorly into the inferior turbinate IT (e.g., between about 1.0 mm and 1.5 mm from the posterior tip of the inferior turbinate IT), while another branch enters the middle turbinate MT and branches anteriorly and posteriorly.

[0036] Beyond the SPF, studies have shown that over 30% of human patients have one or more accessory foramen that also carries arteries and nerves into the nasal cavity. The accessory foramena are typically smaller than the SPF and positioned inferior to the SPF. For example, there can be one, two, three or more branches of the posterior nasal artery and posterior nasal nerves that extend through corresponding accessory foramen. The variability in location, size, and quantity associated with the accessory foramen and the associated branching arteries and nerves that travel through the accessory foramen gives rise to a great deal of uncertainty regarding the positions of the vasculature and nerves of the sphenopalatine region. Furthermore, the natural anatomy extending from the SPF often

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includes deep inferior and/or superior grooves that carry neural and arterial pathways, which make it difficult to locate arterial and neural branches. For example the grooves can extend more than 5 mm long, more than 2 mm wide, and more than 1 mm deep, thereby creating a path significant enough to carry both arteries and nerves. The variations caused by the grooves and the accessory foramen in the sphenopalatine region make locating and accessing the arteries and nerves (positioned posterior to the arteries) extremely difficult for surgeons.

[0037] Recent microanatomic dissection of the pterygopalatine fossa (PPF) have further evidenced the highly variable anatomy of the region surrounding the SPF, showing that a multiplicity of efferent rami that project from the pterygopalatine ganglion ("PPG"; Figure 1) to innervate the orbit and nasal mucosa via numerous groups of small nerve fascicles, rather than an individual postganglionic autonomic nerves (e.g., the posterior nasal nerve). Studies have shown that at least 87% of humans have microforamina and micro rami in the palatine bone. Figure 1C, for example, is a front view of a left palatine bone illustrating geometry of microforamina and micro rami in a left palatine bone. In Figure 1C, the solid regions represent nerves traversing directly through the palatine bone, and the open circles represent nerves that were associated with distinct microforamina. Indeed, Figure 1C illustrates that a medial portion of the palatine bone can include at least 25 accessory posterolateral nerves.

[0038] The respiratory portion of the nasal cavity mucosa is composed of a type of ciliated pseudostratified columnar epithelium with a basement membrane. Nasal secretions (e.g., mucus) are secreted by goblet cells, submucosal glands, and transudate from plasma. Nasal seromucous glands and blood vessels are highly regulated by parasympathetic innervation deriving from the vidian and other nerves. Parasympathetic (cholinergic) stimulation through acetylcholine and vasoactive intestinal peptide generally results in mucus production. Accordingly, the parasympathetic innervation of the mucosa is primarily responsible submucosal gland activation/hyper activation, venous engorgement (e.g., congestion), and increased blood flow to the blood vessels lining the nose. Accordingly, severing or modulating the parasympathetic pathways that innervate the mucosa are expected to reduce or eliminate the hyper activation of the submucosal glands and engorgement of vessels that cause symptoms associated with rhinosinusitis and other indications.

[0039] As discussed above, postganglionic parasympathetic fibers that innervate the nasal mucosa (i.e., posterior superior nasal nerves) were thought to travel exclusively through the SPF as a sphenopalatine neurovascular bundle. The posterior nasal nerves are branches of the maxillary nerve that innervate the nasal cavity via a number of smaller medial and

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lateral branches extending through the mucosa of the superior and middle turbinates ST, MT (i.e., nasal chonchea) and to the nasal septum. The nasopalatine nerve is generally the largest of the medial posterior superior nasal nerves. It passes antero-inferiorly in a groove on the vomer to the floor of the nasal cavity. From here, it passes through the incisive fossa of the hard palate and communicates with the greater palatine nerve to supply the mucosa of the hard palate. The posterior superior nasal nerves pass through the pterygopalatine ganglion PPG without synapsing and onto the maxillary nerve via its ganglionic branches.

[0040] Based on the understanding that the posterior nasal nerves exclusively traverse the SPF to innervate the nasal mucosa, surgeries have been performed to selectively sever the posterior nasal nerve as it exits the SPF. However, as discussed above, the sinonasal parasympathetic pathway actually comprises individual rami project from the pterygopalatine ganglion (PPG) to innervate the nasal mucosa via multiple small nerve fascicles (i.e., accessory posterolateral nerves), not a single branch extending through the SPF. These rami are transmitted through multiple fissures, accessory foramina, and microforamina throughout the palatine bone and may demonstrate anastomotic loops with both the SPF and other accessory nerves. Thus, if only the parasympathetic nerves traversing the SPF were severed, almost all patients (e.g., 90% of patients or more) would retain intact accessory secretomotor fibers to the posterolateral mucosa, which would result in the persistence of symptoms the neurectomy was meant to alieve.

[0041] Accordingly, embodiments of the present technology are configured to therapeutically modulate nerves at precise and focused treatment sites corresponding to the sites of rami extending through fissures, accessory foramina, and microforamina throughout the palatine bone (e.g., target region T shown in Figure 1B). In certain embodiments, the targeted nerves are postganglionic parasympathetic nerves that go on to innervate the nasal mucosa. This selective neural treatment is also expected to decrease the rate of postoperative nasal crusting and dryness because it allows a clinician to titrate the degree of anterior denervation through judicious sparing of the rami orbitonasalis. Furthermore, embodiments of the present technology are also expected to maintain at least some sympathetic tone by preserving a portion of the sympathetic contributions from the deep petrosal nerve and internal maxillary periarteriolar plexi, leading to improved outcomes with respect to nasal obstruction. In addition, embodiments of the present technology are configured to target a multitude of parasympathetic neural entry locations (e.g., accessory foramen, fissures, and

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microforamina) to the nasal region to provide for a complete resection of all anastomotic loops, thereby reducing the rate of long-term re-innervation.

Selected Embodiments of Systems for Therapeutic Nasal Neuromodulation and Neural Mapping

[0042] Figure 2 is a partially schematic view of a therapeutic neuromodulation system 200 ("system 200") for therapeutically modulating nerves in a nasal region in accordance with an embodiment of the present technology. The system 200 includes a therapeutic neuromodulation catheter or device 202, a console 204, and a cable 206 extending therebetween. The therapeutic neuromodulation device 202 includes a shaft 208 having a proximal portion 208a, a distal portion 208b, a handle 210 at a proximal portion 208a of the shaft 208, and a therapeutic assembly or element 212 at the distal portion 208b of the shaft 208. The shaft 208 is configured to locate the distal portion 208b intraluminally at a treatment or target site within a nasal region proximate to postganglionic parasympathetic nerves that innervate the nasal mucosa. The target site may be a region, volume, or area in which the target nerves are located and may differ in size and shape depending upon the anatomy of the patient. For example, the target site may be a 3 cm area inferior to the SPF. In other embodiments, the target site may be larger, smaller, and/or located elsewhere in the nasal cavity to target the desired neural fibers. The therapeutic assembly 212 can include at least one energy delivery element 214 configured to therapeutically modulate the postganglionic parasympathetic nerves. In certain embodiments, for example, the therapeutic assembly 212 can therapeutically modulate the postganglionic parasympathetic nerves branching from the pterygopalatine ganglion and innervating the nasal region and nasal mucosa, such as parasympathetic nerves (e.g., the posterior nasal nerves) traversing the SPF, accessory foramen, and microforamina of a palatine bone.

[0043] As shown in Figure 2, the therapeutic assembly 212 includes at least one energy delivery element 214 configured to provide therapeutic neuromodulation to the target site. In certain embodiments, for example, the energy delivery element 214 can include one or more electrodes configured to apply electromagnetic neuromodulation energy (e.g., RF energy) to target sites. In other embodiments, the energy delivery element 214 can be configured to provide therapeutic neuromodulation using various other modalities, such as cryotherapeutic cooling, ultrasound energy (e.g., high intensity focused ultrasound ("HIFU") energy), microwave energy (e.g., via a microwave antenna), direct heating, high and/or low power laser energy, mechanical vibration, and/or optical power. In further embodiments, the

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therapeutic assembly 212 can be configured to deliver chemicals or drugs to the target site to chemically ablate or embolize the target nerves. For example, the therapeutic assembly 212 can include a needle applicator extending through an access portion of the shaft 208 and/or a separate introducer, and the needle applicator can be configured to inject a chemical into the target site to therapeutically modulate the target nerves, such as botox, alcohol, guanethidine, ethanol, phenol, a neurotoxin, or another suitable agent selected to alter, damage, or disrupt nerves.

[0044] In certain embodiments, the therapeutic assembly 212 can include one or more sensors (not shown), such as one or more temperature sensors (e.g., thermocouples, thermistors, etc.), impedance sensors, and/or other sensors. The sensor(s) and/or the energy delivery element 214 can be connected to one or more wires (not shown; e.g., copper wires) extending through the shaft 208 to transmit signals to and from the sensor(s) and/or convey energy to the energy delivery element 214.

[0045] The therapeutic neuromodulation device 202 can be operatively coupled to the console 204 via a wired connection (e.g., via the cable 206) and/or a wireless connection. The console 204 can be configured to control, monitor, supply, and/or otherwise support operation of the therapeutic neuromodulation device 202. The console 204 can further be configured to generate a selected form and/or magnitude of energy for delivery to tissue or nerves at the target site via the therapeutic assembly 212, and therefore the console 204 may have different configurations depending on the treatment modality of the therapeutic neuromodulation device 202. For example, when therapeutic neuromodulation device 202 is configured for electrode-based, heat-element-based, and/or transducer-based treatment, the console 204 can include an energy generator 216 configured to generate RF energy (e.g., monopolar, bipolar, or multi-polar RF energy), pulsed electrical energy, microwave energy, optical energy, ultrasound energy (e.g., intraluminally- delivered ultrasound and/or HIFU), direct heat energy, radiation (e.g., infrared, visible, and/or gamma radiation), and/or another suitable type of energy. When the therapeutic neuromodulation device 202 is configured for cryotherapeutic treatment, the console 204 can include a refrigerant reservoir (not shown), and can be configured to supply the therapeutic neuromodulation device 202 with refrigerant. Similarly, when the therapeutic neuromodulation device 202 is configured for chemical-based treatment (e.g., drug infusion), the console 204 can include a chemical reservoir (not shown) and can be configured to supply the therapeutic neuromodulation device 202 with one or more chemicals.

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[0046] As further shown in Figure 2, the system 200 can further include a controller 218 communicatively coupled to the therapeutic neuromodulation device 202. In the illustrated embodiment, the controller 218 is housed in the console 204. In other embodiments, the controller 218 can be carried by the handle 210 of the therapeutic neuromodulation device 202, the cable 206, an independent component, and/or another portion of the system 200. The controller 218 can be configured to initiate, terminate, and/or adjust operation of one or more components (e.g., the energy delivery element 214) of the therapeutic neuromodulation device 202 directly and/or via the console 204. The controller 218 can be configured to execute an automated control algorithm and/or to receive control instructions from an operator (e.g., a clinician). For example, the controller 218 and/or other components of the console 204 (e.g., memory) can include a computer-readable medium carrying instructions, which when executed by the controller 218, causes the therapeutic assembly 202 to perform certain functions (e.g., apply energy in a specific manner, detect impedance, detect temperature, detect nerve locations or anatomical structures, etc.). A memory includes one or more of various hardware devices for volatile and non-volatile storage, and can include both read-only and writable memory. For example, a memory can comprise random access memory (RAM), CPU registers, read-only memory (ROM), and writable non-volatile memory, such as flash memory, hard drives, floppy disks, CDs, DVDs, magnetic storage devices, tape drives, device buffers, and so forth. A memory is not a propagating signal divorced from underlying hardware; a memory is thus non-transitory.

[0047] Further, the console 204 can be configured to provide feedback to an operator before, during, and/or after a treatment procedure via evaluation/feedback algorithms 220. For example, the evaluation/feedback algorithms 220 can be configured to provide information associated with the temperature of the tissue at the treatment site, the location of nerves at the treatment site, and/or the effect of the therapeutic neuromodulation on the nerves at the treatment site. In certain embodiments, the evaluation/feedback algorithm 220 can include features to confirm efficacy of the treatment and/or enhance the desired performance of the system 200. For example, the evaluation/feedback algorithm 220, in conjunction with the controller 218, can be configured to monitor temperature at the treatment site during therapy and automatically shut off the energy delivery when the temperature reaches a predetermined maximum (e.g., when applying RF energy) or predetermined minimum (e.g., when applying cryotherapy). In other embodiments, the evaluation/feedback algorithm 220, in conjunction with the controller 218, can be configured

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to automatically terminate treatment after a predetermined maximum time, a predetermined maximum impedance rise of the targeted tissue (i.e., in comparison to a baseline impedance measurement), a predetermined maximum impedance of the targeted tissue), and/or other threshold values for biomarkers associated with autonomic function. This and other information associated with the operation of the system 200 can be communicated to the operator via a display 222 (e.g., a monitor or touchscreen) on the console 204 and/or a separate display (not shown) communicatively coupled to the console 204.

[0048] In various embodiments, the therapeutic assembly 212 and/or other portions of the system 200 can be configured to detect various parameters of the heterogeneous tissue at the target site to determine the anatomy at the target site (e.g., tissue types, tissue locations, vasculature, bone structures, foramen, sinuses, etc.), locate nerves and/or other structures, and allow for neural mapping. For example, the therapeutic assembly 212 can be configured to detect impedance, dielectric properties, temperature, and/or other properties that indicate the presence of neural fibers in the target region. As shown in Figure 2, the console 204 can include a nerve monitoring assembly 221 (shown schematically) that receives the detected electrical and/or thermal measurements of tissue at the target site taken by the therapeutic assembly 212, and process this information to identify the presence of nerves, the location of nerves, and/or neural activity at the target site. This information can then be communicated to the operator via a high resolution spatial grid (e.g., on the display 222) and/or other type of display. The nerve monitoring assembly 221 can be operably coupled to the energy delivery element 214 and/or other features of the therapeutic assembly 212 via signal wires (e.g., copper wires) that extend through the cable 206 and through the length of the shaft 208. In other embodiments, the therapeutic assembly 212 can be communicatively coupled to the nerve monitoring assembly 221 using other suitable communication means.

[0049] The nerve monitoring assembly 221 can determine neural locations and activity before therapeutic neuromodulation to determine precise treatment regions corresponding to the positions of the desired nerves, during treatment to determine the effect of the therapeutic neuromodulation, and/or after treatment to evaluate whether the therapeutic neuromodulation treated the target nerves to a desired degree. This information can be used to make various determinations related to the nerves proximate to the target site, such as whether the target site is suitable for neuromodulation. In addition, the nerve monitoring assembly 221 can also compare the detected neural locations and/or activity before and after therapeutic neuromodulation, and compare the change in neural activity to a predetermined threshold to

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assess whether the application of therapeutic neuromodulation was effective across the treatment site. For example, the nerve monitoring assembly 221 can determine electroneurogram (ENG) signals based on recordings of electrical activity of neurons taken by the therapeutic assembly 212 before and after therapeutic neuromodulation. Statistically meaningful (e.g., measurable or noticeable) decreases in the ENG signal(s) taken after neuromodulation can serve as an indicator that the nerves were sufficiently ablated.

[0050] The system 200 can further include a channel 224 extending along at least a portion of the shaft 208 and a port 226 at the distal portion 208b of the shaft in communication with the port 226. In certain embodiments, the channel 224 is a fluid pathway to deliver a fluid to the distal portion 208b of the shaft 208 via the port 226. For example, the channel 224 can deliver saline solution or other fluids to rinse the intraluminal nasal pathway during delivery of the therapeutic assembly 212, flush the target site before applying therapeutic neuromodulation to the target site, and/or deliver fluid to the target site during energy delivery to reduce heating or cooling of the tissue adjacent to the energy delivery element 214. In other embodiments, the channel 224 allows for drug delivery to the treatment site. For example, a needle (not shown) can project through the port 226 to inject or otherwise deliver a nerve block, a local anesthetic, and/or other pharmacological agent to tissue at the target site.

[0051] The therapeutic neuromodulation device 202 provides access to target sites deep within the nasal region, such as at the immediate entrance of parasympathetic fibers into the nasal cavity to therapeutically modulate autonomic activity within the nasal cavity. In certain embodiments, for example, the therapeutic neuromodulation device 202 can position the therapeutic assembly 212 inferior to the SPF at the site of access foramen and/or microforamina (e.g., as shown in Figures 1B and 1C). By manipulating the proximal portion 208a of the shaft 208 from outside the entrance of the nose, a clinician may advance the shaft 208 through the tortuous intraluminal path through the nasal cavity and remotely manipulate the distal portion 208b of the shaft 208 via the handle 210 to position the therapeutic assembly 212 at the target site. In certain embodiments, the shaft 208 can be a steerable device (e.g., a steerable catheter) with a small bend radius (e.g., a 5 mm bend radius, a 4 mm bend radius, a 3 mm bend radius or less) that allows the clinician to navigate through the tortuous nasal anatomy. The steerable shaft can further be configured to articulate in at least two different directions. For example, the steerable shaft 208 can include dual pull wire rings that allow a clinician to form the distal portion 208b of the shaft 208 into an "S"-shape to

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correspond to the anatomy of the nasal region. In other embodiments, the articulating shaft 208 can be made from a substantially rigid material (e.g., a metal material) and include rigid links at the distal portion 208b of the shaft 208 that resist deflection, yet allow for a small bend radius (e.g., a 5 mm bend radius, a 4 mm bend radius, a 3 mm bend radius or less). In further embodiments, the steerable shaft 208 may be a laser-cut tube made from a metal and/or other suitable material. The laser-cut tube can include one or more pull wires operated by the clinician to allow the clinician to deflect the distal portion 208b of the shaft 208 to navigate the tortuous nasal anatomy to the target site.

[0052] In various embodiments, the distal portion 208b of the shaft 208 is guided into position at the target site via a guidewire (not shown) using an over-the-wire (OTW) or a rapid exchange (RX) technique. For example, the distal end of the therapeutic assembly 212 can include a channel for engaging the guidewire. Intraluminal delivery of the therapeutic assembly 212 can include inserting the guide wire into an orifice in communication with the nasal cavity (e.g., the nasal passage or mouth), and moving the shaft 208 and/or the therapeutic assembly 212 along the guide wire until the therapeutic assembly 212 reaches a target site (e.g., inferior to the SPF).

[0053] In further embodiments, the therapeutic neuromodulation device 202 can be configured for delivery via a guide catheter or introducer sheath (not shown) with or without using a guide wire. The introducer sheath can first be inserted intraluminally to the target site in the nasal region, and the distal portion 208b of the shaft 208 can then be inserted through the introducer sheath. At the target site, the therapeutic assembly 212 can be deployed through a distal end opening of the introducer sheath or a side port of the introducer sheath. In certain embodiments, the introducer sheath can include a straight portion and a pre-shaped portion with a fixed curve (e.g., a 5 mm curve, a 4 mm curve, a 3 mm curve, etc.) that can be deployed intraluminally to access the target site. In this embodiment, the introducer sheath may have a side port proximal to or along the pre-shaped curved portion through which the therapeutic assembly 212 can be deployed. In other embodiments, the introducer sheath may be made from a rigid material, such as a metal material coated with an insulative or dielectric material. In this embodiment, the introducer sheath may be substantially straight and used to deliver the therapeutic assembly 212 to the target site via a substantially straight pathway, such as through the middle meatus MM (Figure 1A).

[0054] Image guidance may be used to aid the clinician's positioning and manipulation of the distal portion 208b of the shaft 208 and the therapeutic assembly 212. For example, as

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described in further detail below with respect to Figures 3A-3E, an endoscope (not shown) can be positioned to visualize the target site, the positioning of the therapeutic assembly 212 at the target site, and/or the therapeutic assembly 212 during therapeutic neuromodulation. In certain embodiments, the distal portion 208b of the shaft 208 is delivered via a working channel extending through an endoscope, and therefore the endoscope can provide direct in-line visualization of the target site and the therapeutic assembly 212. In other embodiments, an endoscope is incorporated with the therapeutic assembly 212 and/or the distal portion 208b of the shaft 208 to provide in-line visualization of the assembly 212 and/or the surrounding nasal anatomy. In still further embodiments, image guidance can be provided with various other guidance modalities, such as image filtering in the infrared (IR) spectrum to visualize the vasculature and/or other anatomical structures, computed tomography (CT), fluoroscopy, ultrasound, optical coherence tomography (OCT), and/or combinations thereof. Further, in some embodiments, image guidance components may be integrated with the therapeutic neuromodulation device 202 to provide image guidance during positioning of the therapeutic assembly 212.

[0055] Once positioned at the target site, the therapeutic modulation may be applied via the energy delivery element 214 and/or other features of the therapeutic assembly 212 to precise, localized regions of tissue to induce one or more desired therapeutic neuromodulating effects to disrupt parasympathetic motor sensory function. The therapeutic assembly 212 can selectively target postganglionic parasympathetic fibers that innervate the nasal mucosa at a target or treatment site proximate to or at their entrance into the nasal region. For example, the therapeutic assembly 212 can be positioned to apply therapeutic neuromodulation at least proximate to the SPF (Figure 1A) to therapeutically modulate nerves entering the nasal region via the SPF. The therapeutic assembly 212 can also be positioned to inferior to the SPF to apply therapeutic neuromodulation energy across accessory foramen and microforamina (e.g., in the palatine bone) through which smaller medial and lateral branches of the posterior superior lateral nasal nerve enter the nasal region. The purposeful application of the energy at the target site may achieve therapeutic neuromodulation along all or at least a portion of posterior nasal neural fibers entering the nasal region. The therapeutic neuromodulating effects are generally a function of, at least in part, power, time, and contact between the energy delivery elements and the adjacent tissue. For example, in certain embodiments therapeutic neuromodulation of autonomic neural fibers are produced by applying RF energy at a power of about 2-20 W (e.g., 5 W, 7 W, 10 W, etc.)

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for a time period of about 1-20 sections (e.g., 5-10 seconds, 8-10 seconds, 10-12 seconds, etc.). The therapeutic neuromodulating effects may include partial or complete denervation via thermal ablation and/or non-ablative thermal alteration or damage (e.g., via sustained heating and/or resistive heating). Desired thermal heating effects may include raising the temperature of target neural fibers above a desired threshold to achieve non-ablative thermal alteration, or above a higher temperature to achieve ablative thermal alteration. For example, the target temperature may be above body temperature (e.g., approximately 37° C) but less than about 90° C (e.g., 70-75°C) for non-ablative thermal alteration, or the target temperature may be about 100°C or higher (e.g., 110°C, 120°C, etc.) for the ablative thermal alteration. Desired non-thermal neuromodulation effects may include altering the electrical signals transmitted in a nerve.

[0056] Hypothermic effects may also provide neuromodulation. As described in further detail below, for example, a cryotherapeutic applicator may be used to cool tissue at a target site to provide therapeutically-effective direct cell injury (e.g., necrosis), vascular injury (e.g., starving the cell from nutrients by damaging supplying blood vessels), and sublethal hypothermia with subsequent apoptosis. Exposure to cryotherapeutic cooling can cause acute cell death (e.g., immediately after exposure) and/or delayed cell death (e.g., during tissue thawing and subsequent hyperperfusion). Embodiments of the present technology can include cooling a structure positioned at or near tissue such that the tissue is effectively cooled to a depth where the targeted postganglionic parasympathetic nerves reside. For example, the cooling structure is cooled to the extent that it causes therapeutically effective, cryogenic posterior nasal nerve modulation.

[0057] In certain embodiments, the system 200 can determine the locations of the nerves, accessory foramen, and/or microforamina before therapy such that the therapeutic neuromodulation can be applied to precise regions including parasympathetic neural fibers. For example, the system 200 may identify a target site that has a length and/or width of about 3 mm inferior to the SPF, and the therapeutic assembly 212 can apply therapeutic neuromodulation to the identified target site via one or more applications of therapeutic neuromodulation. In other embodiments, the target site may be smaller or larger (e.g., a 3 cm-long target region) based on the detected locations of neural fibers and foramena. This neural and anatomical mapping allows the system 200 to accurately detect and therapeutically modulate the postganglionic parasympathetic neural fibers that innervate the mucosa at the numerous neural entrance points into the nasal cavity. Further, because there are not any

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clear anatomical markers denoting the location of the SPF, accessory foramen, and microforamina, the neural mapping allows the operator to identify and therapeutically modulate nerves that would otherwise be unidentifiable without intricate dissection of the mucosa. In addition, anatomical mapping can also allow the operator to identify certain structures that the operator may wish to avoid during therapeutic neural modulation (e.g., certain arteries).

[0058] Sufficiently modulating at least a portion of the parasympathetic nerves is expected to slow or potentially block conduction of autonomic neural signals to the nasal mucosa to produce a prolonged or permanent reduction in nasal parasympathetic activity. This is expected to reduce or eliminate activation or hyperactivation of the submucosal glands and venous engorgement and, thereby, reduce or eliminate the symptoms of rhinosinusitis. Further, because the system 200 applies therapeutic neuromodulation to the multitude of branches of the posterior nasal nerves rather than a single large branch of the posterior nasal nerve branch entering the nasal cavity at the SPF, the system 200 provides a more complete disruption of the parasympathetic neural pathway that affects the nasal mucosa and results in rhinosinusitis. Accordingly, the system 200 is expected to have enhanced therapeutic effects for the treatment of rhinosinusitis and reduced re-innervation of the treated mucosa.

[0059] In other embodiments, the system 200 can be configured to therapeutically modulate nerves and/or other structures to treat different indications. As discussed in further detail below, for example, the system 200 can be used to locate and/or therapeutically modulate nerves that innervate the para-nasal sinuses to treat chronic sinusitis. In further embodiments, the system 200 and the devices disclosed herein can be configured therapeutically modulate the vasculature within the nasal anatomy to treat other indications, such as epistaxis (i.e., excessive bleeding from the nose). For example, the system 200 and the therapeutic neuromodulation devices described herein can be used to apply therapeutically effective energy to arteries (e.g., the sphenopalatine artery and its branches) as they enter the nasal cavity (e.g., via the SPF, accessory foramen, etc.) to partially or completely coagulate or ligate the arteries. In other embodiments, the system 200 can be configured to partially or completely coagulate or ligate veins and/or other vessels. For such embodiments in which the therapeutic assembly 212 ligates or coagulates the vasculature, the system 200 would be modified to deliver energy at significantly higher power (e.g., about 100 W) and/or longer times (e.g., 1 minute or longer) than would be required for therapeutic

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neuromodulation. In various embodiments, the system 100 could apply the anatomical mapping techniques disclosed herein to locate or detect the targeted vasculature and surrounding anatomy before, during, and/or after treatment.

[0060] Figures 3A-3E are partial cut-away side views illustrating various approaches for delivering a distal portion of the therapeutic neuromodulation device 202 of Figure 2 to a target site within a nasal region in accordance with embodiments of the present technology. As shown in Figure 3A, in various embodiments the distal portion 208b of the shaft 208 extends into the nasal passage NP, through the inferior meatus IM between the inferior turbinate IT and the nasal sill NS, and around the posterior portion of the inferior turbinate IT where the therapeutic assembly 212 is deployed at a treatment site. As shown in Figure 3A, the treatment site can be located proximate to the access point or points of postganglionic parasympathetic nerves (e.g., branches of the posterior nasal nerve and/or other parasympathetic neural fibers that innervate the nasal mucosa) into the nasal cavity. In other embodiments, the target site can be elsewhere within the nasal cavity depending on the location of the target nerves. An endoscope 330 and/or other visualization device is delivered proximate to the target site by extending through the nasal passage NP and through the middle meatus MM between the inferior and middle turbinates IT and MT. From the visualization location within the middle meatus MM, the endoscope 330 can be used to visualize the treatment site, surrounding regions of the nasal anatomy, and the therapeutic assembly 212.

[0061] As further shown in Figure 3A, the shaft 208 of the therapeutic neuromodulation device 202 can include a positioning member 332 positioned proximal to the therapeutic assembly 212 and the target site. In the illustrated embodiment, the positioning member 332 is a balloon that is expanded in an opening (e.g., in one of the meatuses) against opposing structures (e.g., between the turbinates) to consistently hold the distal portion 208b of the shaft 208 in a desired position relative to the target site and provide stability for deployment of the therapeutic assembly 212. In other embodiments, the positioning member 332 may include other expandable structures (e.g., a mesh baskets) or anchor features that can be deployed to maintain a desired position of the shaft 208 within the nasal cavity. In further embodiments, the positioning member 332 can be positioned distal to the therapeutic assembly 212 and expanded in a region distal to the therapeutic assembly 212 and the treatment site. In still further embodiments, the positioning member 332 is positioned on an introducer sheath (not shown) through which the shaft 208 and/or other devices (e.g., a fluid

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line for delivery of saline or local anesthetics, an endoscope, a sensor, etc.) can pass. The positioning member 332 can be positioned proximal to the target site (e.g., similar to the position shown in Figure 3A) or distal to the treatment site. When positioned distally, the introducer sheath can include a side exit port through which the therapeutic assembly 212 and other features can be deployed at the target site. When the positioning member 332 is positioned on the introducer sheath, the positioning member 332 can provide stability for delivery and deployment of the distal portion 208b of the shaft 208 and the therapeutic assembly 212. The positioning member 332 can be incorporated on the shaft 208, an associated introducer sheath, and/or other deliver features of the system 200 (Figure 2) when the therapeutic assembly 212 is delivered through different intraluminal passageways.

[0062] Figure 3B illustrates a differ embodiment in which the distal portion 208b of the shaft 208 extends into the nasal passage NP, through the middle meatus MM between the inferior turbinate IT and the middle turbinate, and in posterior direction where the therapeutic assembly 212 is deployed at a treatment site. In this embodiment, the endoscope 330 and/or other visualization device is delivered alongside the shaft 208 through the same intraluminal pathway as the therapeutic assembly 212. The pathway through the middle meatus MM may provide for generally straight access to the target site depending on the specific region of interest and anatomical variations of the patient. Accordingly, an approach through the middle meatus MM may require less steering and/or articulation of the shaft 208 and the endoscope 330. Further, because the distal portion 208b of the shaft 208 and the endoscope 330 travel along the same delivery path, the endoscope can provide in-line or side-by-side visualization of the therapeutic assembly 212.

[0063] Similar to the embodiment shown in Figure 3B, Figure 3C illustrates another intraluminal pathway in which the distal portion 208b of the shaft 208 and the endoscope 330 travel next to each other such that the endoscope 330 can provide in-line or side-by-side visualization of the distal portion 208b of the shaft 208, the therapeutic assembly 212, and/or the nasal anatomy. In the embodiment shown in Figure 3C, however, the intraluminal pathway extends through the inferior meatus IM to a posterior treatment site.

[0064] As shown in Figure 3D, in other embodiments the distal portion 208b of the shaft 208 extends to the treatment site via the middle meatus MM, and the endoscope 330 extends through the inferior meatus IM to a position proximate to the target site. In this embodiment, the endoscope 330 may have an articulating, steerable, or curved distal end that directs the endoscope 330 superiorly to visualize the nasal anatomy and the therapeutic

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assembly 332 at the target site. For example, the distal end portion of the endoscope 330 can be configured to bend at least 30° to visualize the treatment site.

[0065] As shown in Figure 3E, in further embodiments the distal portion 208b of the shaft 208 can be delivered to the treatment site via the mouth. In this embodiment, therapeutic neuromodulation can be applied at a treatment site posterior to the nasal cavity (e.g., posterior to the SPF). The endoscope 330 (not shown) can extend into the nasal passage NP, through the middle meatus MM or the inferior meatus IM to a position proximate to the treatment site. Alternatively, the endoscope 330 (not shown) can travel along the same pathway as the shaft 208.

[0066] Figure 4 is an isometric view of a distal portion of a therapeutic neuromodulation device 402 configured in accordance with an embodiment of the present technology. The therapeutic neuromodulation device 402 can be used in conjunction with the system 200 described above with respect to Figures 2-3E. As shown in Figure 4, the therapeutic neuromodulation device 402 can include a shaft 408 having a proximal portion (not shown) and a distal portion 408b, and a therapeutic assembly 412 at the distal portion 408b of the shaft 408. The therapeutic assembly 412 is transformable between a low-profile delivery state to facilitate intraluminal delivery of the therapeutic assembly 412 to a treatment site within the nasal region and an expanded state (shown in Figure 4). The therapeutic assembly 412 includes a plurality of struts 440 that are spaced apart from each other to form a frame or basket 442 when the therapeutic assembly 412 is in the expanded state. The struts 440 can carry one or more energy delivery elements, such as a plurality of electrodes 444. In the expanded state, the struts 440 can position at least two of the electrodes 444 against tissue at a target site within the nasal region (e.g., proximate to the palatine bone inferior to the SPF). The electrodes 444 can apply bipolar or multi-polar radiofrequency (RF) energy to the target site to therapeutically modulate postganglionic parasympathetic nerves that innervate the nasal mucosa proximate to the target site. In various embodiments, the electrodes 444 can be configured to apply pulsed RF energy with a desired duty cycle (e.g., 1 second on/0.5 seconds off) to regulate the temperature increase in the target tissue.

[0067] In the embodiment illustrated in Figure 4, the basket 442 includes eight branches 446 spaced radially apart from each other to form at least a generally spherical structure, and each of the branches 446 includes two struts 440 positioned adjacent to each other. In other embodiments, however, the basket 442 can include fewer than eight branches 446 (e.g., two, three, four, five, six, or seven branches) or more than eight branches 446. In further

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embodiments, each branch 446 of the basket 442 can include a single strut 440, more than two struts 440, and/or the number of struts 440 per branch can vary. In still further embodiments, the branches 446 and struts 440 can form baskets or frames having other suitable shapes for placing the electrodes 444 in contact with tissue at the target site. For example, when in the expanded state, the struts 440 can form an ovoid shape, a hemispherical shape, a cylindrical structure, a pyramid structure, and/or other suitable shapes.

[0068] As shown in Figure 4, the therapeutic assembly 412 can further include an internal or interior support member 448 that extends distally from the distal portion 408b of the shaft 408. A distal end portion 450 of the support member 448 can support the distal end portions of the struts 440 to form the desired basket shape. For example, as shown in Figure 4, the struts 440 can extend distally from the distal potion 408b of the shaft 408 and the distal end portions of the struts 440 can attach to the distal end portion 450 of the support member 448. In certain embodiments, the support member 448 can include an internal channel (not shown) through which electrical connectors (e.g., wires) coupled to the electrodes 444 and/or other electrical features of the therapeutic element 412 can run. In various embodiments, the internal support member 448 can also carry an electrode (not shown) at the distal end portion 450 and/or along the length of the support member 448.

[0069] The basket 442 can transform from the low-profile delivery state to the expanded state (Figure 4) by manipulating a handle (e.g., the handle 210 of Figure 2) and/or other feature at the proximal portion of the shaft 408 and operably coupled to the basket 442. For example, to move the basket 442 from the expanded state to the delivery state, an operator can push the support member 448 distally to bring the struts 440 inward toward the support member 448. An introducer or guide sheath (not shown) can be positioned over the low-profile therapeutic assembly 412 to facilitate intraluminal delivery or removal of the therapeutic assembly 412 from or to the target site. In other embodiments, the therapeutic assembly 412 is transformed between the delivery state and the expanded state using other suitable means.

[0070] The individual struts 440 can be made from a resilient material, such as a shape-memory material (e.g., Nitinol) that allows the struts 440 to self-expand into the desired shape of the basket 442 when in the expanded state. In other embodiments, the struts 440 can be made from other suitable materials and/or the therapeutic assembly 412 can be mechanically expanded via a balloon or by proximal movement of the support member 448. The basket 442 and the associated struts 440 can have sufficient rigidity to support the

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electrodes 444 and position or press the electrodes 444 against tissue at the target site. In addition, the expanded basket 442 can press against surrounding anatomical structures proximate to the target site (e.g., the turbinates, the palatine bone, etc.) and the individual struts 440 can at least partially conform to the shape of the adjacent anatomical structures to anchor the therapeutic element 412 at the treatment site during energy delivery. In addition, the expansion and conformability of the struts 440 can facilitate placing the electrodes 444 in contact with the surrounding tissue at the target site.

[0071] At least one electrode 444 is disposed on individual struts 440. In the illustrated embodiment, two electrodes 444 are positioned along the length of each strut 440. In other embodiments, the number of electrodes 444 on individual struts 440 be only one, more than two, zero, and/or the number of electrodes 444 on the different struts 440 can vary. The electrodes 444 can be made from platinum, iridium, gold, silver, stainless steel, platinum-iridium, cobalt chromium, iridium oxide, polyethylenedioxythiophene ("PEDOT"), titanium, titanium nitride, carbon, carbon nanotubes, platinum grey, Drawn Filled Tubing ("DFT") with a silver core made by Fort Wayne Metals of Fort Wayne, Indiana, and/or other suitable materials for delivery RF energy to target tissue.

[0072] In certain embodiments, each electrode 444 can be operated independently of the other electrodes 444. For example, each electrode can be individually activated and the polarity and amplitude of each electrode can be selected by an operator or a control algorithm (e.g., executed by the controller 218 of Figure 2). Various embodiments of such independently controlled electrodes 444 are described in further detail below with reference to Figures 5A-5G. The selective independent control of the electrodes 444 allows the therapeutic assembly 412 to deliver RF energy to highly customized regions. For example, a select portion of the electrodes 444 can be activated to target neural fibers in a specific region while the other electrodes 444 remain inactive. In certain embodiments, for example, electrodes 444 may be activated across the portion of the basket 442 that is adjacent to tissue at the target site, and the electrodes 444 that are not proximate to the target tissue can remain inactive to avoid applying energy to non-target tissue. Such configurations facilitate selective therapeutic modulation of nerves on the lateral nasal wall within one nostril without applying energy to structures in other portions of the nasal cavity.

[0073] The electrodes 444 can be electrically coupled to an RF generator (e.g., the generator 216 of Figure 2) via wires (not shown) that extend from the electrodes 444, through the shaft 408, and to the RF generator. When each of the electrodes 444 is independently

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controlled, each electrode 444 couples to a corresponding wire that extends through the shaft 408. In other embodiments, multiple electrodes 444 can be controlled together and, therefore, multiple electrodes 444 can be electrically coupled to the same wire extending through the shaft 408. The RF generator and/or components operably coupled (e.g., a control module) thereto can include custom algorithms to control the activation of the electrodes 444. For example, the RF generator can deliver RF power at about 200-300 W to the electrodes 444, and do so while activating the electrodes 444 in a predetermined pattern selected based on the position of the therapeutic element 412 relative to the treatment site and/or the identified locations of the target nerves. In other embodiments, the RF generator delivers power at lower levels (e.g., less than 15 W, 15-50 W, 50-150 W, etc.) and/or higher power levels.

[0074] As shown in Figure 4, the therapeutic assembly 412 can further include one or more temperature sensors 452 disposed on the struts 440 and/or other portions of the therapeutic assembly 412 and configured to detect the temperature adjacent to the temperature sensor 452. The temperature sensors 452 can be electrically coupled to a console (e.g., the console 204 of Figure 2) via wires (not shown) that extend through the shaft 408. In various embodiments, the temperature sensors 452 can be positioned proximate to the electrodes 444 to detect the temperature at the interface between tissue at the target site and the electrodes 444. In other embodiments, the temperature sensors 452 can penetrate the tissue at the target site (e.g., a penetrating thermocouple) to detect the temperature at a depth within the tissue. The temperature measurements can provide the operator or the system with feedback regarding the effect of the therapeutic neuromodulation on the tissue. For example, in certain embodiments the operator may wish to prevent or reduce damage to the tissue at the treatment site (e.g., the nasal mucosa), and therefore the temperature sensors 452 can be used to determine if the tissue temperature reaches a predetermined threshold for irreversible tissue damage. Once the threshold is reached, the application of therapeutic neuromodulation energy can be terminated to allow the tissue to remain intact. In certain embodiments, the energy delivery can automatically terminate based on an evaluation/feedback algorithm (e.g., the evaluation/feedback algorithm 220 of Figure 2) stored on a console (e.g., the console 204 of Figure 2) operably coupled to the temperature sensors 452.

[0075] Figures 5A-5G are isometric views of examples of electrode configurations of therapeutic neuromodulation devices (identified individually as first through fourth therapeutic neuromodulation devices 502a-502d, respectively; referred to collectively as

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therapeutic neuromodulation devices 502) for therapeutic neuromodulation in accordance with embodiments of the present technology. The therapeutic neuromodulation devices 502 of Figures 5A-5G can include features generally similar to the features of the therapeutic neuromodulation device 402 of Figure 4. For example, the therapeutic neuromodulation devices 502 include a plurality of struts 440 that form a basket 442 when in an expanded state, and a plurality of electrodes 444 disposed on one or more of the struts 440. In the illustrated embodiments, the first through third therapeutic neuromodulation device 502a-c shown in Figures 5A-5E include a single strut 440 corresponding to each branch 446 of the basket 442, whereas the fourth therapeutic neuromodulation device 502d shown in Figures 5F and 5G includes two adjacent struts 440 in each branch 446 of the basket 442. In other embodiments, however, the branches 446 of the therapeutic neuromodulation devices 502 may have different quantities of struts 440, and apply RF energy in the same manner as described below with reference to Figures 5A-5G. As shown in Figures 5A-5G, the electrodes 444 can be independently controlled and activated via instructions from a controller (e.g., the controller 218 of Figure 2) or a generator (e.g., the generator 216 of Figure 2) to apply RF energy across selected regions or segments of the therapeutic assembly 412.

[0076] In the embodiment shown in Figure 5A, two electrodes 444 of the therapeutic assembly 412 are activated in the first therapeutic neuromodulation device 502a. More specifically, a first electrode 444a on a first strut 440a is activated at a positive polarity, and a second electrode 444b on a second strut 440b spaced radially apart from the first strut 440a is activated at a negative polarity. The remainder of the electrodes 444 remain inactive. Accordingly, as indicated by the arrows, current can flow from the first electrode 444a to the second electrode 444b through the target tissue across a circumferential or peripheral segment of the therapeutic assembly 412. This configuration may be used to therapeutically modulate nerves positioned proximate to the peripheral segment. In other embodiments, different or additional electrodes 444 can be activated to have a selected polarity to apply therapeutic neuromodulation across selected regions of the therapeutic assembly 412 in a predetermined manner.

[0077] In the embodiment shown in Figure 5B, the first therapeutic neuromodulation device 502a is configured to have three selectively active electrodes 444. A first electrode 444a on a first strut 440a is activated at a positive polarity, and second and third electrodes 444b and 444c on corresponding second and third struts 440b and 440c are activated at a

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negative polarity. The remainder of the electrodes 444 remain inactive. As indicated by the arrows, current can flow through the tissue from the first electrode 444a to the second and third electrodes 444b and 444c across a segment of the therapeutic assembly 412, and therefore therapeutically modulate nerves positioned proximate to the peripheral segment. In the illustrated embodiment, the second and third activated electrodes 444b and 444c are positioned on struts 440b, 440c that are radially spaced apart from but adjacent to the first strut 440a carrying the first active electrode 444a. In other embodiments, however, electrodes 444 positioned on struts 440 spaced further from the first strut 440a to apply energy across a larger and/or wider segment of the therapeutic assembly 412.

[0078] In the embodiment shown in Figure 5C, all of the electrodes 444 in a first hemispherical region 501a of the therapeutic assembly 412 are activated, while the electrodes 444 of the second hemispherical region 501b are not activated. A first electrode on a first strut 440a is selectively activated at a positive polarity, and a plurality of electrodes 444 (identified individually as second through fifth electrodes 444b-444e, respectively) within the first hemispherical region 501a are selectively activated at a negative polarity such that RF energy is applied across the first hemispherical region 501a. This electrode activation configuration may be used to apply RF energy across one side of the basket 442 to therapeutically modulate nerves on the lateral nasal wall in one nostril. When the therapeutic assembly 412 is positioned in the other nostril, a different set of electrodes 444 can be activated across a hemispherical region of the therapeutic assembly 412 based on the orientation of the basket 442 with respect to the lateral nasal wall. Further, because the basket 442 has a generally symmetrical shape (e.g., circular, oval, etc.) and because the electrodes 444 can be selectively activated, the orientation of the basket 442 with respect to the target site on the lateral nasal wall does not matter. Instead, the operator can deploy the therapeutic assembly 412 at the target site irrespective of orientation, and selectively activate the electrodes 444 in a desired arrangement to apply RF energy across the target site.

[0079] In the embodiment shown in Figure 5D, the second therapeutic neuromodulation device 502b is configured to selectively control the polarity of a plurality of the electrodes 444 across at least a portion of the therapeutic assembly 412 to apply RF energy in a sesquipolar fashion (i.e., the sequential or transient bipolar pairing of electrodes). In the illustrated embodiment, a first electrode 444a is biased at a positive polarity and second through seventh electrodes 444b-444g are controlled to have negative polarities. The second through seventh electrodes 444b-444g are spaced substantially equal distances apart from the

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first electrode 444a such that the electrodes 444 are dimensionally predisposed to multiplex in sequence. In operation, the first through seventh electrodes 444a-444g are concurrently activated. However, rather than all of the negative electrodes 444 pairing or multiplexing with the positive first electrode 444a simultaneously, the first electrode 444a will pair with the individual negative electrodes 444 in a sequential manner based on the path of least resistance. This path of least resistance is dictated by the natural anatomy of the treatment site in contact with the electrodes 444. For example, based on the anatomy at the target site, the first electrode 444a may initially pair with the second electrode 444b. After this initial pairing preference has dissipated, a second pairing (e.g., with the third electrode 444c) will occur based on the path of least resistance. The first electrode 444a will continue to sequentially pair with the remaining activated negative electrodes in a similar manner until a threshold is reached and the electrodes 444 are in a state of equilibrium in which there is homogenized current flow between all of the electrode pairs. With each sequential pairing, the therapeutic assembly 412 increases the size of the ablation zone (i.e., the region in which therapeutic neuromodulation energy is applied). As indicated by the numbers 1-6 in Figure 5D, this sequential pairing of the electrodes 444 may occur in a circular direction (e.g., in a counter clockwise or clockwise direction) based on the impedance changes between the electrodes 444. In other embodiments, the sequential pairing of electrodes 444 may occur in a different pattern based on the anatomical surroundings and/or the positioning of the electrodes 444. For example, in the illustrated embodiment, the activated electrodes 444 are positioned in a quadrant of the therapeutic element 412 with equal radial distances between the individual electrode pairs. In other embodiments, the activated electrodes 444 can be positioned across larger or smaller regions of the therapeutic element 412 to apply energy across larger or smaller treatment regions.

[0080] The sesquipolar application of RF energy allows the therapeutic assembly 412 to intelligently apply RF energy across a target site to therapeutically modulate nerves proximate to the treatment site. For example, when in an equidistant radial relationship to each other, the naturally occurring impedance changes between the electrode pairs cause the therapeutic assembly 412 to radially increase the zone of energy application with each pairing. In other embodiments, the electrodes 444 can be configured to sequentially pair with each other in a manner such that the zone of energy application increases in a transverse and/or longitudinal manner based on the naturally occurring impedance changes between the electrodes 444. Further, due to the sequential impedance-based pairing of the electrodes 444,

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the sesquipolar arrangement of the therapeutic assembly 412 can inherently limit the energy applied to tissue at the target site because once the impedance exceeds a threshold in one electrode pairing, the next electrode pairing will occur with a lower impedance. In other embodiments, a controller (e.g., the controller 218 of Figure 2) can include instructions (e.g., software) that provides for the sequential pairing of electrodes in a radial, transverse, longitudinal, and/or spiral manner.

[0081] In further embodiments, portions of the struts 440 themselves can define the electrodes 444. In this embodiment, the struts 440 are made from an electrically conductive material and coated with an insulative material (e.g., poly-xylene polymers, including Paralyene C). Portions of the struts 440 can remain uncoated to define electrodes 444. The locations of the uncoated portions of the struts 440 (i.e., the electrodes 444) can be selected to provide a desired neuromodulation pattern. For example, the uncoated portions can be spaced equally apart from a central electrode 444 to allow for sesquipolar RF application. In this embodiment, the conductive struts 440 serve as the electrical connectors and, therefore, the therapeutic assembly 412 does not require as many wires as if the electrodes 444 were separate elements positioned on the struts 440.

[0082] In the embodiment shown in Figure 5E, the third therapeutic neuromodulation device 502c includes a return electrode 503 at the distal end portion 450 of the support member 448 and selective polarity control of the individual electrodes 444 on the struts 440 to provide radial multiplexing of the electrodes 444. The return electrode 503 has a negative polarity, and the other electrodes 444 have a positive polarity. In the illustrated embodiment, all of the electrodes 444 are activated, but in other embodiments the electrodes 444 can be selectively activated based on a desired energy application zone. As indicated by the arrows, this configuration applies RF energy across a distal hemispherical region of the basket 442. In other embodiments, the return electrode 503 can be positioned elsewhere on the therapeutic assembly 412, and the electrodes 444, 503 can be used to apply RF energy across different regions of the basket 442. In further embodiments, the return electrode 503 can be activated in conjunction with two or more of the electrodes 444 on the struts to apply RF energy in a sesquipolar manner.

[0083] In the embodiment shown in Figure 5F, the fourth therapeutic neuromodulation device 502d includes branches 446 having two adjacent struts 440, and the electrodes 444 on the adjacent struts are spaced apart from each other in a longitudinal direction and selectively activated to apply energy in a radial direction across discrete zones. For example, a first

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electrode 444a on a first strut 440a of a first branch 446a may be selectively activated to have a first polarity and a second electrode 444b on the adjacent second strut 440b of the first branch 446a may be selectively activated to have a second polarity opposite the first polarity. As indicated by the arrows in Figure 5F, the first and second electrodes 444a and 444b can then apply bipolar RF energy in a radial direction within a specific region of the therapeutic assembly 412.

[0084] As further shown in Figure 5F, the individual struts 440 can include multiple electrodes 444 disposed thereon, and the adjacent strut 440 in the same branch 446 can have a corresponding quantity of electrodes 444 to allow for bipolar coupling of each of the electrode pairs along discrete regions of the branch 446. In certain embodiments, the electrodes of one strut 440 can all have the same polarity (e.g., coupled to a first wire; not shown), and the electrodes 444 of the adjacent strut 440 in the same branch 446 can all have the opposite polarity (e.g., coupled to a second wire; not shown). In other embodiments, the electrodes 444 on an individual strut 440 can be independently controlled to have a desired polarity.

[0085] In various embodiments, the electrode pairing configurations shown in Figure 5F can be used to detect impedance across selected regions of the therapeutic assembly 412 defined by the bipolar electrode pairs. The impedance measurements can then be used to identify the presence of neural fibers in the selected regions. If nerves are detected in one or more specific regions associated with an electrode pair, the same electrode pair can be used to apply RF energy to that region and therapeutically modulate the nerves in that region.

[0086] In the embodiment shown in Figure 5G, the fourth therapeutic neuromodulation device 502d is configured to selectively control the polarity of a plurality of the electrodes 444 across at least a portion of the therapeutic assembly 412 to apply RF energy in a multi-polar manner in a circular or spiral pattern. As shown in Figure 5G, electrodes 444 of one branch 446 can be activated to have negative polarities and electrodes 444 of another branch 446 can be activated to have positive polarities. The arrangement of the electrodes 444 and the variable distances between the electrodes 444 can differ such that the energy application zone has a different shape or pattern. In other embodiments, the positive and negative electrodes 444 are spaced apart from each other at variable distances. Impedance changes resulting from the surrounding anatomical structures causes the electrodes to pair with each other in a sequential manner and, thereby, continuously increase

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the zone or region in which energy is applied in a radial direction and in a generally spiral manner.

[0087] Energy generally travels deeper into the adjacent target tissue the further the positive and negative electrode pairs are spaced apart from each other. Thus, the depth of influence of the therapeutic neuromodulation energy is expected to increase as the coupled electrode pairs are spaced further apart from each other on the basket 442. In the embodiment illustrated in Figure 5G, for example, electrode pairs at the distal and proximal regions of the basket 442 apply energy to shallower depths in the target tissue than the electrode pairs positioned on the medial region of the basket 442. Accordingly, the electrodes pairs positioned closer together can therapeutically modulate nerves at shallower depths than the electrode pairs spaced further apart from each other. As shown in the illustrated embodiment, some of the electrodes 444 and/or entire branches 446 of the basket 442 can remain inactive to achieve the desired depth of energy application and/or neuromodulation pattern.

Selected Embodiments of Neural Detection and Mapping

[0088] Various embodiments of the present technology can include features that measure bio-electric, dielectric, and/or other properties of heterogeneous tissue at target sites within the nasal region to determine the presence, location, and/or activity of neural fibers and, optionally, map the locations of the detected nerves. The features discussed below can be incorporated into any of the systems and/or devices disclosed herein to provide an accurate depiction of nerves at the target site.

[0089] Neural detection can occur (a) before the application of a therapeutic neuromodulation energy to determine the presence or location of nerves at the target site and/or record baseline levels of neural activity; (b) during therapeutic neuromodulation to determine the effect of the energy application on the neural fibers at the treatment site; and/or (c) after therapeutic neuromodulation to confirm the efficacy of the treatment on the targeted nerves. Due to the anatomical variations of the number and locations of the parasympathetic neural fibers that innervate the nasal cavity and the numerous access points (e.g., the SPF, accessory foramen, and microforamina) through which they enter the nasal cavity, such neural detection and mapping can provide an accurate representation of the neural anatomy to adequately treat the parasympathetic nerves, not just the one or two main branches of the posterior nasal nerves traversing the SPF.

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[0090] In certain embodiments, the systems disclosed herein can use bioelectric measurements, such as impedance, resistance, voltage, current density, and/or other parameters (e.g., temperature) to determine the anatomy, in particular the neural anatomy, at the target site. The location of the neural anatomy can then be used to determine where the treatment site(s) should be with respect to various anatomical structures for therapeutically effective neuromodulation of the targeted parasympathetic nasal nerves. For example, the information can be used to determine the treatment site(s) with respect to the location of the turbinates or meatuses.

[0091] The bioelectric properties can be detected via electrodes (e.g., the electrodes 444 of the therapeutic neuromodulation devices 402-502d of Figures 4-5G). The electrode pairings on a device (e.g., the therapeutic assemblies 412 described with respect to Figures 4-5G) can be selected to obtain the bioelectric data at specific zones or regions and at specific depths of the targeted regions. Figures 6A and 6B, for example, are partially schematic diagrams illustrating configurations of electrodes 644 for nerve detection configured in accordance with embodiments of the present technology. As shown in Figure 6A, the further the electrodes 644 are apart from each other, the deeper into the tissue the current flows. Accordingly, electrodes 644 can be selectively activated based on the depth at which the desired measurements should be taken. As shown in Figure 6B, the spacing between the electrodes 644 along a plane (e.g., the surface of the tissue, can affect the region in which the measurements are taken. Thus, electrodes 644 can be selectively activated to obtain information (e.g., impedance) at a desired depth and across a desired region. In other embodiments, the bioelectric properties can be detected using optical coherent tomography (OCT), ultrasound, and/or other suitable detection modalities.

[0092] The measurement of bioelectric properties can provide information associated not only with neural fiber locations, but also the identification of gross anatomy (e.g., turbinates, meatuses, bone, etc.), which can be used to facilitate system delivery and identification of the target nerves with respect to the gross anatomy. For example, gross target identification can be determined by evaluating of the incident electromagnetic field on soft and hard tissues within the nasal region, which is in turn dependent upon the local geometry and the dielectric properties of those features. For example, because of the layered structure of the anatomy of the nasal cavity (e.g., nasal mucosa, submucosa, periosteum, and bony plates), there are large distinctions in the relative conductance of the soft and hard

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tissues that can be used to differentiate the "deeper" mucosal tissue on the turbinates from the "shallow" tissue off the turbinates.

[0093] In certain embodiments, measurements for neuro-mapping can be obtained by applying a constant current to electrodes and measuring the voltage differences between adjacent pairs of electrodes to produce a spectral profile or map the tissues at the target site. Impedance data can be obtained while applying high, medium, and/or low frequencies to the target tissue. At high frequencies, the current passes directly through cell membranes, and the resultant measurements are indicative of the tissue and liquids both inside and outside the cells. At low frequencies, cell membranes impede current flow to provide different defining characteristics of the tissue. Accordingly, bioimpedance can be used to measure targeted shapes or electrical properties of tissue and/or other structures of the nasal cavity. In addition, complex neural mapping can be performed using frequency difference reconstruction, which requires measurement data (e.g., impedance) at two different frequencies.

[0094] When detecting neural locations and activity via bioelectric properties, the spatial orientation, direction, and activity of the detected nerve bundles can be used to further identify and characterize the nerves. For example, the measured bioelectric properties can distinguish between terminating axons (i.e., entering a detection region, but not exiting), branching axons (i.e., entering the detection region and increasing in number upon exiting the detecting region), travelling axons (i.e., entering and exiting the detection region within no change in geometry or numerical value), and/or other properties of nerves. In addition, axon orientations relative to the electrode array can be identified to indicate whether the neural fibers extend parallel (X direction), perpendicular (Y direction), depth penetrating (Z direction), and/or any relative position or angulation to these parameters. This information can then be used to selectively treat specific neural fibers. For example, selected electrode configurations can be applied to treat a specific region and/or the therapeutic assembly can be moved or manipulated to treat the nerves from a different orientation or location.

[0095] In certain embodiments, temperature measurements can be taken to determine the effect of therapeutic neuromodulation on nasal tissue. Figure 7, for example, is a graph illustrating threshold levels of electrical conductivity of nasal tissue with respect to temperature. A first curve 701 depicts the electrical conductivity (σ) of tissue in response to temperature and indicates that a temperature of about 70°C corresponds to a first threshold of the irreversible change in impedance of the tissue. A second curve 703 shows that the

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electrical conductivity of the tissue permanently increases significantly (i.e., impedance decreases) after the tissue has been exposed to temperatures of 70°C, as it may during therapeutic neuromodulation. If the therapeutic neuromodulation was stopped when the tissue temperature was detected to be about 70°C, it is expected that there would be a permanent measurable change in the conductivity of the tissue without reaching a phase in which the tissue is structurally changed or damaged (e.g., due to vaporization, desiccation, etc.). However, if the tissue is exposed to temperatures above a second thermal threshold of about 90°C, the tissue undergoes a high degree of tissue desiccation, and thus a significant decrease in electrical conductivity (i.e., and a higher level of in the electrical impedance). A third curve 705 illustrates this lower electrical conductivity of the tissue after exposure to temperatures above 90°C. Accordingly, in various embodiments, systems disclosed herein can be configured to stop neuromodulation when the temperature reaches about 70°C (e.g., 70-80°C) to avoid structural changes or damage to the mucosa, but still providing what is expected to be therapeutically effective neuromodulation.

[0096] Neural detection and mapping can provide a pre-procedural assessment of the neural anatomy, a mid-procedure assessment and feedback on temporal changes in tissue during neuromodulation, and/or a post procedural assessment of the neural activity as a confirmation of effectiveness. In various embodiments, the bioelectric measurements taken pre-, mid-, and post-procedurally can be taken multiple times during each stage of the procedure to assess and confirm findings. Pre-procedural assessment can be used to evaluate the bioelectric properties of the native/host tissue to determine a baseline for subsequent actions and as a reference guide against source biological signatures to identify anatomical targets of interest (e.g., nerves, microforamina, etc.). This information can be determined by placing a multi-electrode array in a known spatial configuration to detect and then map electro-anatomical characteristics (e.g., variations in the impedance of different tissue types). The resultant anatomical mapping can comprise a composition of multiple (high density) activation sequence in multiple planes, relying on the variations in impedance to identify different tissue types and structures. During the procedure, the impedance measurements can be used to confirm that the electrodes maintain good contact with tissue at the target site. During and after the procedure, the data can be used to determine whether the mid- or post-procedural recorded spectra has a shape consistent with the expected tissue types. Post-procedurally, the information can be used to determine whether the targeted nerves were therapeutically treated.

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[0097] In other embodiments, the action potentials of neural fibers can be detected via electrodes and or other contacts to dynamically map the locations and/or activity of nerves in the target region. For example, the recorded action potentials can be used to numerically measure, map, and/or produce images of fast neuronal depolarization to generate an accurate picture of neural activity. In general, the depolarization of the neuronal membrane can cause drops in voltage of about 110 μV, has about 2 ms, and have an impedance/resistance from 1000 Ω cm to 25 Ω cm. In further embodiments, the metabolic recovery processes associated with action potential activity (i.e., to restore ionic gradients to normal) can also be detected and used for dynamically mapping nerves at the target site. The detection of the bioelectric properties associated with these features has the advantage that the changes are much larger (e.g., approximately a thousand times larger) and, therefore, easier to measure.

[0098] In various embodiments, a nontherapeutic stimulation (e.g., RF energy) can be applied to the tissue at the detection region via two or more electrodes of an electrode array to enhance the recording of action potentials. The stimulating energy application can temporarily activate the neural fibers and the resultant action potential can be recorded. For example, two or more electrodes of a therapeutic assembly can deliver a stimulating pulse of energy, and two or more other electrodes can be configured to detect the resultant action potential. The stimulating energy pulses are expected to enhance the action potential signal, making it easier to record.

Selected Embodiments of Therapeutic Neuromodulation Devices

[0099] Figures 8 and 9 are isometric views of a distal portion of a therapeutic neuromodulation device 802 ("device 802") configured in accordance with an embodiment of the present technology. The device 802 can include various features generally similar to the features of the therapeutic neuromodulation devices 402 and 502a-d described above with reference to Figures 4-5G. For example, the device 802 includes a therapeutic assembly 812 at a distal portion 408b of a shaft 408. The therapeutic assembly 812 includes a plurality of struts 440 that form branches 446 and define an expandable frame or basket 442, and one or more electrodes 444 disposed on one or more of the struts 440. As shown in Figures 8 and 9, the device 902 can further include an expandable member 856 (e.g., a balloon) carried by the support member 448 and expandable within the basket 442. The expandable member 856 can include a plurality of electrodes 858 disposed on the outer surface of the expandable member 856. The electrodes 858 can be used for detection of bioelectric features (e.g.,

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impedance) to allow for mapping of the neural anatomy at the target site before, during, and/or after therapeutic neuromodulation via the other electrodes 444. In other embodiments, the electrodes 858 can be configured to apply energy for therapeutic neuromodulation.

[00100] As shown in Figures 8 and 9, the electrodes 858 can be positioned on the expandable member 856 in a substantially symmetrical manner and a uniform distribution. This provides an expansive array with which impedance and/or other properties can be detected across the tissue and, therefore, may provide a more detailed mapping of the tissue and nerves at the treatment site. In other embodiments, the electrodes 858 can be clustered toward the medial portion of the expandable member 856 and/or around different portions of the expandable member 856. In certain embodiments, the electrodes 858 can be selectively activated at a specific polarity, and therefore the electrode array can be configured in a variety of static configurations and a dynamically change sequences (e.g., sesquipolar application of current) that may be advantageous for mapping functions.

[00101] In operation, the expandable member 856 can be inflated or otherwise expanded (Figure 9) to place at least a portion of the electrodes 858 into contact with tissue at the target site. The electrodes 858 can measure various bioelectric properties of the tissue (e.g., impedance, action potentials, etc.) to detect, locate, and/or map the nerves at the treatment site. In certain embodiments, the electrodes 444 on the struts 440 and/or a portion of the electrodes 858 on the expandable member 856 can apply a stimulating pulse of RF energy, and the electrodes 858 can detect the resultant neural response. After mapping, the expandable member 856 can be deflated or collapsed (Figure 8), and the electrodes 444 on the struts 440 can apply therapeutically effective neuromodulation energy to the target site. For example, the ablation pattern of the electrodes 444 can be based on the neural locations identified via the information detected from the sensing electrodes 858 on the expandable member 856. In other embodiments, the expandable member 856 may remain expanded during neuromodulation, and the electrodes 858 can detect neural activity during the neuromodulation procedure or the electrodes 858 can themselves be configured to apply neuromodulation energy to the treatment site. After applying the neuromodulation energy, the electrodes 858 on the expandable member 856 can again be placed into contact with tissue at the target site, and used to record bioelectric properties (e.g., impedance). The detected properties (e.g., impedances) taken before, during, and/or after neuromodulation can be compared to each other to determine whether the neuromodulation was therapeutically effective. If not, the electrodes 444 can again apply therapeutic neuromodulation energy to

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the same treatment site, or the configuration of the active electrodes 444 can be changed to apply therapeutic neuromodulation energy in a different pattern or sequence, and/or the therapeutic assembly 812 can be moved to a different treatment site.

[00102] Figure 10A is an isometric view of a distal portion of a therapeutic neuromodulation device 1002 ("device 1002") configured in accordance with another embodiment of the present technology, and Figure 10B is an isometric view illustrating the therapeutic neuromodulation device 1002 of Figure 10A at a treatment site. The device 1002 can include various features generally similar to the features of the therapeutic neuromodulation devices 402, 502a-d, and 802 described above with reference to Figures 4-5G, 8 and 9. For example, the device 1002 includes a shaft 1008 and a therapeutic assembly 1012 at a distal portion 1008b of the shaft 1008. The therapeutic assembly 1012 includes a plurality of struts 1040 that form branches 1046 and define an expandable frame or basket 1042, and one or more electrodes 1044 disposed on one or more of the struts 1040. As shown in Figure 10A, the device 1002 can further include a secondary or return electrode 1060 disposed along the distal portion of the shaft 1008. In the illustrated embodiment, the return electrode 1060 is a ring electrode having a ring-like shape, but in other embodiments the return electrode 1060 may have other shapes or configurations.

[00103] The return electrode 1060 may be biased at a negative polarity, and at least a portion of the electrodes 1044 on the struts 1040 and/or on other portions of the therapeutic assembly 1012 may be biased at a positive polarity. As indicated by the arrows in Figure 10A, bipolar RF energy can flow across a region spanning from the therapeutic assembly 1012 to the return electrode 1060 on this distal portion 1008b of the shaft 1008. In various embodiments, the RF energy can be applied in a sesquipolar manner (i.e., imbalanced bipolar energy).

[00104] As shown in Figure 10B, the therapeutic assembly 1012 can be positioned inferior to the SPF and superior to the inferior turbinate IT and at least a portion of the microforamina MF and nerves N traversing the palatine bone. The return electrode 1060 can be positioned inferior to the inferior turbinate IT and at least a portion of the microforamina MF and nerves N traversing the palatine bone. RF energy can then be applied across a wide region spanning from the therapeutic assembly 1012 to the return electrode 1060. As shown in Figure 10B, for example, the device 1002 can apply energy across the top and bottom portions of the inferior turbinate, where a high density of microforamina reside.

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[00105] Figures 11A-11D are isometric views illustrating distal portions of therapeutic neuromodulation devices 1102 (referred to individually as a first device 1102a and a second device 1102b) configured in accordance with further embodiments of the present technology. The first device 1102a can include various features generally similar to the features of the therapeutic neuromodulation devices 402, 502a-d, 802 and 1002 described above with reference to Figures 4-5G and 8-10B. For example, the first device 1102a includes a shaft 1108 and a therapeutic assembly 1112 at a distal portion 1108b of the shaft 1108. The therapeutic assembly 1112 includes a flexible membrane 1162 that carries a plurality of electrodes 1144 and/or other energy delivery elements arranged in an array across the flexible membrane 1162.

[00106] As shown in Figures 11A-11C, the flexible membrane 1162 can be configured to transform from a low-profile delivery state (Figure 11A), to an expanded state (Figure 11B) via self-expansion or mechanical expansion means, and back to the low-profile delivery or retrieval state (Figure 11C) for removal of the device from the nasal cavity. In the expanded state shown in Figure 11B, the flexible membrane can conform to the irregular anatomy of the nasal space (e.g., turbinates, sinus, and/or other para-nasal) to enhance the contact area between the flexible membrane 1162 (and the electrodes 1144 disposed thereon) with the non-planar anatomy. The flexible membrane 1162 can be made from a flexible and dynamic material to support the electrodes 1144. For example, in certain embodiments the flexible membrane 1162 can comprise polymer filaments and/or other materials that add support and structure to the flexible membrane 1162. In various embodiments, the flexible membrane 1162 can have pre-set geometry to retain a predetermined shape. For example, the flexible membrane 1162 and/or the electrode array on the flexible membrane 1162 can retain spherical curvature (e.g., as shown in Figure 11A).

[00107] In various embodiments, the shaft 1108 can be movable relative to the flexible membrane 1162 to allow for deployment and recapture of the flexible membrane 1162. For example, the flexible membrane 1162 may be curled or otherwise folded into a circular shape when in the delivery state (Figure 11A). To move to the expanded state (Figure 11B), components of the shaft 1108 can be rotated and/or moved axially relative to the flexible membrane 1162 to unwind or otherwise expand the flexible membrane 1162 such that the flexible membrane 1162 at least partially opens and conforms to the structures of the surrounding anatomy to place the electrodes 1144 into contact with tissue at the target site.

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To recapture the device to the retracted state (Figure 11C), the shaft 1108 can again be moved axially or rotational manner to close wind or otherwise fold the flexible membrane 1162.

[00108] As shown in Figures 11A-11C, the electrodes 1144 may be interconnected through a plurality of connectors 1164, such as nano-ribbons, nano-wires, direct inking, multidirectional printing/deposition, and/or other suitable electrical connectors. In various embodiments, the interconnections 1164 between the electrodes 1144 can include periodic undulating conduits or lines having a "U", "S", or elliptical shapes. These undulating connectors 1164 may form a multidimensional spring within the flexible membrane 1162 and/or impose a predetermined shape on the flexible membrane 1162 that facilitates apposition of the flexible membrane 1162 to the tissue at the target site to improve energy conductivity/transference.

[00109] The electrodes 1144 may be surface mounted on the flexible membrane 1162 or embedded within a multi-layered composite structure of the flexible membrane 1162. In various embodiments, the electrodes 1144 may be relatively small in size, having diameters ranging from 50-2,000 microns. The electrodes 1144 may be configured to deliver energy in a mono-polar, bipolar, or multipolar manner. For example, multipolar electrodes can be used in a bipolar arrangement and in a quad-polar arrangement to facilitate a linear and an angulated (diagonal) energy connectivity between the electrodes 1144.

[00110] The electrodes 1144 can be connected to a connection pad (not shown) housed within the shaft 1108 and/or features connected to proximal portions of the shaft 1108, such as a handle or console. The electrodes 1144 can be connected to the connection pad through a conductive connector cable (e.g., a metallic cable, a polymeric cable, and/or combinations thereof).

[00111] In certain embodiments, the flexible membrane 1162 may also house a feedback system (not shown) to control the delivery of the RF energy and maintain predefined treatment parameters. For example, the electronic circuits of the flexible membrane 1162 may include thermal sensors that provide temperature feedback to control energy dissipation and depth penetration of the RF energy. The features of electronic circuits of the flexible membrane 1162 may also measure resistance and temperature at the treatment site to determine the effects of the therapeutic energy application. This information may be used to regulate energy application and avoid collateral damage to host tissue. For example, energy delivery via the electrodes 1144 may be automatically terminated if the detected temperature

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and/or resistance reaches a predetermined threshold maximum (e.g., a threshold temperature associated with tissue damage). Energy delivery via the electrodes 1144 may be automatically or manually adjusted if the detected temperature and/or resistance is below a predetermined threshold range indicative of parameters associated with therapeutically effective modulation of the parasympathetic nasal nerves. In other embodiments, the feedback system can be incorporated to components communicatively coupled with the electrodes 1144 and any additional sensors on the flexible membrane 1162. For example, the feedback system can be stored on the console 204 of Figure 2 and executed by the controller 218 (Figure 2).

[00112] In the embodiment shown in Figure 11D, the second device 1102b can include various features generally similar to the features of the first device 1102a described above with reference to Figures 11A-11C. For example, the device 1102b of Figure 11D includes the flexible membrane 1162 that carries a plurality of electrodes 1144 and associated electrical connectors 1164 disposed on or embedded in the flexible membrane 1162. The device 1102b further includes an expandable frame 1166 carrying the flexible membrane 1162. The frame 1166 may have a U-shape and can be made from a shape memory material (e.g., Nitinol). In other embodiments, the frame may have different shapes and/or be made from different materials suitable for supporting the flexible membrane 1162.

[00113] In operation, the frame 1166 facilitates the deployment of the flexible membrane 1162 against the anatomy of the nasal cavity, and provides support for the flexible membrane 1162 and the associated array of electrodes 1144. The U-shaped frame 1166 can enhance the ability of the flexible membrane 1162 to contact the non-planar anatomy at the target site. In various embodiments, for example, the frame 1166 may act as a cantilever spring to establish a positive directional apposition of the membrane 1162 to the target surface tissue to improve energy conductivity/transference from the electrodes 1144 to the target tissue.

[00114] Figure 12 is a side view of a distal portion of a therapeutic neuromodulation device 1202 ("device 1202") configured in accordance with a further embodiment of the present technology. The device 1202 includes include various features generally similar to the features of the therapeutic neuromodulation devices 402, 502a-d, 802, 1002 and 1102 described above with reference to Figures 4-5G and 8-11. For example, the device 1202 includes a shaft 1208 and a therapeutic assembly 1212 including a plurality of energy delivery elements, such as electrodes 1244, at a distal portion 1208b of the shaft 1208. In the illustrated embodiment, the therapeutic assembly 1212 includes four electrodes 1244 are

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arranged along a spiral/helical section 1268 at the distal portion 1208b of the shaft 1208. In other embodiments, however, the therapeutic assembly 1212 may include one, two, three, or more than four electrodes 1244, and/or may include different energy delivery elements. The therapeutic assembly 1212 can also include a temperature sensor 1252 (e.g., a thermocouple) and/or other type of sensor to detect various properties at the treatment site before, during, and/or after applying therapeutic neuromodulation energy, and provide feedback that may be used to control the operation of the therapeutic assembly 1212. Such sensors can be incorporated in any of the other embodiments of therapeutic assemblies disclosed herein.

[00115] During delivery of the therapeutic assembly 1212, the spiral/helical section 1168 of the shaft 1208 is positioned in a low-profile delivery state in which the section 1268 is substantially straitened or flattened within an introducer sheath and/or via mechanical components associated with the shaft 1208. At the target site, the operator can transform the spiral/helical section 1268 to an expanded state (shown in Figure 12) to place one or more of the electrodes 1244 in contact with the target tissue. One or more of the electrodes 1244 can then be selectively activated to apply RF energy (e.g., monopolar and/or bipolar RF energy) to tissue at a target site in the nasal region to therapeutically modulate nerves proximate to the treatment site. In other embodiments, the distal section of the shaft 1208 can have other suitable shapes, sizes, and/or configurations that facilitate placing the electrodes 1244 in contact with tissue at the target site. For example, in further embodiments, the distal portion 1208b of the shaft 1208 can have a semi-circular, curved, bent, or straight shape and/or the therapeutic assembly 1212 can include multiple support members configured to carry one or more of the electrodes 1244.

[00116] Figure 13 is a side view of a distal portion of a therapeutic neuromodulation device 1302 ("device 1302") configured in accordance with a still further embodiment of the present technology. The device 1302 includes include various features generally similar to the features of the therapeutic neuromodulation devices 402, 502a-d, 802, 1002, 1102 and 1202 described above with reference to Figures 4-5G and 8-12. For example, the device 1302 includes a shaft 1308 and a therapeutic assembly 1312 including a plurality of energy delivery elements, such as an array of electrodes 1344, at a distal portion 1308b of the shaft 1308. In the embodiment illustrated in Figure 13, the therapeutic assembly 1312 includes a balloon 1370 that carries the electrodes 1344. A support member 1372 can extend through the length of the balloon 1370 to support the balloon 1370 and, optionally, include a channel through which a guidewire (not shown) can extend to facilitate delivery of the therapeutic

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assembly 1312 to the target site. In other embodiments, the support member 1372 may be omitted.

[00117] The electrodes 1344 can be made from conductive ink that is printed, sprayed, and/or otherwise disposed on the surface of the balloon 1370. Such conductive ink electrodes facilitates the use of complex electrode configurations. In addition, thermocouples (not shown) can also be incorporated onto the surface of the balloon 1370 using conductive ink and/or other suitable methods. In other embodiments, the electrodes 1344 can be made from foil and adhered to the surface of the balloon 1370. In further embodiments, the electrodes 1344 can be made from other suitable materials that may be disposed on the surface of the balloon 1370 and/or embedded within the material of the balloon 1370.

[00118] The balloon 1370 can be made from various different materials and have various different shapes. As shown in Figure 13, for example, the balloon 1370 can have an ovoid shape when in the expanded state, which is expected to improve the conformance to anatomical variations at the target site within the nasal cavity. In other embodiments, the balloon 1370 can have a circular shape, a spherical shape, an irregular shape, and/or other suitable shape for expansion within the nasal anatomy. The balloon 1370 can be made from a compliant material (e.g., a urethane material) that allows the balloon 1370 to conform to anatomical variances when expanded within the nasal region. In other embodiments, the balloon may be made from a non-compliant material (e.g., polyethylene terephthalate, nylon, etc.) that allows the balloon 1370 to have a defined shape when expanded and facilitates the attachment of electrodes 1344 to the balloon surface. In further embodiments, the balloon 1370 may be dip-coated and form a bulbous tip at the distal end of the shaft 1308.

[00119] The balloon 1370 may be inflated with a fluid via an opening or port 1374 in the support member 1372 and/or an opening in the shaft 1308 in fluid communication with the interior of the balloon 1370. For example, the support member 1372 and/or the shaft 1308 can include a channel extending along the length of the shaft 1308 and connected to a fluid supply at the proximal portion of the shaft 1308 such that fluid can be delivered to the balloon 1370. The balloon 1370 can inflate against the nasal anatomy at the target site to places the electrodes 1344 in contact with tissue at the target site.

[00120] At the target site, the electrodes 1344 deliver RF energy to tissue to therapeutically modulate nerves at the treatment site. In certain embodiments, the array of electrodes 1344 can be arranged on the balloon 1370 and/or selectively activated to apply

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transverse bipolar RF energy across a radial regions of the balloon 1370 (i.e., extending around circumferential portions of the balloon 1370). In other embodiments, the array of electrodes 1344 can be arranged on the balloon 1370 and/or selectively activated to apply longitudinal bipolar RF energy across longitudinal regions of the balloon 1370 (i.e., extending between proximal and distal portions of the balloon 1370).

[00121] In various embodiments, the therapeutic assembly 1312 may include features that facilitate with positioning of the balloon 1370 within the nasal anatomy and proper placement of the electrodes 1344 at the treatment site. As shown in Figure 13, for example, an endoscope 1371 may be positioned on the surface of the balloon 1370 to provide direct, in-line visualization of the balloon 1370 and the target site during placement at the target site. The therapeutic assembly 1312 can also include graduated markings 1373 along the support member 1372 and/or the surface of the balloon 1370 to depict spatial orientation and/or depth positioning of the therapeutic assembly 1312.

[00122] In certain embodiments, the balloon 1370 can be configured to allow for a slow perfusion of fluid through the balloon wall to cool the electrodes 1344 while energy is applied to the target tissue. For example, such a "weeping" balloon 1370 can include laser-driller holes and/or other small openings or pores along at least a portion of the balloon 1370 to allow for the slow perfusion of a fluid (e.g., saline solution) through the balloon wall. When the balloon perfuses saline solution, the saline solution is expected to improve the electrical conductivity between the electrodes 1344 and the target tissue and may enhance the effect of the RF energy on the nerves at the target site. In other embodiments, a cooled fluid can be circulated through the balloon 1470 during activation of the electrodes 1444 to cool the electrodes 1444 and the surrounding tissue during energy delivery.

[00123] Figure 14 is a side view of a distal portion of a therapeutic neuromodulation device 1402 ("device 1402") configured in accordance with an additional embodiment of the present technology. The device 1402 includes include various features generally similar to the features of the therapeutic neuromodulation device 1302 described above with reference to Figure 13. For example, the device 1402 includes a shaft 1408 and a therapeutic assembly 1412 at a distal portion 1408b of the shaft 1408. The therapeutic assembly 1412 includes a balloon 1470, a support member 1472 supporting the balloon 1470, and a plurality of energy delivery elements, such as an array of electrodes 1444 disposed on the balloon 1470. In the embodiment illustrated in Figure 14, the electrodes 1444 are part of a flex circuit 1476 adhered to the surface of the balloon 1470. The flex circuit 1476 facilitates the creation of

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complex electrode arrays that can create highly customizable neuromodulation patterns. In certain embodiments, for example, the flex circuit 1476 can include a conductive return electrode along the surface of the balloon 1470 and a plurality of electrodes on a proximal or distal portion of the balloon 1470 (e.g., a conical end portion of the balloon 1470). In addition, the flex circuit 1476 can incorporate thermocouples and/or thermistors into the circuitry on the surface of the balloon 1470 to detect temperature at the treatment site before, during, and/or after energy application.

[00124] Figure 15 is an isometric side view of a distal portion of a therapeutic neuromodulation device 1502 ("device 1502") configured in accordance with an additional embodiment of the present technology. The device 1502 includes include various features generally similar to the features of the therapeutic neuromodulation devices 1302 and 1402 described above with reference to Figures 13 and 14. For example, the device 1502 includes a shaft 1508 and a therapeutic assembly 1512 at a distal portion 1508b of the shaft 1508. The therapeutic assembly 1512 includes a plurality of balloons 1578 positioned around an inner support member 1580, and a plurality of energy delivery elements, such as electrodes 1544 disposed on one or more of the balloons 1578. In certain embodiments, the balloons 1578 are independently inflatable. This allows for asymmetrical or variable inflation of the balloons 1578 and, thereby, enhances the ability of the therapeutic assembly 1512 to conform to the irregular geometry of the nasal region at the target site and facilitates apposition of the electrodes 1544 against tissue at the target site.

[00125] In the illustrated embodiment, four independently inflated balloons 1578 are positioned around the perimeter of the inner support member 1580. In other embodiments, however, the device 1502 can include less than four balloons 1578 or more than four balloons 1578 arranged around the inner support member 1580. In further embodiments, the balloons 1578 can have different sizes and/or shapes, and can be positioned along various portions of the inner support member 1580. In still further embodiments, the balloons 1578 re configured as struts that are attached at end portions to the inner support member 1580 and extend outwardly away from the inner support member 1580 when inflated (e.g., in a similar manner as the struts 440 of the therapeutic neuromodulation device 402 of Figure 4).

[00126] During energy delivery, the electrodes 1544 can be configured to apply bipolar RF energy across the electrodes 1544 on different balloons 1578 and/or between electrodes 1544 on the same balloon 1578. In other embodiments, the electrodes 1544 apply energy in a sesquipolar manner. For example, the inner support member 1580 can include a return

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electrode (not shown), and the electrodes 1544 on two or more of the balloons 1578 may be activated for sesquipolar RF energy delivery.

[00127] Figure 16 is a cross-sectional side view of a distal portion of a therapeutic neuromodulation device 1602 ("device 1602") configured in accordance with an additional embodiment of the present technology. The device 1602 includes various features generally similar to the features of the therapeutic neuromodulation devices described above. For example, the device 1602 includes a shaft 1608 and a therapeutic assembly 1612 at a distal portion 1608b of the shaft 1608. In the embodiment illustrated in Figure 16, the therapeutic assembly 1612 is configured to apply cryotherapeutic cooling to therapeutically modulate nerves at the target site. As shown in Figure 16, the cryotherapeutic assembly 1612 can include an expansion chamber 1682 (e.g., a balloon, inflatable body, etc.) in fluid communication with one or more supply tubes or lumens 1684 via corresponding orifices 1686 in the supply lumens 1684. The supply lumens 1682 can extend along at least a portion of the shaft 1608 and be configured to transport a refrigerant in an at least a partially liquid state to the distal portion 1608b of the shaft 1608. An exhaust tube or lumen 1689 (e.g., defined by a portion of the shaft 1608) can be placed in fluid communication with the interior of the expansion chamber 1682 via an outlet 1688 such that the exhaust lumen 1689 can return the refrigerant to the proximal portion of the shaft 1608. For example, in one embodiment, a vacuum (not shown) at the proximal portion of the shaft 1608 may be used to exhaust the refrigerant from the expansion chamber 1682 via the exhaust lumen 1689. In other embodiments, the refrigerant may be transported to the proximal portion of the shaft 1608 using other suitable mechanisms known to those having skill in the art.

[00128] During cryotherapy, the orifices 1686 of the supply lumens 1684 can restrict refrigerant flow to provide a high pressure differential between the supply lumen 1684 and the expansion chamber 1682, thereby facilitating the expansion of the refrigerant to the gas phase within the expansion chamber 1682. The pressure drop as the liquid refrigerant passes through the orifices 1682 causes the refrigerant to expand to a gas and reduces the temperature to a therapeutically effective temperature that can modulate neural fibers proximate a treatment site within the nasal cavity. In the illustrated embodiment, the expansion chamber 1682 includes heat transfer portions 1691 that contact and cool tissue at the target site at a rate sufficient to cause cryotherapeutic neuromodulation of postganglionic parasympathetic neural fibers that innervate the nasal mucosa. For example, the therapeutic assembly 1602 can operate at temperatures of -40°C, -60°C, -80°C, or lower. In other

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embodiments, the therapeutic assembly 1602 can operated at higher cryotherapeutic temperatures (e.g., 5°C and -15°C, -20°C, etc.).

[00129] The refrigerant used for cryogenic cooling in the device 1602 can be a compressed or condensed gas that is stored in at least a substantially liquid phase, such as nitrous oxide (N_2O), carbon dioxide (CO_2), hydrofluorocarbon (e.g., FREON made available by E. I. du Pont de Nemours and Company of Wilmington, DE), and/or other suitable fluids that can be stored at a sufficiently high pressure to be in at least a substantially liquid phase at about ambient temperature. For example, R-410A, a zeotropic, but near-azeotropic mixture of difluoromethane (CH_2F_2; also known as HFC-32 or R-32) and pentafluoroethane (CHF_2CF_3; also known as HFC-125 or R-125), can be in at least a substantially liquid phase at about ambient temperature when contained at a pressure of about 1.45 MPa (210 psi). Under proper conditions, these refrigerants can reach cryotherapeutic temperatures at or near their respective normal boiling points (e.g., approximately -88°C for nitrous oxide) to effectuate therapeutic neuromodulation.

[00130] In other embodiments, the therapeutic assembly 1612 can include a cryotherapeutic applicator rather than the expansion chamber 1682 of Figure 16. Such a cryotherapeutic applicator can be used for very targeted treatment of the nerves.

[00131] As further shown in Figure 16, the device 1602 can also include a support member 1690 extending through the expansion chamber 1682 and configured to carry the distal portion of the expansion chamber 1682. The support member 1690 can also include a channel extending along its length and an opening 1692 at the distal end portion of the support member 1690 to facilitate delivery of the therapeutic assembly 1612 to the treatment site via a guidewire GW.

[00132] Figure 17 is a cross-sectional side view of a distal portion of a therapeutic neuromodulation device 1702 ("device 1702") configured in accordance with an additional embodiment of the present technology. The device 1702 includes various features generally similar to the features of the therapeutic neuromodulation devices described above. For example, the device 1702 includes a shaft 1708 and a therapeutic assembly 1712 at a distal portion 1708b of the shaft 1708. In the embodiment illustrated in Figure 17, the therapeutic assembly 1712 is configured to apply direct conductive heating to thermally therapeutically modulate nerves at the target site. As shown in Figure 17, the therapeutic assembly 1712 can include a balloon 1770 in fluid communication with a supply tube or lumen 1794 (e.g.,

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defined by a portion of the shaft 1708) via an outlet at a distal portion of the supply lumen 1794. The supply lumen 1794 can extend along at least a portion of the shaft 1708 and be insulated to transport a heated fluid (e.g., heated saline) to the balloon 1770 at the distal portion 1708b of the shaft 1708. An exhaust or return tube or lumen 1796 (e.g., defined by a portion of the shaft 1708) can be placed in fluid communication with the interior of the balloon 1770 via an outlet such that the return lumen 1796 can exhaust the fluid to the proximal portion of the shaft 1708 (e.g., using a vacuum at the proximal portion of the shaft 1708).

[00133] During thermal therapeutic neural modulation, the supply lumen 1794 can supply a heated fluid to the balloon 1770, and the exhaust lumen 1796 can be used to exhaust the fluid from the balloon 1770 such that the heated fluid circulates through the balloon 1770 (e.g., as indicated by the arrows). The heated fluid can be heated to a therapeutically effective temperature that causes time-dependent thermal damage (e.g., determined using the Arrhenius equation) to the target tissue at a treatment site within the nasal cavity and modulates neural fibers within or proximate to the heated target tissue. In the illustrated embodiment, for example, the wall of the balloon 1770 and/or portions thereof can contact and heat tissue at the target site at a rate and time sufficient to cause thermal damage to the target tissue to provide therapeutic neuromodulation of postganglionic parasympathetic neural fibers that innervate the nasal mucosa.

[00134] As shown in Figure 17, the device 1702 can also include a support member 1790 extending through the balloon 1770 and configured to carry the distal portion of the balloon 1770. The support member 1790 can also include a channel extending along its length and an opening 1792 at the distal end portion of the support member 1790 that can be used to facilitate delivery of the therapeutic assembly 1712 to the treatment site via a guidewire GW.

[00135] Figure 18 is a cross-sectional side view of a distal portion of a therapeutic neuromodulation device 1802 ("device 1802") configured in accordance with an additional embodiment of the present technology. The device 1802 includes various features generally similar to the features of the therapeutic neuromodulation devices described above. For example, the device 1802 includes a shaft 1808 and a therapeutic assembly 1812 at a distal portion 1808b of the shaft 1808. The therapeutic assembly 1812 can include an inflatable balloon 1870 and a support member 1890 extending through the balloon 1870. The support member 1890 may also include a channel with an opening 1892 that allows for guidewire delivery of the therapeutic assembly 1812 to the treatment site.

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[00136] Similar to the therapeutic assembly 1712 of Figure 17, the therapeutic assembly 1812 can apply therapeutically effective heating to tissue at a target site to cause time-dependent thermal tissue damage (e.g., determined using the Arrhenius equation) and modulate neural fibers within or proximate to the heated target tissue. In the embodiment illustrated in Figure 18, however, heating is supplied via a heating element 1898 positioned within the balloon 1880 and carried by the support member 1890 and/or another feature of the therapeutic assembly 1812. The heating element 1898 may be a plate or other structure heated using resistive heating (via a generator) and/or other suitable heating mechanism. In operation, the heat from the heating element 1898 can transfer from the heating element 1898 to the fluid within the balloon 1870, and then through the wall of the balloon 1870 to the adjacent tissue at the treatment site. The fluid heated by the heating element 1898 can be heated to a therapeutically effective temperature that causes thermal damage to the target tissue at a treatment site within the nasal cavity and modulates neural fibers within or proximate to the heated target tissue. In certain embodiments, the balloon 1870 can include conductive features (e.g., metallic panels) on its surface to concentrate the heating effect at targeted regions of the balloon 1870.

[00137] In other embodiments, the balloon 1870 can be heated via capacitive coupling to reach therapeutically effective temperatures that causes thermal damage to the target tissue at a treatment site within the nasal cavity and modulate neural fibers within or proximate to the heated target tissue. For example, the balloon 1870 can be inflated with an isotonic solution, and the balloon 1870 can be ionically agitated at a high frequency to allow capacitive energy to discharge across the membrane of the balloon 1870 to the target tissue.

[00138] Figure 19 is a side view of a distal portion of a therapeutic neuromodulation device 1902 ("device 1902") configured in accordance with an additional embodiment of the present technology. The device 1902 includes various features generally similar to the features of the therapeutic neuromodulation devices described above. For example, the device 1902 includes a shaft 1908 and a therapeutic assembly 1912 at a distal portion 1908b of the shaft 1908. In the embodiment illustrated in Figure 19, the therapeutic assembly 1912 is configured to apply plasma or laser ablation to therapeutically modulate nerves at the target site. As shown in Figure 19, the therapeutic assembly 1912 can include an ablation element 1999 (e.g., an electrode) on a distal end portion of the shaft 1908. The ablation element 1999 can apply high energy laser pulses to ionize molecules within the first few portion of the pulse. This process leads to a small bubble or field of plasma (e.g., 100-200 μm) that can be

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used to desiccate or otherwise destroy tissue and nerves at the target site. The ablation element 1999 can operate at temperatures lower than 100°C and can limit the thermal effects on surrounding tissue.

[00139] In other embodiments, the ablation element 1999 can perform laser ablation of nerves at the target site. For example, a nerve tracer (e.g., indocyanine green (ICG)) can be injected at the target site to dye nerves at the target site. The ablation element 1999 can be a laser that is tuned to absorb the spectrum of the nerve tracer and, thereby, ablate the dyed nerves in the target site.

Selected Embodiments of Therapeutic Neuromodulation for the Treatment of Chronic Sinusitis

[00140] Figure 20 is a partial cut-away side view illustrating target sites proximate to ostia of nasal sinuses for a therapeutic neuromodulation device configured in accordance with embodiments of the present technology. Any of the therapeutic modulation devices and system described above can be used to therapeutically modulate nerves that innervate the para-nasal sinuses to treat chronic sinusitis and/or similar indications. Referring to Figure 20, the para-nasal sinuses include the frontal sinuses FS, the sphenoidal sinuses SS, the maxillary sinuses ("MS"; not shown), and the ethmoidal sinuses or ethmoidal cells (not shown), which include the posterior ethmoidal cells ("PEC"), the middle ethmoidal cells ("MEC"), and the anterior ethmoidal cells ("AEC"). Each sinus opens to the nasal cavity at one or more discrete ostia. Figure 20 illustrates the general locations of the ostium of the frontal sinus, the sphenoidal sinus, the maxillary sinus, and the ostia of posterior, middle, and anterior ethmoidal cells.

[00141] Parasympathetic nerves innervate the mucosa of the sinuses and stimulate the production of mucus in the sinuses. Hyperactivity of the parasympathetic nerves innervating the sinuses can cause hyper production of mucus and the soft tissue engorgement. The inflammation of the soft tissue proximate to the sinuses can cause can obstruct the conduit between a sinus and the nasal cavity and block the ostium to the sinus. In addition, the hyperactive mucosa and/or the blockage of the ostium can cause the pooling of mucosal secretions within the sinus occurs due to the lack of drainage from the sinus. This can lead to infection and, eventually, a chronic sinusitis state.

[00142] Therapeutic modulation the parasympathetic nerves that control autonomic function of the sinuses is expected to reduce or eliminate the hyperactive mucosal secretions

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and soft tissue engorgement and, thereby, treat chronic sinusitis or related indications. Any of the therapeutic neuromodulation devices described above can be used to apply therapeutically effective neuromodulation energy at or proximate to the ostia of the affected sphenoidal, maxillary, frontal, and/or ethmoidal sinuses to modulate the autonomic function of the sinuses. For example, therapeutic neuromodulation devices can be used to apply RF energy, microwave energy, ultrasound energy, cryotherapeutic cooling, therapeutic heating, plasma ablation, and/or laser ablation to treatment sites at and around the ostia of the sinuses. Similar to the devices described above, the therapeutic neuromodulation devices can be delivered intraluminally via the nasal passage and through the superior, middle, and/or inferior meatuses to access the ostium or ostia of the desired sinus. In various embodiments, neural mapping techniques similar to those described above with respect to Figures 6A-9 can be used to locate or detect the parasympathetic nerves that innervate the ostia before, during, and/or after treatment. The application of therapeutic neuromodulation at the target sites proximate to the sinus ostia can disrupt the parasympathetic signals to the sinus tissues, leading to the opening of the ostia and the ability to drain fluid.

Additional Examples

1. A system for therapeutic neuromodulation in a nasal region of a human patient, the system comprising:

a shaft having a proximal portion and a distal portion, wherein the shaft is configured to locate the distal portion intraluminally at a target site inferior to a sphenopalatine foramen of the human patient; and

a therapeutic assembly at the distal portion of the shaft, wherein the therapeutic assembly comprises an energy delivery element configured to therapeutically modulate postganglionic parasympathetic nerves innervating nasal mucosa at microforamina of a palatine bone of the human patient.

2. The system of example 1 wherein the energy delivery element is configured to deliver at least one of ultrasound energy, microwave energy, laser energy, or radiofrequency (RF) energy to therapeutically modulation the postganglionic parasympathetic nerves.

3. The system of example 1 or 2 wherein the therapeutic assembly is configured to dispense a drug to chemically modulate the postganglionic parasympathetic nerves.

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4. The system of any one of examples 1-3 wherein the shaft comprises a drug delivery channel with an outlet at the distal portion of the shaft, and wherein the drug delivery channel is configured to deliver at least one of a local anesthetic or a nerve block to the target site.

5. The system of any one of examples 1-4 wherein the shaft comprises a fluid channel with an outlet at the distal portion of the shaft, and wherein the fluid channel is configured to deliver saline to the target site to rinse the treatment area with saline.

6. The system of any one of examples 1-5, further comprising an introducer having a rigid metal portion, and wherein the rigid metal portion is sized and shaped to extend through a nasal meatus to the target site to deliver the therapeutic assembly to the target site.

7. The system of any one of examples 1-6 wherein the shaft is a steerable catheter shaft and the distal portion of the shaft has a bend radius of 3 mm or less.

8. The system of any one of examples 1-6 wherein the distal portion of the shaft comprises an articulating region with rigid links sized and shaped to have a bend radius of 3 mm or less.

9. The system of any one of examples 1-8, further comprising an anchor member along the shaft, wherein the anchor member includes a balloon configured to expand in a lumen of the nasal region to hold the distal portion of the shaft in place for deployment of the therapeutic assembly at the target site.

10. The system of any one of examples 1-9 wherein the energy delivery element of the therapeutic assembly comprises a plurality of electrodes configured to apply RF energy to therapeutically modulate postganglionic parasympathetic nerves.

11. The system of any one of examples 1-10 wherein the therapeutic assembly comprises a plurality of sensing electrodes configured to detect neural activity at least one of before therapeutic modulation, during therapeutic modulation, or after therapeutic neuromodulation.

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12. The system of any one of examples 1-11 wherein the therapeutic assembly comprises:

a basket transformable between a low-profile delivery state and an expanded state, wherein the basket includes plurality of struts spaced radially apart from each other when the basket is in the expanded state; and

a plurality of electrodes disposed on the struts, wherein the plurality of struts are configured to position at least two of the electrodes at the target site when the basket is in the expanded state, and

wherein the electrodes are configured to apply radiofrequency (RF) energy to the target site to therapeutically modulate parasympathetic nerves proximate to the target site.

13. The system of any one of examples 1-11 wherein the therapeutic assembly comprises:

a flexible membrane transformable between a low-profile delivery state and an expanded state; and

a plurality of electrodes disposed on the flexible membrane,

wherein the electrodes are configured to apply radiofrequency (RF) energy to the target site to therapeutically modulate parasympathetic nerves proximate to the target site.

14. The system of example 13 wherein the therapeutic assembly further comprises a frame supporting the flexible membrane.

15. The system of any one of examples 1-11 wherein:

the distal portion of the shaft is transformable between a low-profile delivery state and an expanded state,

the distal portion of the shaft has a spiral/helical shape when the distal portion of the shaft is in the expanded state; and

the energy delivery element comprises a plurality of electrodes disposed on the distal portion of the shaft and configured to deliver radiofrequency (RF) energy to the target site to therapeutically modulate parasympathetic nerves proximate to the target site,

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wherein the distal portion of the shaft is configured to place at least one of the electrodes in contact tissue at the target site when the distal portion of the shaft is in the expanded state.

16. The system of any one of examples 1-11 wherein the therapeutic assembly comprises:

a balloon transformable between a low-profile delivery state to an expanded state; and

a plurality of electrodes disposed on the balloon, wherein the plurality of electrodes are configured to deliver radiofrequency (RF) energy to the target site to therapeutically modulate parasympathetic nerves proximate to the target site.

17. The system of example 16 wherein the balloon comprises a plurality of holes configured to allow perfusion of a fluid through the balloon when the balloon is in the expanded state.

18. The system of example 16, further comprising:

a support extending through the balloon; and

a plurality of graduated markings on at least one of the support or the balloon to identify spatial positioning of the balloon.

19. The system of any one of examples 1-11 wherein the therapeutic assembly comprises:

a balloon transformable between a low-profile delivery state to an expanded state, wherein the balloon comprises a proximal cone portion;

a return electrode on the balloon; and

a flex circuit on the proximal cone portion, wherein the return electrode and the flex circuit are configured to deliver radiofrequency (RF) energy to the target site to therapeutically modulate parasympathetic nerves proximate to the target site.

20. The system of any one of examples 1-11 wherein the therapeutic assembly comprises:

a plurality of balloons extending distally from the distal portion of the shaft, wherein the balloons are independently expandable; and

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at least one electrode on each of the balloons, wherein the electrodes are configured to deliver radiofrequency (RF) energy to the target site to therapeutically modulate parasympathetic nerves proximate to the target site.

21. The system of example 20, further comprising:

an internal support member extending through a region between the balloons and configured to carry the balloons, wherein the internal support member includes a return electrode.

22. The system of any one of examples 1-9 wherein the therapeutic assembly comprises a cryotherapeutic balloon configured to apply cryogenic cooling to tissue at the target site to therapeutically modulate autonomic activity.

23. The system of any one of examples 1-9 wherein the therapeutic assembly comprises a balloon sized and shaped to contact tissue at the target state when expanded, and wherein the balloon is configured to circulate a fluid heated to at least 60° C to thermally modulate autonomic activity.

24. The system of any one of examples 1-9 wherein the therapeutic assembly comprises:

a balloon configured to be expanded with a fluid, wherein the balloon is sized and shaped to contact tissue at the target state when expanded; and

a heating member within the balloon, wherein the heating member is configured to heat the fluid in the balloon to thermally modulate autonomic activity.

25. The system of any one of examples 1-9 wherein the therapeutic assembly comprises a plasma ablation probe.

26. A system for therapeutic neuromodulation in a nasal region of a human patient, the system comprising:

a shaft having a proximal portion and a distal portion, wherein the shaft is configured to locate the distal portion intraluminally at a target site, wherein the target site is at least one of proximate to the sphenopalatine foramen of a human patient or inferior to the sphenopalatine foramen; and

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a therapeutic assembly at the distal portion of the shaft and transformable between a low-profile delivery state and an expanded state, wherein the therapeutic assembly comprises a plurality of struts and a plurality of electrodes disposed on the struts, and wherein the plurality of struts form a basket that positions at least two of the electrodes at the target site inferior to a sphenopalatine foramen of the human patient when the therapeutic assembly is in the expanded state, and

wherein the electrodes are configured to apply radiofrequency (RF) energy to the target site to therapeutically modulate parasympathetic nerves proximate to the target site.

27. The system of example 26 wherein:

the plurality of struts comprise at least three struts spaced radially apart from each other in the expanded state to define the basket; and

each of the three struts includes at least one of the electrodes.

28. The system of example 26 or 27 wherein:

the basket comprises at least three branches radially spaced apart from each other in the expanded state to form the basket;

each branch comprises at least two struts positioned adjacent to each other; and

each strut includes at least one of the electrodes.

29. The system of any one of examples 26-28, further comprising a thermocouple positioned at least proximate to one of the electrodes, wherein the thermocouple is configured to detect temperature at an interface between the electrode and tissue adjacent to the electrode when the therapeutic assembly is in the expanded state.

30. The system of any one of examples 26-29 wherein each of the electrodes is configured to be independently activated and independently assigned a selective polarity to apply therapeutic neuromodulation across selected regions of the basket.

31. The system of any one of examples 26-30 wherein the basket has a spherical or ovoid shape, and wherein the electrodes are configured to be selectively activated to apply RF energy across at least one of a segment, quadrant, or hemisphere of the basket.

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32. The system of any one of examples 26-31 wherein:

the plurality of electrodes comprises first through third electrodes disposed on corresponding first through third struts; and

the system further comprises a controller operably coupled to the plurality of electrodes, the controller having a computer-readable medium carrying instructions, which when executed by the controller, activates first through third electrodes of the plurality of electrodes such that—

the first electrode has a positive polarity;

the second and third electrodes have a negative polarity; and

the electrodes apply RF energy in a sesquipolar manner across a selected peripheral region of the basket.

33. The system of any one of examples 26-31 wherein:

the basket comprises an internal support member extending through a region between the plurality of struts and having a distal end portion supporting distal end portions of the plurality of struts;

the plurality of struts comprises at least a first strut and a second strut;

the plurality of electrodes comprises a first electrode disposed on the first strut, a second electrode disposed on the second strut, and a third electrode disposed on the distal end portion of the internal support member; and

the system further comprises a controller operably coupled to the plurality of electrodes, the controller having a computer-readable medium carrying instructions, which when executed by the controller, activates first through third electrodes of the plurality of electrodes such that—

the first and second electrodes have a positive polarity;

the third electrode has a negative polarity; and

the electrodes apply RF energy across a distal region of the basket.

34. The system of any one of examples 26-31 wherein:

the basket comprises at least two branches radially spaced apart from each other when the therapeutic assembly is in the expanded state; and

each branch comprises at least a first strut and a second strut positioned adjacent to each other, the first strut having a first electrode disposed thereon and the second strut having a second electrode disposed thereon, wherein the first and

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second electrodes are configured to have opposite polarity and apply RF energy between the first and second electrodes.

35. The system of any one of examples 26-31 wherein:

the basket comprises at least two branches radially spaced apart from each other when the therapeutic assembly is in the expanded state; and

each branch comprises at least a first strut and a second strut positioned adjacent to each other, the first strut having a first electrode disposed thereon and the second strut having a second strut disposed thereon, wherein—

the first and second electrodes of the first branch are configured to have a positive polarity,

the first and second electrodes of the second branch are configured to have a negative polarity, and apply

the therapeutic assembly is configured to delivery RF energy between the first and second branches across a peripheral portion of the basket.

36. The system of any one of examples 26-31, further comprising:

a return electrode disposed on the distal portion of the shaft positioned proximal to the therapeutic assembly,

wherein the electrodes on the struts are configured to have a positive polarity and the return electrode is configured to have a negative polarity.

37. The system of any one of examples 26-36 wherein at least a portion of the electrodes are configured to detect impedance at the target site to determine locations of nerves at the target site.

38. The system of any one of examples 26-37 wherein:

the plurality of electrodes on the struts are a first plurality of electrodes;

the therapeutic assembly further comprises—

an expandable balloon disposed within the struts; and

a second plurality of electrodes on the expandable balloon,

wherein, when in the expanded state, the expandable balloon places at least a portion of the second plurality of electrodes in contact with tissue at the target site to detect neural activity at the target site.

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39. The system of any one of examples 26-38, further comprising an RF generator operably connected to the therapeutic assembly, wherein the RF generator includes a controller having a computer-readable medium carrying instructions, which when executed by the controller, causes the therapeutic assembly to detect at least one of impedance or temperature at least proximate to the target site.

40. The system of any one of examples 26-39, further comprising an RF generator operably connected to the therapeutic assembly, wherein the RF generator includes a controller having a computer-readable medium carrying instructions, which when executed by the controller, causes the therapeutic assembly to apply RF energy to the target site in a predetermined pattern.

41. A system for neural mapping and therapeutic neuromodulation in a nasal region of a human patient, the system comprising:

a shaft having a proximal portion and a distal portion, wherein the shaft is configured to locate the distal portion intraluminally at a target site proximate to a sphenopalatine foramen of the human patient;

a plurality of electrodes at the distal portion of the shaft, wherein the electrodes are configured to detect locations of the parasympathetic nerves at the target site; and

a therapeutic assembly at the distal portion of the shaft, wherein the therapeutic assembly is comprises an energy delivery element configured to therapeutically modulate postganglionic parasympathetic nerves innervating a nasal mucosa at the target site.

42. The system of example 41 wherein the electrodes define the energy delivery element and are configured to apply radiofrequency (RF) energy to the target site.

43. The system of example 41 or 42 wherein the electrodes are configured to detect dielectric properties of heterogeneous tissue at the target site to identify locations of parasympathetic nerves.

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44. The system of any one of examples 41-43 wherein the electrodes are configured to detect impedance properties of heterogeneous tissue at the target site to identify locations of parasympathetic nerves.

45. A method of therapeutically modulating nerves in a nasal region of a human patient, the method comprising:

intraluminally advancing a therapeutic assembly at a distal portion of a shaft of a therapeutic device to a target site within the nasal region, wherein the target site is proximate to parasympathetic nerves spanning across at least one of an accessory foramen or microforamina proximate to the sphenopalatine foramen; and

applying energy, with the therapeutic assembly, to the target site to therapeutically modulate autonomic activity within at least one of a nasal cavity, a nasopharynx, or paranasal cavities.

46. The method of example 45 wherein intraluminally advancing the therapeutic assembly to the target site comprises positioning the therapeutic assembly at a palatine bone of the human patient inferior to the sphenopalatine foramen.

47. The method of example 45 or 46 wherein intraluminally advancing the therapeutic assembly to the target site comprises intraluminally advancing the therapeutic assembly through an entrance of a nose of the human patient, through an inferior meatus, and to the target site.

48. The method of example 45 or 46 wherein intraluminally advancing the therapeutic assembly to the target site comprises intraluminally advancing the therapeutic assembly through an entrance of a nose of the human patient, through a middle meatus, and to the target site.

49. The method of any one of examples 45-48, further comprising intraluminally advancing an endoscope through an entrance of a nose of the human patient and through a middle meatus to visualize the therapeutic assembly at the target site.

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50. The method of any one of examples 45-48, further comprising intraluminally advancing an endoscope through an entrance of a nose of the human patient and through an inferior meatus to visualize the therapeutic assembly at the target site.

51. The method of example 45 or 46 wherein:

intraluminally advancing the therapeutic assembly to the target site comprises intraluminally advancing the therapeutic assembly through an entrance of a nose of the human patient, through an inferior meatus, and to the target site; and

the method further comprises intraluminally advancing an endoscope through the entrance of the nose of the human patient and through the inferior meatus to visualize the therapeutic assembly at the target site.

52. The method of example 45 or 46 wherein:

intraluminally advancing the therapeutic assembly to the target site comprises intraluminally advancing the therapeutic assembly through an entrance of a nose of the human patient, through an middle meatus, and to the target site; and

the method further comprises intraluminally advancing an endoscope through the entrance of the nose of the human patient and through the middle meatus to visualize the therapeutic assembly at the target site.

53. The method of example 45 or 46, further comprising:

intraluminally advancing an endoscope through an entrance of a nose of the human patient, through one of an inferior meatus or a middle meatus, to a region at least proximate to the target site; and

wherein intraluminally advancing the therapeutic assembly to the target site comprises—

advancing the distal portion of the shaft through a channel of the endoscope beyond the target site, and

advancing the therapeutic assembly out of an opening at a distal portion of the endoscope.

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54. The method of example 45 or 46 wherein intraluminally advancing the therapeutic assembly to the target site comprises advancing the distal portion of the shaft through a mouth and oropharynx of the human patient, and to the target site.

55. The method of any one of examples 45-54, further comprising imaging the target site via infrared (IR) spectroscopy to visualize vasculature at least proximate to the target site.

56. The method of any one of examples 45-55, further comprising expanding an anchor member positioned along the distal portion of the shaft in a lumen of the nasal region, wherein the anchor member holds the distal portion of the shaft in place for deployment of the therapeutic assembly at the target site.

57. The method of any one of examples 45-56 wherein the target site is a first target site, wherein applying energy to the target site comprises applying energy to the first target site, and wherein the method further comprises:

repositioning the therapeutic assembly to a second target site within the nasal region; and

applying energy, with the therapeutic assembly, to the second target site to therapeutically modulate parasympathetic nerves proximate to the second target site.

58. The method of any one of examples 45-57 wherein applying energy comprises applying pulsed radiofrequency (RF) energy to the target site via a plurality of electrodes of the thereapeutic element.

59. The method of any one of examples 45-58 further comprising detecting impedance at the target site to identify positions of parasympathetic nerves spanning across at least one of an accessory foramen or microforamina proximate to the sphenopalatine foramen.

60. The method of example 59 wherein applying energy to the target site comprises applying energy to a discrete region of the therapeutic assembly corresponding to the positions of the parasympathetic nerves identified via impedance measurements.

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61. The method of any one of examples 45-60 wherein the therapeutic assembly comprises a plurality of electrodes, and wherein applying energy to the target site comprises independently activating the individual electrodes and selecting the polarity of the individual electrodes to apply therapeutic neuromodulation across a selective region of the therapeutic assembly.

62. The method of example 61 wherein applying energy to the target site further comprises applying energy in a first hemispherical portion of the therapeutic assembly, wherein the therapeutic assembly does not apply energy to a second hemispherical portion of the therapeutic assembly.

63. The method of any one of examples 45-62 wherein the therapeutic assembly comprises an expandable basket having a plurality of struts with a plurality electrodes disposed on the struts, and wherein applying energy to the target site comprises:

activating a first electrode of the plurality of electrodes to have a positive polarity; and

activating at least a second electrode and a third electrode of the plurality of electrodes to have a negative polarity, wherein first, second, and third electrodes are concurrently activated and the second and third electrodes sequentially pair with the first electrode based on path of least resistance to sequentially apply therapeutic neuromodulation across a region of the basket.

64. The method of any one of examples 45-62 wherein the therapeutic assembly comprises an expandable basket having a plurality of struts with a plurality electrodes disposed on the struts, and wherein applying energy to the target site comprises:

activating a first electrode of the plurality of electrodes to have a positive polarity; and

activating at least second through sixth electrodes of the plurality of electrodes to have a negative polarity, wherein first through sixth electrodes are concurrently activated and the second through sixth electrodes sequentially pair with the first electrode based on path of least resistance to sequentially apply therapeutic neuromodulation across a hemispherical region of the basket.

65. The method of any one of examples 45-62 wherein the therapeutic assembly comprises an expandable basket having a plurality of struts with a plurality electrodes

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disposed on the struts and an internal support member comprising a return electrode at a distal end portion of the internal support member, and wherein applying energy to the target site comprises:

activating the electrodes on the struts to have positive polarities; and

activating the return electrode to have a negative polarity, wherein the electrodes apply RF energy across a distal region of the basket.

66. The method of any one of examples 45-62 wherein the therapeutic assembly comprises an expandable basket having a plurality of branches radially spaced apart from each other when the therapeutic assembly is in an expanded state, wherein each branch comprises at least two adjacent struts with an electrode positioned on each strut, and wherein applying energy to the target site comprises:

activating the electrodes on adjacent struts of at least one of the branches such that the electrodes have opposite polarities; and

applying RF energy between the electrodes on the adjacent struts.

67. The method of any one of examples 45-62 wherein the therapeutic assembly comprises a plurality of electrodes, and wherein applying energy to the target site comprises:

activating the electrodes of the therapeutic assembly to have positive polarities; and

activating a return electrode disposed on the distal portion of the shaft proximal to the therapeutic assembly, wherein the return electrode has a negative polarity, and

wherein activating the electrodes and the return electrodes applies RF energy across a turbinate of the human patient.

68. The method of any one of examples 45-67, further comprising:

detecting, via a plurality of sensing electrodes, neural activity at the target site before applying energy to the target site to therapeutically modulate autonomic activity; and

mapping locations of nerves at the target site based on the detected neural activity,

wherein applying energy to the target site comprises selectively applying energy to a region based on the locations of detected nerves.

69. The method of example 68, further comprising applying non-therapeutic neural stimulation to the target site before detecting neural activity.

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70. The method of example 68, further comprising detecting, via the plurality of sensing electrodes, neural activity after applying energy to the target site to determine whether the application of energy has therapeutically modulated nerves at the target site.

71. The method of any one of examples 45-62 wherein:

the therapeutic assembly comprises a flexible membrane carrying a plurality of electrodes;

before applying energy, the method further comprises expanding the flexible membrane at the target site to place at least a portion of the electrodes in contact with tissue at the target site; and

applying energy to the target site comprises applying RF energy to the target site via the electrodes.

72. The method of any one of examples 45-62, further comprising:

transforming the distal portion of the shaft from a low-profile delivery state to an expanded state such that a plurality of electrodes disposed on the distal portion of the shaft are placed in contact with tissue at the target site, wherein the distal portion of the shaft has a spiral/helical shape in the expanded state; and

wherein applying energy at the target site comprises applying RF energy to the target site via the electrodes.

73. The method of any one of examples 45-62 wherein:

the therapeutic assembly comprises a balloon carrying a plurality of electrodes;

before applying energy, the method further comprises expanding the balloon at the target site to place at least a portion of the electrodes in contact with tissue at the target site; and

applying energy to the target site comprises applying RF energy to the target site via the electrodes.

74. The method of example 73 wherein applying energy to the target site further comprises:

selectively activating the electrodes to apply current in a radial direction across a circumferential segment of the balloon.

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75. The method of example 73 wherein applying energy to the target site further comprises:

selectively activating the electrodes to apply current in a longitudinal direction across a longitudinal region of the balloon.

76. The method of example 73 wherein expanding the balloon comprises filling the balloon with a fluid, and wherein the balloon comprises a plurality of holes that allow for perfusion of the fluid through the balloon during energy application.

77. The method of example 73 wherein expanding the balloon comprises circulating a fluid through the balloon, wherein the fluid cools the electrodes during energy application.

78. The method of any one of examples 45-62 wherein:

the therapeutic assembly comprises a plurality of balloons extending distally from the distal portion of the shaft and a plurality of electrodes disposed on the balloons;

before applying energy, the method further comprises independently expanding the balloons at the target site to place at least a portion of the electrodes in contact with tissue at the target site; and

applying energy to the target site comprises applying RF energy to the target site via the electrodes.

79. The method of example 78 wherein applying energy to the target site further comprises:

activating a return electrode on an internal support member extending through the plurality of balloons; and

activating at least a portion of the electrodes on the balloons.

80. The method of any one of examples 45-79, further comprising:

measuring temperature of tissue at the target site during energy application; and

terminating energy application when a threshold maximum temperature is reached.

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81. The method of any one of examples 45-80, further comprising terminating energy application after a predetermined maximum time period.

82. The method of any one of examples 45-81, further comprising:

detecting impedance of tissue at the target site during energy application; and

terminating energy application when a threshold impedance value is reached.

83. The method of any one of examples 45-82, further comprising:

detecting impedance of tissue at the target site before energy application to define a baseline impedance;

detecting impedance of tissue at the target site during energy application; and

terminating energy application when a threshold change in impedance from the baseline impedance is reached.

84. The method of any one of examples 45-57 wherein applying energy to the target site comprises applying therapeutic cryogenic cooling to tissue at the target site to therapeutically modulate autonomic activity within the nasal cavity, the nasopharynx, and/or the paranasal cavities.

85. The method of any one of examples 45-57 wherein applying energy to the target site comprises:

circulating a heated fluid within a balloon such that an exterior surface of the balloon contacts tissue at the target site and heats the tissue to thermally modulate autonomic activity at the target site.

86. The method of any one of examples 45-57 wherein applying energy to the target site comprises:

expanding a balloon such that an exterior surface of the balloon contacts tissue at the target site; and

heating a heating member within the balloon, wherein the heat from the heating member transfers to the fluid and to the tissue adjacent to the balloon to thermally modulate autonomic activity.

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87. The method of any one of examples 45-57 wherein applying energy to the target site comprises generating a plasma field to therapeutically modulate nerves at the target site.

88. The method of any one of examples 45-87 wherein applying energy to the target site therapeutically modulates cholinergic pathways that send signals to submucosal glands.

89. The method of any one of examples 45-88 wherein intraluminally advancing the therapeutic assembly to the target site comprises intraluminally advancing the therapeutic assembly to parasympathetic nerve points of entrance into the nasal region via accessory foramen and/or microforamina within at least one of a superior meatus, a middle meatus, an inferior meatus, or a pterygopalatine fossa.

90. A method of therapeutically modulating nerves in a nasal region, the method comprising:

intraluminally advancing a therapeutic assembly at a distal portion of a shaft of a therapeutic device to a target site within a nasal region, wherein the target site is proximate to parasympathetic nerves proximate to the sphenopalatine foramen;

detecting locations of the parasympathetic nerves at the target site; and

applying energy, with the therapeutic assembly, to the target site based on the detected locations of the parasympathetic nerves, wherein applying energy therapeutically modulates autonomic activity within at least one of a nasal cavity, a nasopharynx, or paranasal cavities.

91. The method of example 90 wherein detecting locations of the parasympathetic nerves at the target site comprises measuring dielectric properties of heterogeneous tissue within at least one of the nasal cavity, the nasopharynx, and/or the paranasal cavities on a high resolution spatial grid.

92. The method of example 90 or 92 wherein detecting locations of the parasympathetic nerves at the target site comprises measuring the dipole properties of

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heterogeneous tissue within the nasal cavity, the nasopharynx, and/or the paranasal cavities on a high resolution spatial grid.

93. The method of any one of examples 90-92 wherein detecting locations of the parasympathetic nerves at the target site comprises detecting impedance of heterogeneous tissue within at least one of the nasal cavity, the nasopharynx, or the paranasal cavities on a high resolution spatial grid.

94. A device for therapeutic neuromodulation in a nasal region of a human patient, the system comprising:

a delivery catheter having a distal portion, wherein the delivery catheter is configured to locate the distal portion at a target site within the nasal region;

a flexible support at the distal portion of the delivery catheter; and

a plurality of electrodes carried by the flexible support,

wherein the flexible support is configured to conform to irregularities of local anatomy at the target site to provide topographical compliance and a linkage for electrical activation of at least a portion of the electrodes, and

wherein the electrodes are configured to therapeutically modulate parasympathetic nerves of mucosal and sub-mucosal structures in direct or in-direct contact with the electrodes.

95. The device of example 94, further comprising a controllable recapturing mechanism configured to recapture the flexible support after energy delivery to allow withdrawal of the flexible support from a nasal cavity.

96. The device of example 94 or 94 wherein the target site is at a sphenopalatine foramen.

97. The device of any one of examples 94-46 wherein the electrodes are configured to be selectively activated to control energy direction and associated dissipation for accurate and localized energy delivery.

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98. A method of therapeutically modulating nerves in a nasal region of a human patient, the method comprising:

intraluminally advancing a therapeutic assembly at a distal portion of a shaft of a therapeutic device to a target site within the nasal region, wherein the target site is at least proximate to an ostium of at least one of a frontal sinus, an ethmoidal sinus, a sphenoidal sinus, or a maxillary sinus of the human patient; and

applying energy, with the therapeutic assembly, to the target site to therapeutically modulate parasympathetic nerves at the target site to treat chronic sinusitis.

99. The method of claim 98 wherein:

intraluminally advancing the therapeutic assembly to the target site comprises positioning the therapeutic assembly proximate to the ostium of the frontal sinus; and

applying energy to the target site comprises applying energy to at least one of a supraorbital nerve, a supratrochlear nerve, branches of the supraorbital nerve, branches of the supratrochlear nerve, or other parasympathetic neural fibers that innervate mucosa of the frontal sinus.

100. The method of claim 98 wherein:

intraluminally advancing the therapeutic assembly to the target site comprises positioning the therapeutic assembly proximate to the ostium of the ethmoidal sinus; and

applying energy to the target site comprises applying energy to at least one of an anterior ethmoidal branch of a nasociliary nerve, a posterior ethmoidal branch of the nasociliary nerve, a maxillary nerve, branches of the nasociliary nerve, branches of the maxillary nerve, or other parasympathetic neural fibers that innervate mucosa of the ethmoidal sinus.

101. The method of claim 98 wherein:

intraluminally advancing the therapeutic assembly to the target site comprises positioning the therapeutic assembly proximate to the ostium of the maxillary sinus; and

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applying energy to the target site comprises applying energy to at least one of an infra-orbital branch of a maxillary nerve, an alveolar branch of the maxillary nerve, or other parasympathetic neural fibers that innervate mucosa of the maxillary sinus.

102. The method of claim 98 wherein:

intraluminally advancing the therapeutic assembly to the target site comprises positioning the therapeutic assembly proximate to the ostium of the sphenoidal sinus; and

applying energy to the target site comprises applying energy to at least one of a posterior ethmoidal branch of an ophthalmic nerve, a maxillary nerve, branches of the ophthalmic nerve, branches of the maxillary nerve, or other parasympathetic neural fibers that innervate mucosa of the sphenoidal sinus.

103. A system for therapeutic neuromodulation in a nasal region of a human patient for treatment of chronic sinusitis, the system comprising:

a shaft having a proximal portion and a distal portion, wherein the shaft is configured to locate the distal portion intraluminally at a target site, wherein the target site is at least proximate to an ostium of at least one of a frontal sinus, an ethmoidal sinus, a sphenoidal sinus, or a maxillary sinus of the human patient; and

a therapeutic assembly at the distal portion of the shaft, wherein the therapeutic assembly is comprises an energy delivery element configured to therapeutically modulate parasympathetic nerves that innervate mucosa of at least one of the frontal sinus, the ethmoidal sinus, the sphenoidal sinus, or the maxillary sinus.

Conclusion

[00143] This disclosure is not intended to be exhaustive or to limit the present technology to the precise forms disclosed herein. Although specific embodiments are disclosed herein for illustrative purposes, various equivalent modifications are possible without deviating from the present technology, as those of ordinary skill in the relevant art will recognize. In some cases, well-known structures and functions have not been shown and/or described in detail to avoid unnecessarily obscuring the description of the

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embodiments of the present technology. Although steps of methods may be presented herein in a particular order, in alternative embodiments the steps may have another suitable order. Similarly, certain aspects of the present technology disclosed in the context of particular embodiments can be combined or eliminated in other embodiments. Furthermore, while advantages associated with certain embodiments may have been disclosed in the context of those embodiments, other embodiments can also exhibit such advantages, and not all embodiments need necessarily exhibit such advantages or other advantages disclosed herein to fall within the scope of the present technology. Accordingly, this disclosure and associated technology can encompass other embodiments not expressly shown and/or described herein.

[00144] Throughout this disclosure, the singular terms "a," "an," and "the" include plural referents unless the context clearly indicates otherwise. Similarly, unless the word "or" is expressly limited to mean only a single item exclusive from the other items in reference to a list of two or more items, then the use of "or" in such a list is to be interpreted as including (a) any single item in the list, (b) all of the items in the list, or (c) any combination of the items in the list. Additionally, the terms "comprising" and the like are used throughout this disclosure to mean including at least the recited feature(s) such that any greater number of the same feature(s) and/or one or more additional types of features are not precluded. Directional terms, such as "upper," "lower," "front," "back," "vertical," and "horizontal," may be used herein to express and clarify the relationship between various elements. It should be understood that such terms do not denote absolute orientation. Reference herein to "one embodiment," "an embodiment," or similar formulations means that a particular feature, structure, operation, or characteristic described in connection with the embodiment can be included in at least one embodiment of the present technology. Thus, the appearances of such phrases or formulations herein are not necessarily all referring to the same embodiment. Furthermore, various particular features, structures, operations, or characteristics may be combined in any suitable manner in one or more embodiments.

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CLAIMS

I/We claim:

1. A system for therapeutic neuromodulation in a nasal region of a human patient, the system comprising:

a shaft having a proximal portion and a distal portion, wherein the shaft is configured to locate the distal portion intraluminally at a target site inferior to a sphenopalatine foramen of the human patient; and

a therapeutic assembly at the distal portion of the shaft, wherein the therapeutic assembly comprises an energy delivery element configured to therapeutically modulate postganglionic parasympathetic nerves innervating nasal mucosa at microforamina of a palatine bone of the human patient.

2. The system of claim 1 wherein the energy delivery element is configured to deliver at least one of ultrasound energy, microwave energy, laser energy, or radiofrequency (RF) energy to therapeutically modulation the postganglionic parasympathetic nerves.

3. The system of claim 1 wherein the therapeutic assembly is configured to dispense a drug to chemically modulate the postganglionic parasympathetic nerves.

4. The system of claim 1 wherein the shaft comprises a drug delivery channel with an outlet at the distal portion of the shaft, and wherein the drug delivery channel is configured to deliver at least one of a local anesthetic or a nerve block to the target site.

5. The system of claim 1 wherein the shaft comprises a fluid channel with an outlet at the distal portion of the shaft, and wherein the fluid channel is configured to deliver saline to the target site to rinse the treatment area with saline.

6. The system of claim 1, further comprising an introducer having a rigid metal portion, and wherein the rigid metal portion is sized and shaped to extend through a nasal meatus to the target site to deliver the therapeutic assembly to the target site.

7. The system of claim 1 wherein the shaft is a steerable catheter shaft and the distal portion of the shaft has a bend radius of 3 mm or less.

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8. The system of claim 1 wherein the distal portion of the shaft comprises an articulating region with rigid links sized and shaped to have a bend radius of 3 mm or less.

9. The system of claim 1, further comprising an anchor member along the shaft, wherein the anchor member includes a balloon configured to expand in a lumen of the nasal region to hold the distal portion of the shaft in place for deployment of the therapeutic assembly at the target site.

10. The system of claim 1 wherein the energy delivery element of the therapeutic assembly comprises a plurality of electrodes configured to apply RF energy to therapeutically modulate postganglionic parasympathetic nerves.

11. The system of claim 1 wherein the therapeutic assembly comprises a plurality of sensing electrodes configured to detect neural activity at least one of before therapeutic modulation, during therapeutic modulation, or after therapeutic neuromodulation.

12. The system of claim 1 wherein the therapeutic assembly comprises:

a basket transformable between a low-profile delivery state and an expanded state, wherein the basket includes plurality of struts spaced radially apart from each other when the basket is in the expanded state; and

a plurality of electrodes disposed on the struts, wherein the plurality of struts are configured to position at least two of the electrodes at the target site when the basket is in the expanded state, and

wherein the electrodes are configured to apply radiofrequency (RF) energy to the target site to therapeutically modulate parasympathetic nerves proximate to the target site.

13. The system of claim 1 wherein the therapeutic assembly comprises:

a flexible membrane transformable between a low-profile delivery state and an expanded state; and

a plurality of electrodes disposed on the flexible membrane,

wherein the electrodes are configured to apply radiofrequency (RF) energy to the target site to therapeutically modulate parasympathetic nerves proximate to the target site.

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14. The system of claim 13 wherein the therapeutic assembly further comprises a frame supporting the flexible membrane.

15. The system of claim 1 wherein:

the distal portion of the shaft is transformable between a low-profile delivery state and an expanded state,

the distal portion of the shaft has a spiral/helical shape when the distal portion of the shaft is in the expanded state; and

the energy delivery element comprises a plurality of electrodes disposed on the distal portion of the shaft and configured to deliver radiofrequency (RF) energy to the target site to therapeutically modulate parasympathetic nerves proximate to the target site,

wherein the distal portion of the shaft is configured to place at least one of the electrodes in contact tissue at the target site when the distal portion of the shaft is in the expanded state.

16. The system of claim 1 wherein the therapeutic assembly comprises:

a balloon transformable between a low-profile delivery state to an expanded state; and

a plurality of electrodes disposed on the balloon, wherein the plurality of electrodes are configured to deliver radiofrequency (RF) energy to the target site to therapeutically modulate parasympathetic nerves proximate to the target site.

17. The system of claim 16 wherein the balloon comprises a plurality of holes configured to allow perfusion of a fluid through the balloon when the balloon is in the expanded state.

18. The system of claim 16, further comprising:

a support extending through the balloon; and

a plurality of graduated markings on at least one of the support or the balloon to identify spatial positioning of the balloon.

19. The system of claim 1 wherein the therapeutic assembly comprises:

a balloon transformable between a low-profile delivery state to an expanded state, wherein the balloon comprises a proximal cone portion;

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a return electrode on the balloon; and

a flex circuit on the proximal cone portion, wherein the return electrode and the flex circuit are configured to deliver radiofrequency (RF) energy to the target site to therapeutically modulate parasympathetic nerves proximate to the target site.

20. The system of claim 1 wherein the therapeutic assembly comprises:

a plurality of balloons extending distally from the distal portion of the shaft, wherein the balloons are independently expandable; and

at least one electrode on each of the balloons, wherein the electrodes are configured to deliver radiofrequency (RF) energy to the target site to therapeutically modulate parasympathetic nerves proximate to the target site.

21. The system of claim 20, further comprising:

an internal support member extending through a region between the balloons and configured to carry the balloons, wherein the internal support member includes a return electrode.

22. The system of claim 1 wherein the therapeutic assembly comprises a cryotherapeutic balloon configured to apply cryogenic cooling to tissue at the target site to therapeutically modulate autonomic activity.

23. The system of claim 1 wherein the therapeutic assembly comprises a balloon sized and shaped to contact tissue at the target state when expanded, and wherein the balloon is configured to circulate a fluid heated to at least 60° C to thermally modulate autonomic activity.

24. The system of claim 1 wherein the therapeutic assembly comprises:

a balloon configured to be expanded with a fluid, wherein the balloon is sized and shaped to contact tissue at the target state when expanded; and

a heating member within the balloon, wherein the heating member is configured to heat the fluid in the balloon to thermally modulate autonomic activity.

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25. The system of claim 1 wherein the therapeutic assembly comprises a plasma ablation probe.

26. A system for therapeutic neuromodulation in a nasal region of a human patient, the system comprising:

a shaft having a proximal portion and a distal portion, wherein the shaft is configured to locate the distal portion intraluminally at a target site, wherein the target site is at least one of proximate to the sphenopalatine foramen of a human patient or inferior to the sphenopalatine foramen; and

a therapeutic assembly at the distal portion of the shaft and transformable between a low-profile delivery state and an expanded state, wherein the therapeutic assembly comprises a plurality of struts and a plurality of electrodes disposed on the struts, and wherein the plurality of struts form a basket that positions at least two of the electrodes at the target site inferior to a sphenopalatine foramen of the human patient when the therapeutic assembly is in the expanded state, and

wherein the electrodes are configured to apply radiofrequency (RF) energy to the target site to therapeutically modulate parasympathetic nerves proximate to the target site.

27. The system of claim 26 wherein:

the plurality of struts comprise at least three struts spaced radially apart from each other in the expanded state to define the basket; and

each of the three struts includes at least one of the electrodes.

28. The system of claim 26 wherein:

the basket comprises at least three branches radially spaced apart from each other in the expanded state to form the basket;

each branch comprises at least two struts positioned adjacent to each other; and

each strut includes at least one of the electrodes.

29. The system of claim 26, further comprising a thermocouple positioned at least proximate to one of the electrodes, wherein the thermocouple is configured to detect

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temperature at an interface between the electrode and tissue adjacent to the electrode when the therapeutic assembly is in the expanded state.

30. The system of claim 26 wherein each of the electrodes is configured to be independently activated and independently assigned a selective polarity to apply therapeutic neuromodulation across selected regions of the basket.

31. The system of claim 26 wherein the basket has a spherical or ovoid shape, and wherein the electrodes are configured to be selectively activated to apply RF energy across at least one of a segment, quadrant, or hemisphere of the basket.

32. The system of claim 26 wherein:

the plurality of electrodes comprises first through third electrodes disposed on corresponding first through third struts; and

the system further comprises a controller operably coupled to the plurality of electrodes, the controller having a computer-readable medium carrying instructions, which when executed by the controller, activates first through third electrodes of the plurality of electrodes such that—

the first electrode has a positive polarity;

the second and third electrodes have a negative polarity; and

the electrodes apply RF energy in a sesquipolar manner across a selected peripheral region of the basket.

33. The system of claim 26 wherein:

the basket comprises an internal support member extending through a region between the plurality of struts and having a distal end portion supporting distal end portions of the plurality of struts;

the plurality of struts comprises at least a first strut and a second strut;

the plurality of electrodes comprises a first electrode disposed on the first strut, a second electrode disposed on the second strut, and a third electrode disposed on the distal end portion of the internal support member; and

the system further comprises a controller operably coupled to the plurality of electrodes, the controller having a computer-readable medium carrying

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instructions, which when executed by the controller, activates first through third electrodes of the plurality of electrodes such that—

the first and second electrodes have a positive polarity;

the third electrode has a negative polarity; and

the electrodes apply RF energy across a distal region of the basket.

34. The system of claim 26 wherein:

the basket comprises at least two branches radially spaced apart from each other when the therapeutic assembly is in the expanded state; and

each branch comprises at least a first strut and a second strut positioned adjacent to each other, the first strut having a first electrode disposed thereon and the second strut having a second electrode disposed thereon, wherein the first and second electrodes are configured to have opposite polarity and apply RF energy between the first and second electrodes.

35. The system of claim 26 wherein:

the basket comprises at least two branches radially spaced apart from each other when the therapeutic assembly is in the expanded state; and

each branch comprises at least a first strut and a second strut positioned adjacent to each other, the first strut having a first electrode disposed thereon and the second strut having a second strut disposed thereon, wherein—

the first and second electrodes of the first branch are configured to have a positive polarity,

the first and second electrodes of the second branch are configured to have a negative polarity, and apply

the therapeutic assembly is configured to delivery RF energy between the first and second branches across a peripheral portion of the basket.

36. The system of claim 26, further comprising:

a return electrode disposed on the distal portion of the shaft positioned proximal to the therapeutic assembly,

wherein the electrodes on the struts are configured to have a positive polarity and the return electrode is configured to have a negative polarity.

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37. The system of claim 26 wherein at least a portion of the electrodes are configured to detect impedance at the target site to determine locations of nerves at the target site.

38. The system of claim 26 wherein:

the plurality of electrodes on the struts are a first plurality of electrodes;

the therapeutic assembly further comprises—

an expandable balloon disposed within the struts; and

a second plurality of electrodes on the expandable balloon,

wherein, when in the expanded state, the expandable balloon places at least a portion of the second plurality of electrodes in contact with tissue at the target site to detect neural activity at the target site.

39. The system of claim 26, further comprising an RF generator operably connected to the therapeutic assembly, wherein the RF generator includes a controller having a computer-readable medium carrying instructions, which when executed by the controller, causes the therapeutic assembly to detect at least one of impedance or temperature at least proximate to the target site.

40. The system of claim 26, further comprising an RF generator operably connected to the therapeutic assembly, wherein the RF generator includes a controller having a computer-readable medium carrying instructions, which when executed by the controller, causes the therapeutic assembly to apply RF energy to the target site in a predetermined pattern.

41. A system for neural mapping and therapeutic neuromodulation in a nasal region of a human patient, the system comprising:

a shaft having a proximal portion and a distal portion, wherein the shaft is configured to locate the distal portion intraluminally at a target site proximate to a sphenopalatine foramen of the human patient;

a plurality of electrodes at the distal portion of the shaft, wherein the electrodes are configured to detect locations of the parasympathetic nerves at the target site; and

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a therapeutic assembly at the distal portion of the shaft, wherein the therapeutic assembly is comprises an energy delivery element configured to therapeutically modulate postganglionic parasympathetic nerves innervating a nasal mucosa at the target site.

42. The system of claim 41 wherein the electrodes define the energy delivery element and are configured to apply radiofrequency (RF) energy to the target site.

43. The system of claim 41 wherein the electrodes are configured to detect dielectric properties of heterogeneous tissue at the target site to identify locations of parasympathetic nerves.

44. The system of claim 41 wherein the electrodes are configured to detect impedance properties of heterogeneous tissue at the target site to identify locations of parasympathetic nerves.

45. A method of therapeutically modulating nerves in a nasal region of a human patient, the method comprising:

intraluminally advancing a therapeutic assembly at a distal portion of a shaft of a therapeutic device to a target site within the nasal region, wherein the target site is proximate to parasympathetic nerves spanning across at least one of an accessory foramen or microforamina proximate to the sphenopalatine foramen; and

applying energy, with the therapeutic assembly, to the target site to therapeutically modulate autonomic activity within at least one of a nasal cavity, a nasopharynx, or paranasal cavities.

46. The method of claim 45 wherein intraluminally advancing the therapeutic assembly to the target site comprises positioning the therapeutic assembly at a palatine bone of the human patient inferior to the sphenopalatine foramen.

47. The method of claim 45 wherein intraluminally advancing the therapeutic assembly to the target site comprises intraluminally advancing the therapeutic assembly

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through an entrance of a nose of the human patient, through an inferior meatus, and to the target site.

48. The method of claim 45 wherein intraluminally advancing the therapeutic assembly to the target site comprises intraluminally advancing the therapeutic assembly through an entrance of a nose of the human patient, through a middle meatus, and to the target site.

49. The method of claim 45, further comprising intraluminally advancing an endoscope through an entrance of a nose of the human patient and through a middle meatus to visualize the therapeutic assembly at the target site.

50. The method of claim 45, further comprising intraluminally advancing an endoscope through an entrance of a nose of the human patient and through an inferior meatus to visualize the therapeutic assembly at the target site.

51. The method of claim 45 wherein:

intraluminally advancing the therapeutic assembly to the target site comprises intraluminally advancing the therapeutic assembly through an entrance of a nose of the human patient, through an inferior meatus, and to the target site; and

the method further comprises intraluminally advancing an endoscope through the entrance of the nose of the human patient and through the inferior meatus to visualize the therapeutic assembly at the target site.

52. The method of claim 45 wherein:

intraluminally advancing the therapeutic assembly to the target site comprises intraluminally advancing the therapeutic assembly through an entrance of a nose of the human patient, through an middle meatus, and to the target site; and

the method further comprises intraluminally advancing an endoscope through the entrance of the nose of the human patient and through the middle meatus to visualize the therapeutic assembly at the target site.

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53. The method of claim 45, further comprising:

intraluminally advancing an endoscope through an entrance of a nose of the human patient, through one of an inferior meatus or a middle meatus, to a region at least proximate to the target site; and

wherein intraluminally advancing the therapeutic assembly to the target site comprises—

advancing the distal portion of the shaft through a channel of the endoscope beyond, and

advancing the therapeutic assembly out of an opening at a distal portion of the endoscope.

54. The method of claim 45 wherein intraluminally advancing the therapeutic assembly to the target site comprises advancing the distal portion of the shaft through a mouth and oropharynx of the human patient, and to the target site.

55. The method of claim 45, further comprising imaging the target site via infrared (IR) spectroscopy to visualize vasculature at least proximate to the target site.

56. The method of claim 45, further comprising expanding an anchor member positioned along the distal portion of the shaft in a lumen of the nasal region, wherein the anchor member holds the distal portion of the shaft in place for deployment of the therapeutic assembly at the target site.

57. The method of claim 45 wherein the target site is a first target site, wherein applying energy to the target site comprises applying energy to the first target site, and wherein the method further comprises:

repositioning the therapeutic assembly to a second target site within the nasal region; and

applying energy, with the therapeutic assembly, to the second target site to therapeutically modulate parasympathetic nerves proximate to the second target site.

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58. The method of claim 45 wherein applying energy comprises applying pulsed radiofrequency (RF) energy to the target site via a plurality of electrodes of the thereapeutic element.

59. The method of claim 45 further comprising detecting impedance at the target site to identify positions of parasympathetic nerves spanning across at least one of an accessory foramen or microforamina proximate to the sphenopalatine foramen.

60. The method of claim 59 wherein applying energy to the target site comprises applying energy to a discrete region of the therapeutic assembly corresponding to the positions of the parasympathetic nerves identified via impedance measurements.

61. The method of claim 45 wherein the therapeutic assembly comprises a plurality of electrodes, and wherein applying energy to the target site comprises independently activating the individual electrodes and selecting the polarity of the individual electrodes to apply therapeutic neuromodulation across a selective region of the therapeutic assembly.

62. The method of claim 61 wherein applying energy to the target site further comprises applying energy in a first hemispherical portion of the therapeutic assembly, wherein the therapeutic assembly does not apply energy to a second hemispherical portion of the therapeutic assembly.

63. The method of claim 45 wherein the therapeutic assembly comprises an expandable basket having a plurality of struts with a plurality electrodes disposed on the struts, and wherein applying energy to the target site comprises:

activating a first electrode of the plurality of electrodes to have a positive polarity; and

activating at least a second electrode and a third electrode of the plurality of electrodes to have a negative polarity, wherein first, second, and third electrodes are concurrently activated and the second and third electrodes sequentially pair with the first electrode based on path of least resistance to sequentially apply therapeutic neuromodulation across a region of the basket.

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64. The method of claim 45 wherein the therapeutic assembly comprises an expandable basket having a plurality of struts with a plurality electrodes disposed on the struts, and wherein applying energy to the target site comprises:

activating a first electrode of the plurality of electrodes to have a positive polarity; and

activating at least second through sixth electrodes of the plurality of electrodes to have a negative polarity, wherein first through sixth electrodes are concurrently activated and the second through sixth electrodes sequentially pair with the first electrode based on path of least resistance to sequentially apply therapeutic neuromodulation across a hemispherical region of the basket.

65. The method of claim 45 wherein the therapeutic assembly comprises an expandable basket having a plurality of struts with a plurality electrodes disposed on the struts and an internal support member comprising a return electrode at a distal end portion of the internal support member, and wherein applying energy to the target site comprises:

activating the electrodes on the struts to have positive polarities; and

activating the return electrode to have a negative polarity, wherein the electrodes apply RF energy across a distal region of the basket.

66. The method of claim 45 wherein the therapeutic assembly comprises an expandable basket having a plurality of branches radially spaced apart from each other when the therapeutic assembly is in an expanded state, wherein each branch comprises at least two adjacent struts with an electrode positioned on each strut, and wherein applying energy to the target site comprises:

activating the electrodes on adjacent struts of at least one of the branches such that the electrodes have opposite polarities; and

applying RF energy between the electrodes on the adjacent struts.

67. The method of claim 45 wherein the therapeutic assembly comprises a plurality of electrodes, and wherein applying energy to the target site comprises:

activating the electrodes of the therapeutic assembly to have positive polarities; and

activating a return electrode disposed on the distal portion of the shaft proximal to the therapeutic assembly, wherein the return electrode has a negative polarity, and

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wherein activating the electrodes and the return electrodes applies RF energy across a turbinate of the human patient.

68. The method of claim 45, further comprising:

detecting, via a plurality of sensing electrodes, neural activity at the target site before applying energy to the target site to therapeutically modulate autonomic activity; and

mapping locations of nerves at the target site based on the detected neural activity,

wherein applying energy to the target site comprises selectively applying energy to a region based on the locations of detected nerves.

69. The method of claim 68, further comprising applying non-therapeutic neural stimulation to the target site before detecting neural activity.

70. The method of claim 68, further comprising detecting, via the plurality of sensing electrodes, neural activity after applying energy to the target site to determine whether the application of energy has therapeutically modulated nerves at the target site.

71. The method of claim 45 wherein:

the therapeutic assembly comprises a flexible membrane carrying a plurality of electrodes;

before applying energy, the method further comprises expanding the flexible membrane at the target site to place at least a portion of the electrodes in contact with tissue at the target site; and

applying energy to the target site comprises applying RF energy to the target site via the electrodes.

72. The method of claim 45, further comprising:

transforming the distal portion of the shaft from a low-profile delivery state to an expanded state such that a plurality of electrodes disposed on the distal portion of the shaft are placed in contact with tissue at the target site, wherein the distal portion of the shaft has a spiral/helical shape in the expanded state; and

wherein applying energy at the target site comprises applying RF energy to the target site via the electrodes.

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73. The method of claim 45 wherein:

the therapeutic assembly comprises a balloon carrying a plurality of electrodes;

before applying energy, the method further comprises expanding the balloon at the target site to place at least a portion of the electrodes in contact with tissue at the target site; and

applying energy to the target site comprises applying RF energy to the target site via the electrodes.

74. The method of claim 73 wherein applying energy to the target site further comprises:

selectively activating the electrodes to apply current in a radial direction across a circumferential segment of the balloon.

75. The method of claim 73 wherein applying energy to the target site further comprises:

selectively activating the electrodes to apply current in a longitudinal direction across a longitudinal region of the balloon.

76. The method of claim 73 wherein expanding the balloon comprises filling the balloon with a fluid, and wherein the balloon comprises a plurality of holes that allow for perfusion of the fluid through the balloon during energy application.

77. The method of claim 73 wherein expanding the balloon comprises circulating a fluid through the balloon, wherein the fluid cools the electrodes during energy application.

78. The method of claim 45 wherein:

the therapeutic assembly comprises a plurality of balloons extending distally from the distal portion of the shaft and a plurality of electrodes disposed on the balloons;

before applying energy, the method further comprises independently expanding the balloons at the target site to place at least a portion of the electrodes in contact with tissue at the target site; and

applying energy to the target site comprises applying RF energy to the target site via the electrodes.

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79. The method of claim 78 wherein applying energy to the target site further comprises:

activating a return electrode on an internal support member extending through the plurality of balloons; and

activating at least a portion of the electrodes on the balloons.

80. The method of claim 45, further comprising:

measuring temperature of tissue at the target site during energy application; and

terminating energy application when a threshold maximum temperature is reached.

81. The method of claim 45, further comprising terminating energy application after a predetermined maximum time period.

82. The method of claim 45, further comprising:

detecting impedance of tissue at the target site during energy application; and

terminating energy application when a threshold impedance value is reached.

83. The method of claim 45, further comprising:

detecting impedance of tissue at the target site before energy application to define a baseline impedance;

detecting impedance of tissue at the target site during energy application; and

terminating energy application when a threshold change in impedance from the baseline impedance is reached.

84. The method of claim 45 wherein applying energy to the target site comprises applying therapeutic cryogenic cooling to tissue at the target site to therapeutically modulate autonomic activity within the nasal cavity, the nasopharynx, and/or the paranasal cavities.

85. The method of claim 45 wherein applying energy to the target site comprises:

circulating a heated fluid within a balloon such that an exterior surface of the balloon contacts tissue at the target site and heats the tissue to thermally modulate autonomic activity at the target site.

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86. The method of claim 45 wherein applying energy to the target site comprises:

expanding a balloon such that an exterior surface of the balloon contacts tissue at the target site; and

heating a heating member within the balloon, wherein the heat from the heating member transfers to the fluid and to the tissue adjacent to the balloon to thermally modulate autonomic activity.

87. The method of claim 45 wherein applying energy to the target site comprises generating a plasma field to therapeutically modulate nerves at the target site.

88. The method of claim 45 wherein applying energy to the target site therapeutically modulates cholinergic pathways that send signals to submucosal glands.

89. The method of claim 45 wherein intraluminally advancing the therapeutic assembly to the target site comprises intraluminally advancing the therapeutic assembly to parasympathetic nerve points of entrance into the nasal region via accessory foramen and/or microforamina within at least one of a superior meatus, a middle meatus, an inferior meatus, or a pterygopalatine fossa.

90. A method of therapeutically modulating nerves in a nasal region, the method comprising:

intraluminally advancing a therapeutic assembly at a distal portion of a shaft of a therapeutic device to a target site within a nasal region, wherein the target site is proximate to parasympathetic nerves proximate to the sphenopalatine foramen;

detecting locations of the parasympathetic nerves at the target site; and

applying energy, with the therapeutic assembly, to the target site based on the detected locations of the parasympathetic nerves, wherein applying energy therapeutically modulates autonomic activity within at least one of a nasal cavity, a nasopharynx, or paranasal cavities.

91. The method of claim 90 wherein detecting locations of the parasympathetic nerves at the target site comprises measuring dielectric properties of heterogeneous

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tissue within at least one of the nasal cavity, the nasopharynx, and/or the paranasal cavities on a high resolution spatial grid.

92. The method of claim 90 wherein detecting locations of the parasympathetic nerves at the target site comprises measuring the dipole properties of heterogeneous tissue within the nasal cavity, the nasopharynx, and/or the paranasal cavities on a high resolution spatial grid.

93. The method of claim 90 wherein detecting locations of the parasympathetic nerves at the target site comprises detecting impedance of heterogeneous tissue within at least one of the nasal cavity, the nasopharynx, or the paranasal cavities on a high resolution spatial grid.

94. A device for therapeutic neuromodulation in a nasal region of a human patient, the system comprising:

a delivery catheter having a distal portion, wherein the delivery catheter is configured to locate the distal portion at a target site within the nasal region;

a flexible support at the distal portion of the delivery catheter; and

a plurality of electrodes carried by the flexible support,

wherein the flexible support is configured to conform to irregularities of local anatomy at the target site to provide topographical compliance and a linkage for electrical activation of at least a portion of the electrodes, and

wherein the electrodes are configured to therapeutically modulate parasympathetic nerves of mucosal and sub-mucosal structures in direct or in-direct contact with the electrodes.

95. The device of claim 94, further comprising a controllable recapturing mechanism configured to recapture the flexible support after energy delivery to allow withdrawal of the flexible support from a nasal cavity.

96. The device of claim 94 wherein the target site is at a sphenopalatine foramen.

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97. The device of claim 94 wherein the electrodes are configured to be selectively activated to control energy direction and associated dissipation for accurate and localized energy delivery.

98. A method of therapeutically modulating nerves in a nasal region of a human patient, the method comprising:

intraluminally advancing a therapeutic assembly at a distal portion of a shaft of a therapeutic device to a target site within the nasal region, wherein the target site is at least proximate to an ostium of at least one of a frontal sinus, an ethmoidal sinus, a sphenoidal sinus, or a maxillary sinus of the human patient; and

applying energy, with the therapeutic assembly, to the target site to therapeutically modulate parasympathetic nerves at the target site to treat chronic sinusitis.

99. The method of claim 98 wherein:

intraluminally advancing the therapeutic assembly to the target site comprises positioning the therapeutic assembly proximate to the ostium of the frontal sinus; and

applying energy to the target site comprises applying energy to at least one of a supraorbital nerve, a supratrochlear nerve, branches of the supraorbital nerve, branches of the supratrochlear nerve, or other parasympathetic neural fibers that innervate mucosa of the frontal sinus.

100. The method of claim 98 wherein:

intraluminally advancing the therapeutic assembly to the target site comprises positioning the therapeutic assembly proximate to the ostium of the ethmoidal sinus; and

applying energy to the target site comprises applying energy to at least one of an anterior ethmoidal branch of a nasociliary nerve, a posterior ethmoidal branch of the nasociliary nerve, a maxillary nerve, branches of the nasociliary nerve, branches of the maxillary nerve, or other parasympathetic neural fibers that innervate mucosa of the ethmoidal sinus.

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101. The method of claim 98 wherein:

intraluminally advancing the therapeutic assembly to the target site comprises positioning the therapeutic assembly proximate to the ostium of the maxillary sinus; and

applying energy to the target site comprises applying energy to at least one of an infra-orbital branch of a maxillary nerve, an alveolar branch of the maxillary nerve, or other parasympathetic neural fibers that innervate mucosa of the maxillary sinus.

102. The method of claim 98 wherein:

intraluminally advancing the therapeutic assembly to the target site comprises positioning the therapeutic assembly proximate to the ostium of the sphenoidal sinus; and

applying energy to the target site comprises applying energy to at least one of a posterior ethmoidal branch of an ophthalmic nerve, a maxillary nerve, branches of the ophthalmic nerve, branches of the maxillary nerve, or other parasympathetic neural fibers that innervate mucosa of the sphenoidal sinus.

103. A system for therapeutic neuromodulation in a nasal region of a human patient for treatment of chronic sinusitis, the system comprising:

a shaft having a proximal portion and a distal portion, wherein the shaft is configured to locate the distal portion intraluminally at a target site, wherein the target site is at least proximate to an ostium of at least one of a frontal sinus, an ethmoidal sinus, a sphenoidal sinus, or a maxillary sinus of the human patient; and

a therapeutic assembly at the distal portion of the shaft, wherein the therapeutic assembly is comprises an energy delivery element configured to therapeutically modulate parasympathetic nerves that innervate mucosa of at least one of the frontal sinus, the ethmoidal sinus, the sphenoidal sinus, or the maxillary sinus.

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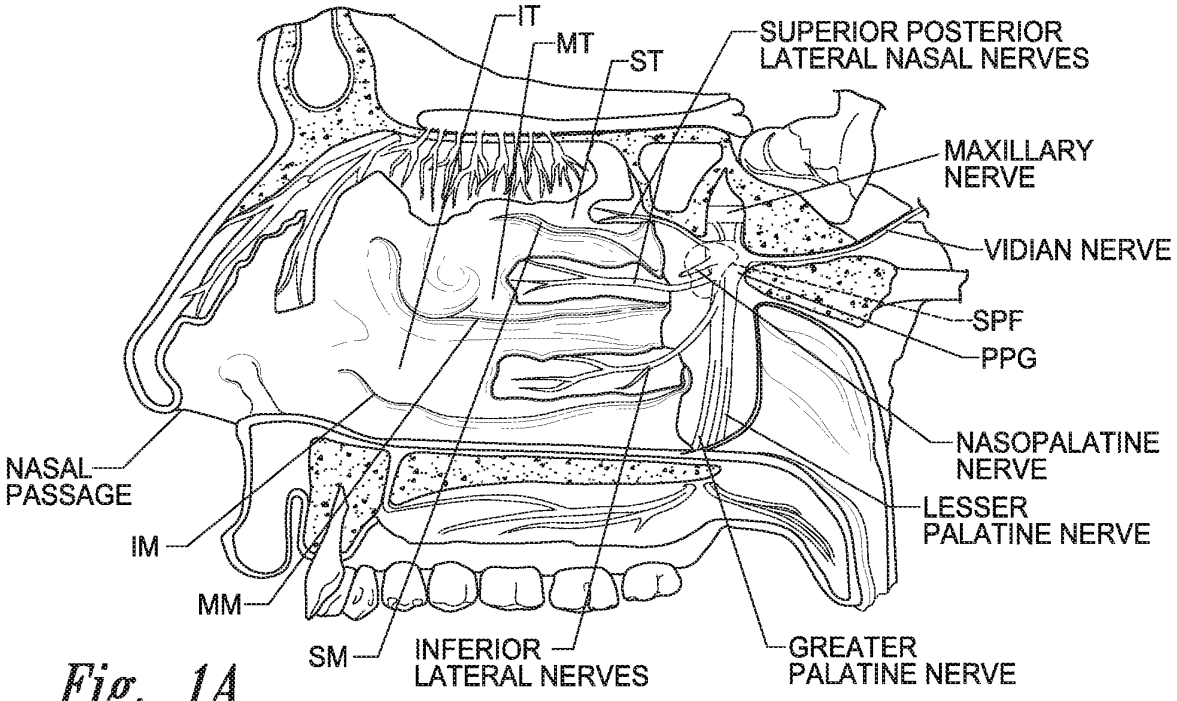

IT
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SUPERIOR POSTERIOR LATERAL NASAL NERVES
MAXILLARY NERVE
VIDIAN NERVE
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NASOPALATINE NERVE
LESSER PALATINE NERVE
NASAL PASSAGE
IM
MM
SM
INFERIOR LATERAL NERVES
GREATER PALATINE NERVE

Fig. 1A

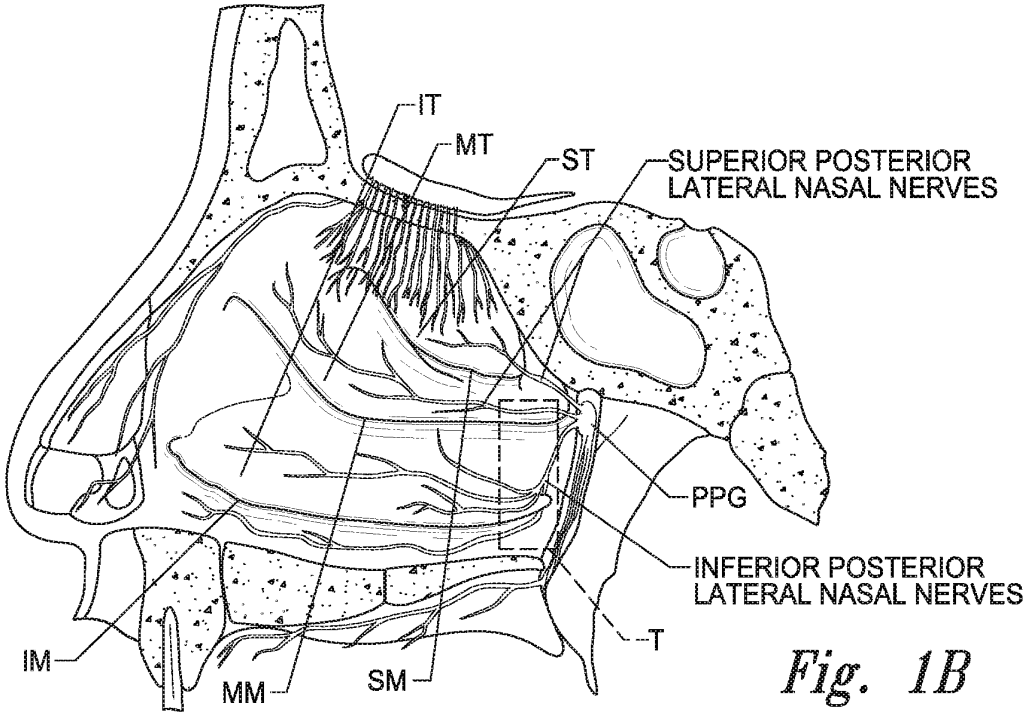

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Fig. 1B

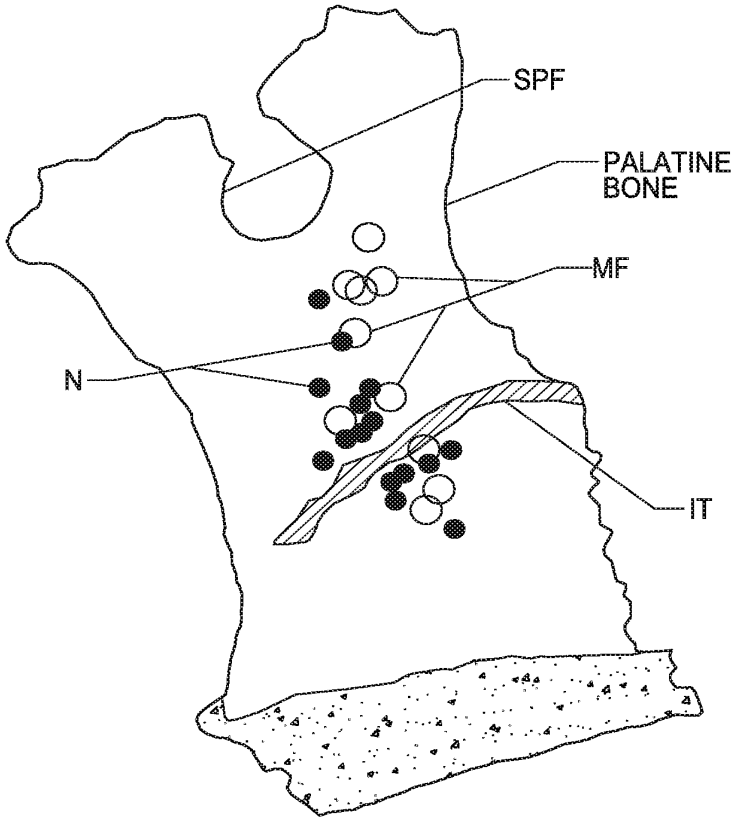


Fig. 1C

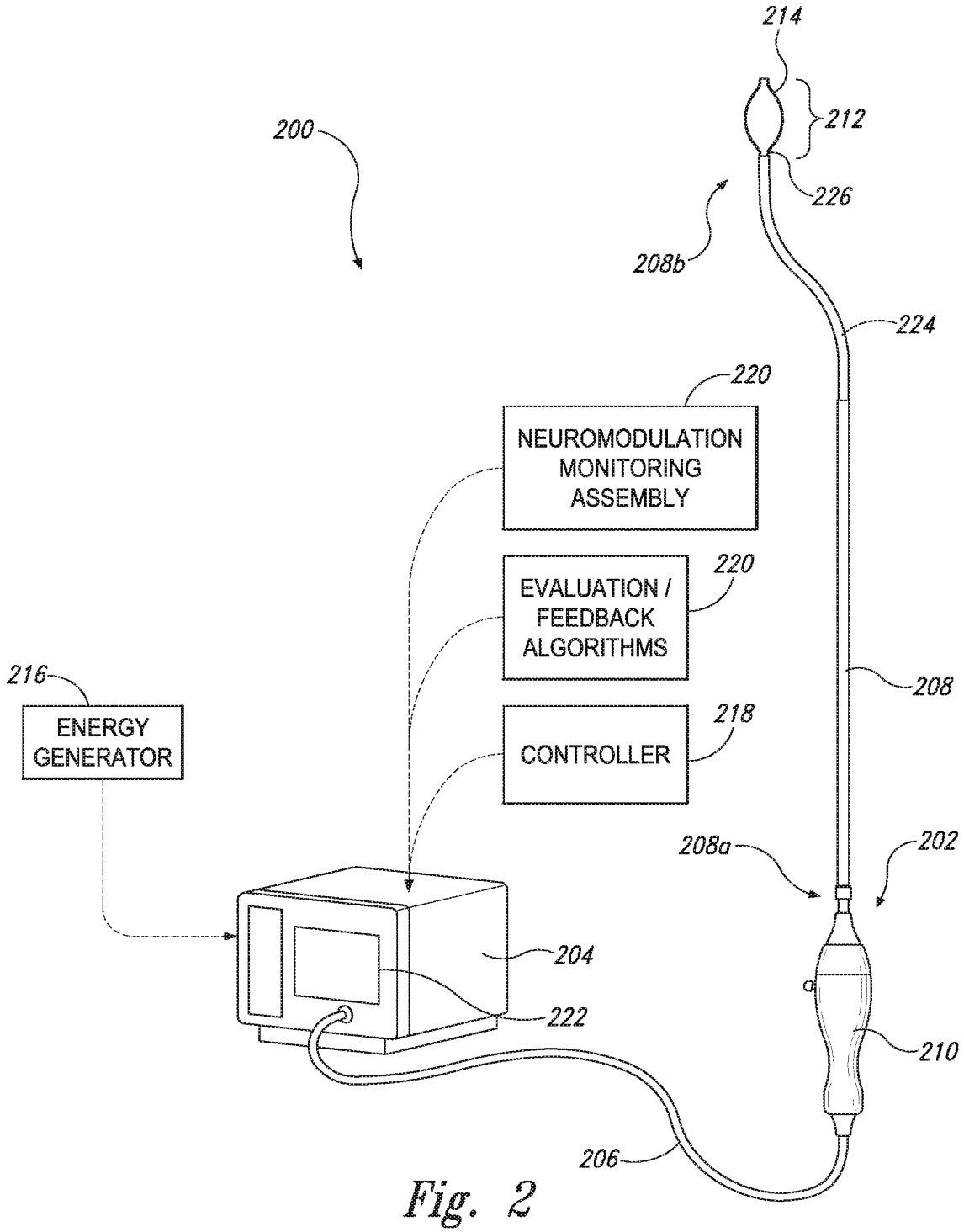

214
212
200
226
208b
224
220
NEUROMODULATION MONITORING ASSEMBLY
220
EVALUATION / FEEDBACK ALGORITHMS
208
216
ENERGY GENERATOR
218
CONTROLLER
208a
202
204
222
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206

Fig. 2

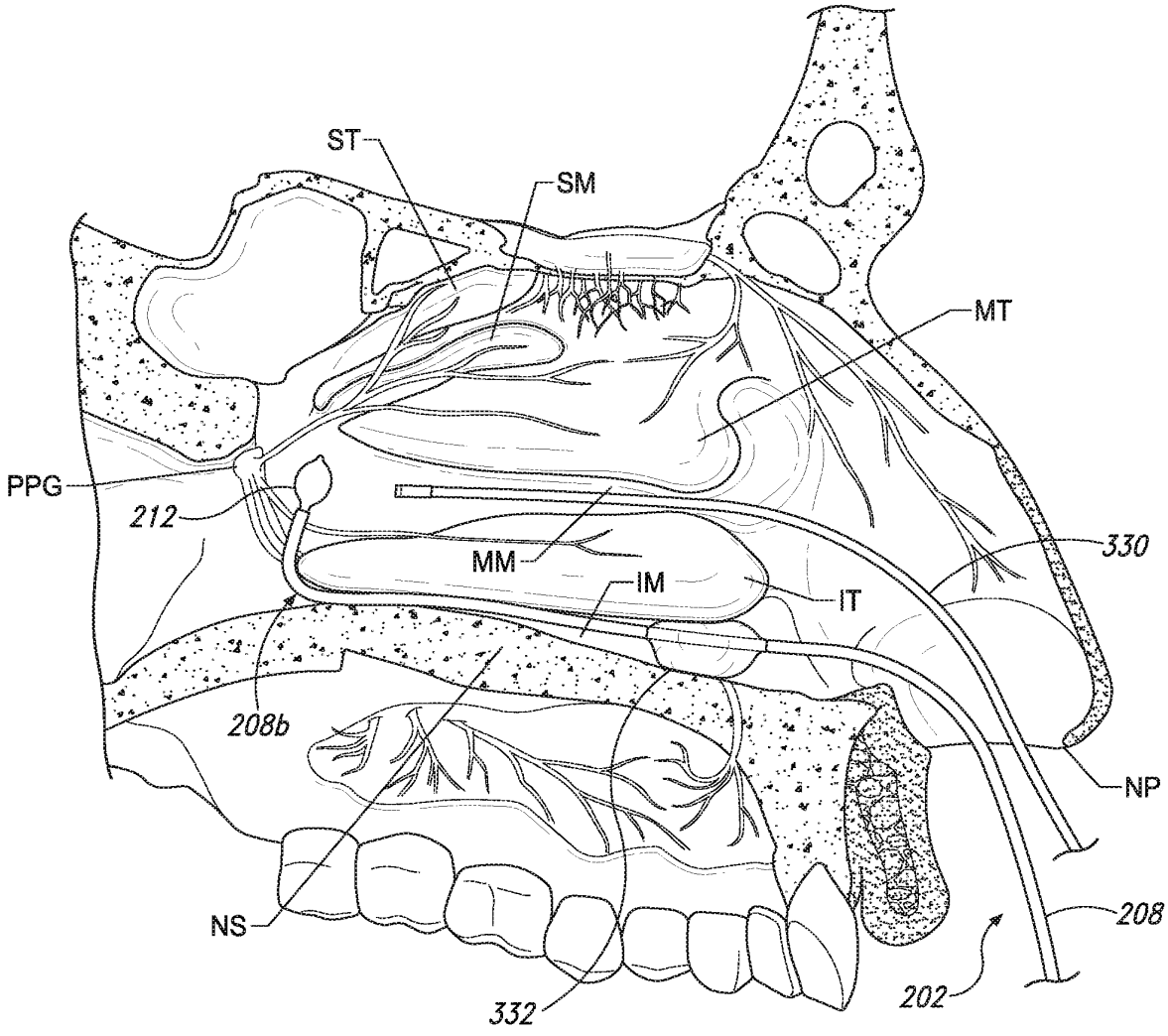


Fig. 3A

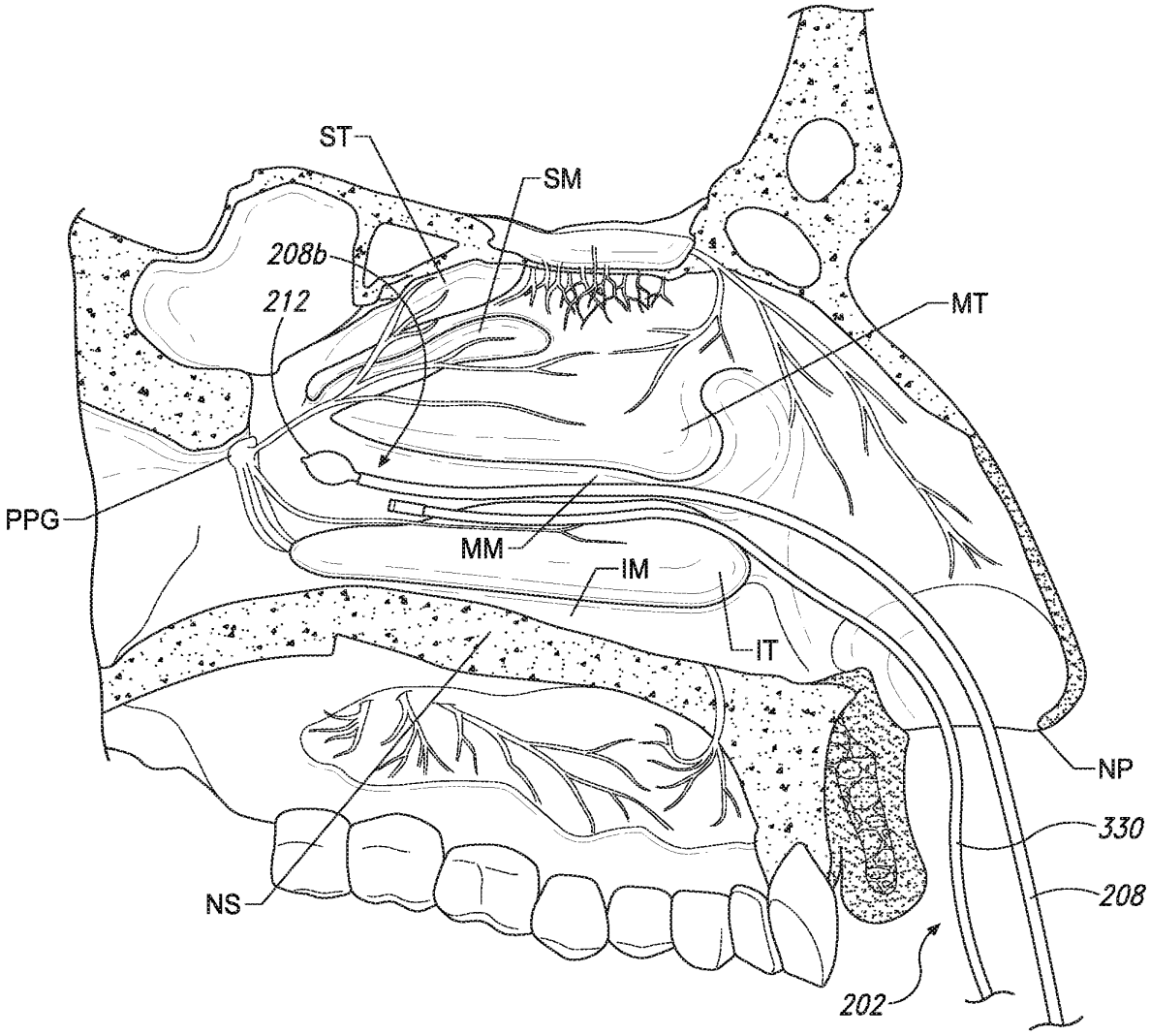


Fig. 3B

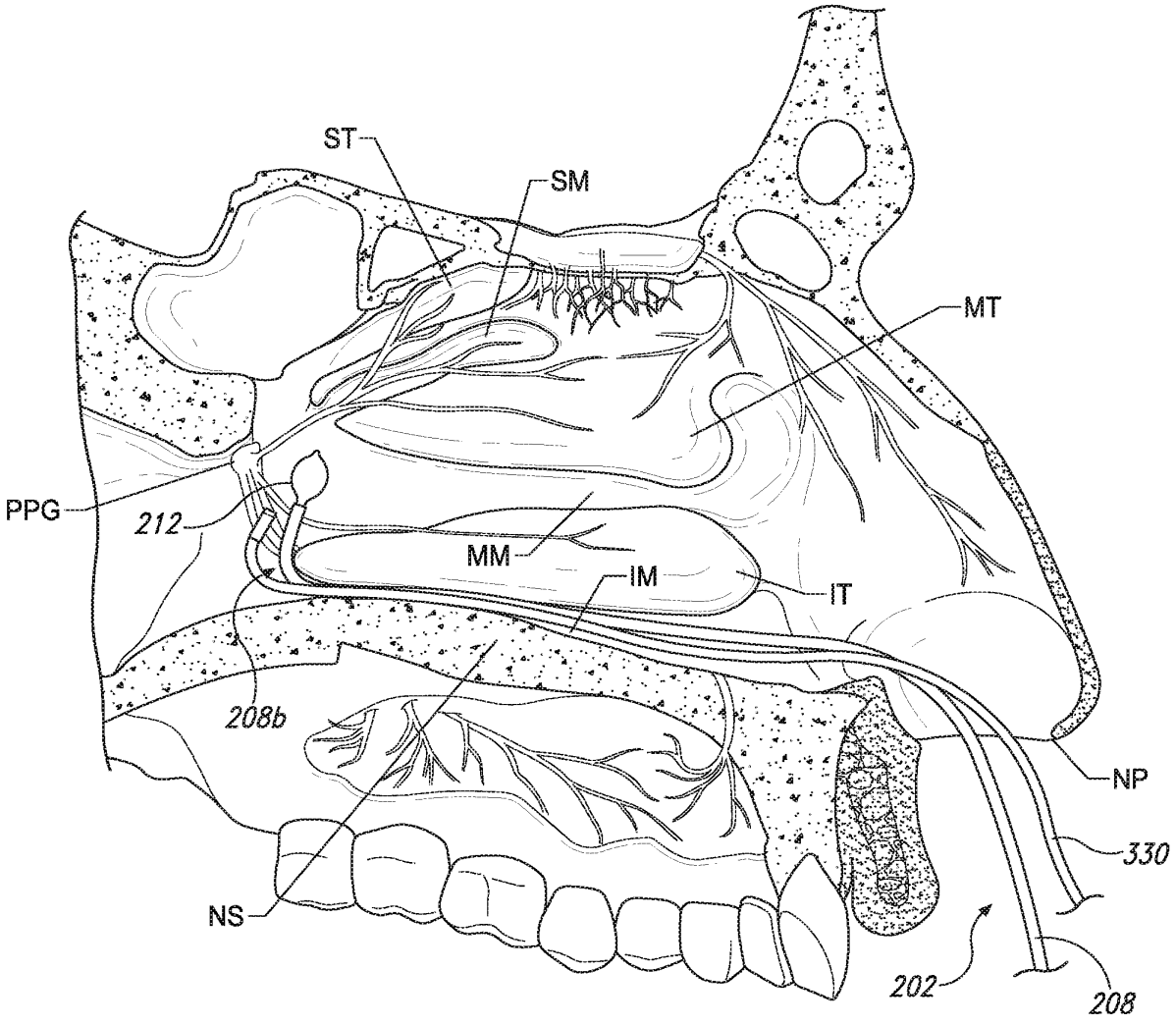


Fig. 3C

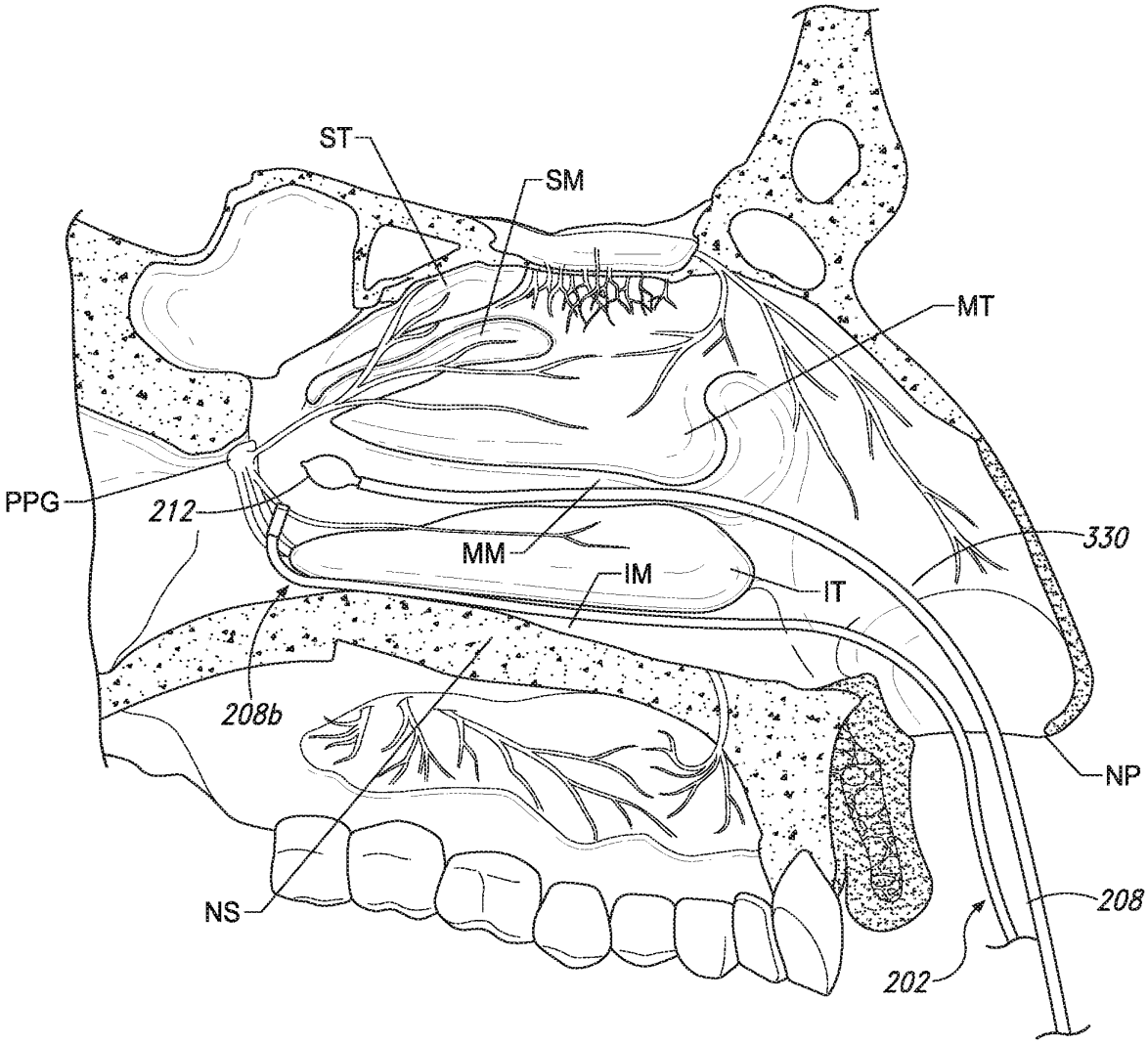


Fig. 3D

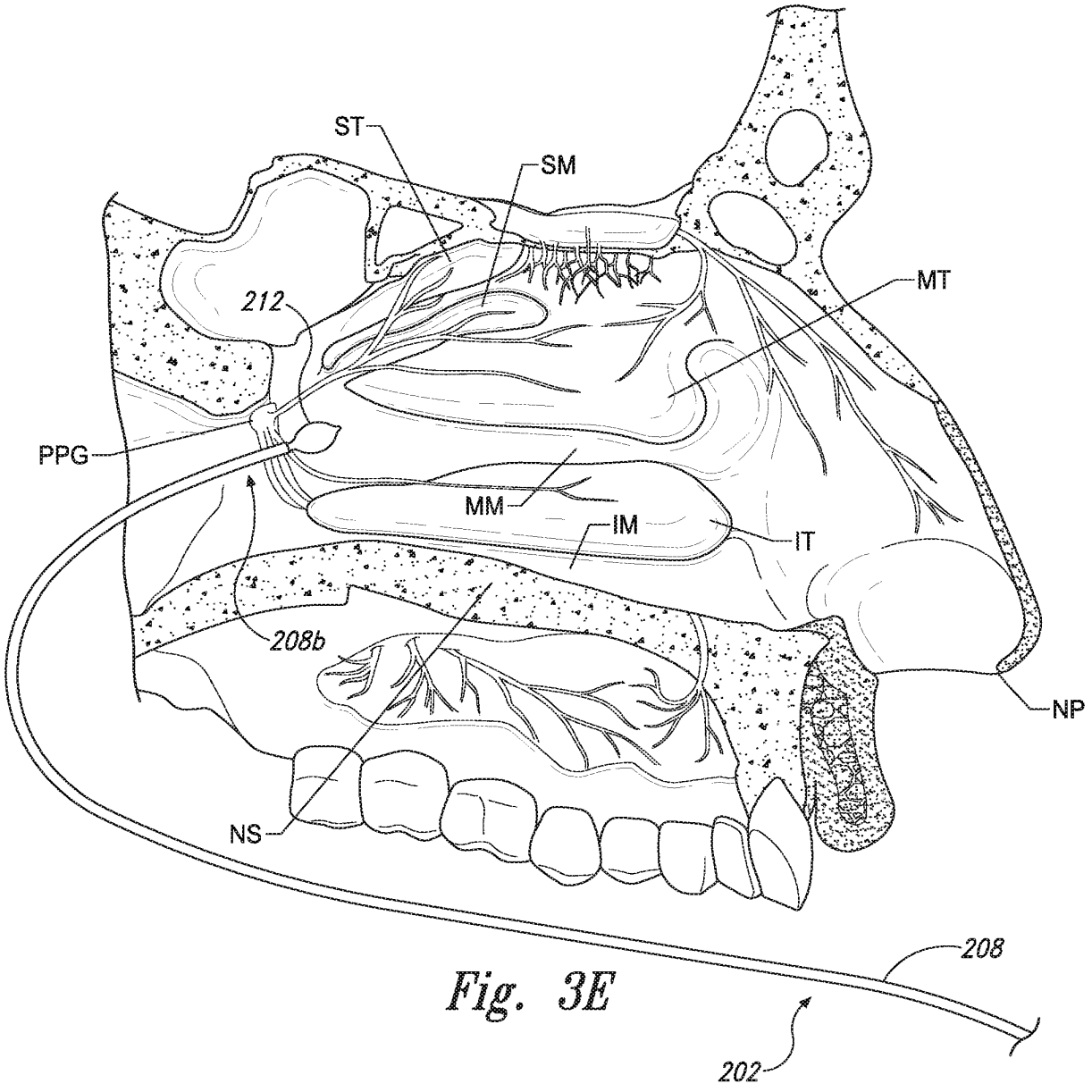


Fig. 3E

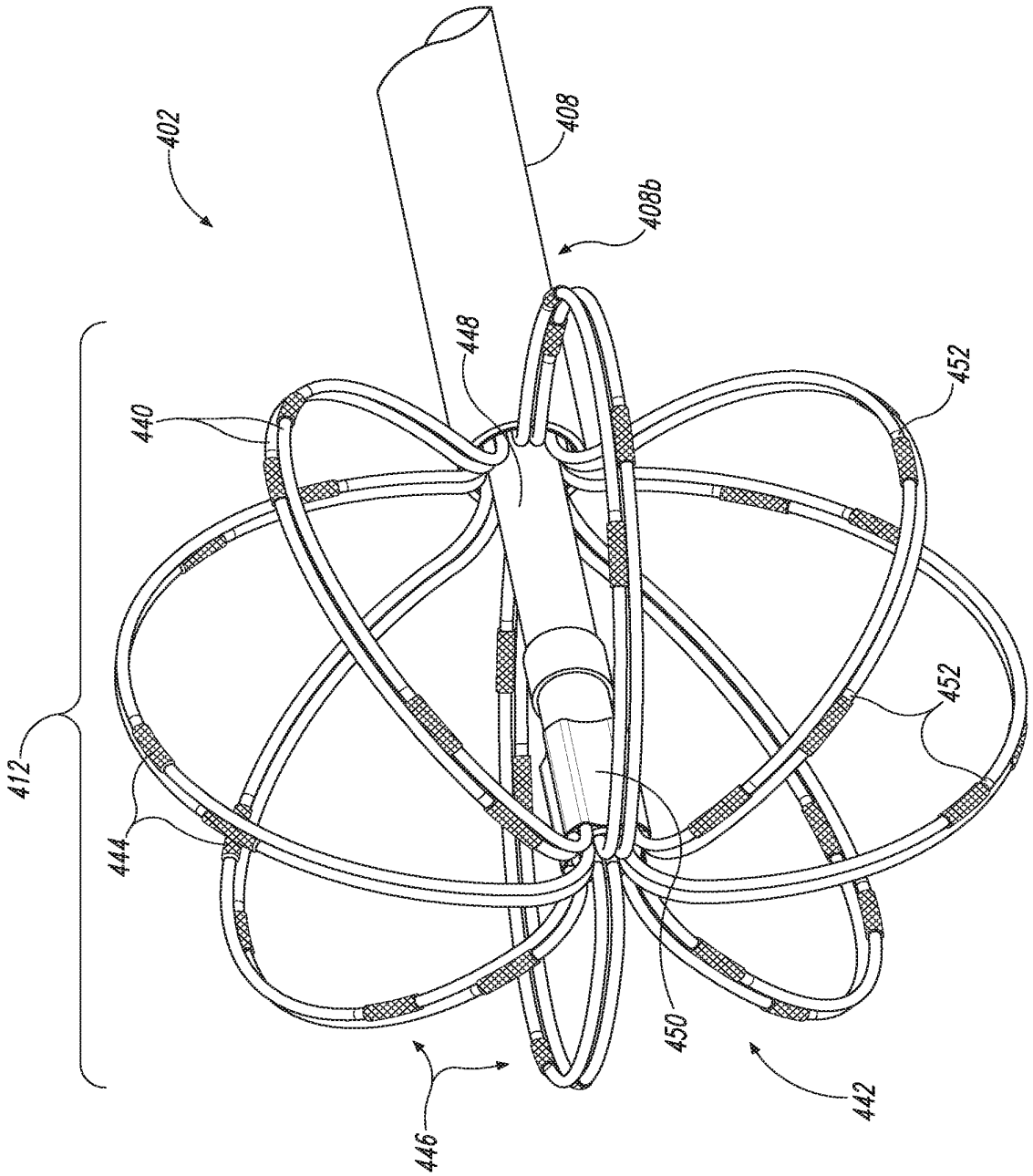


Fig. 4

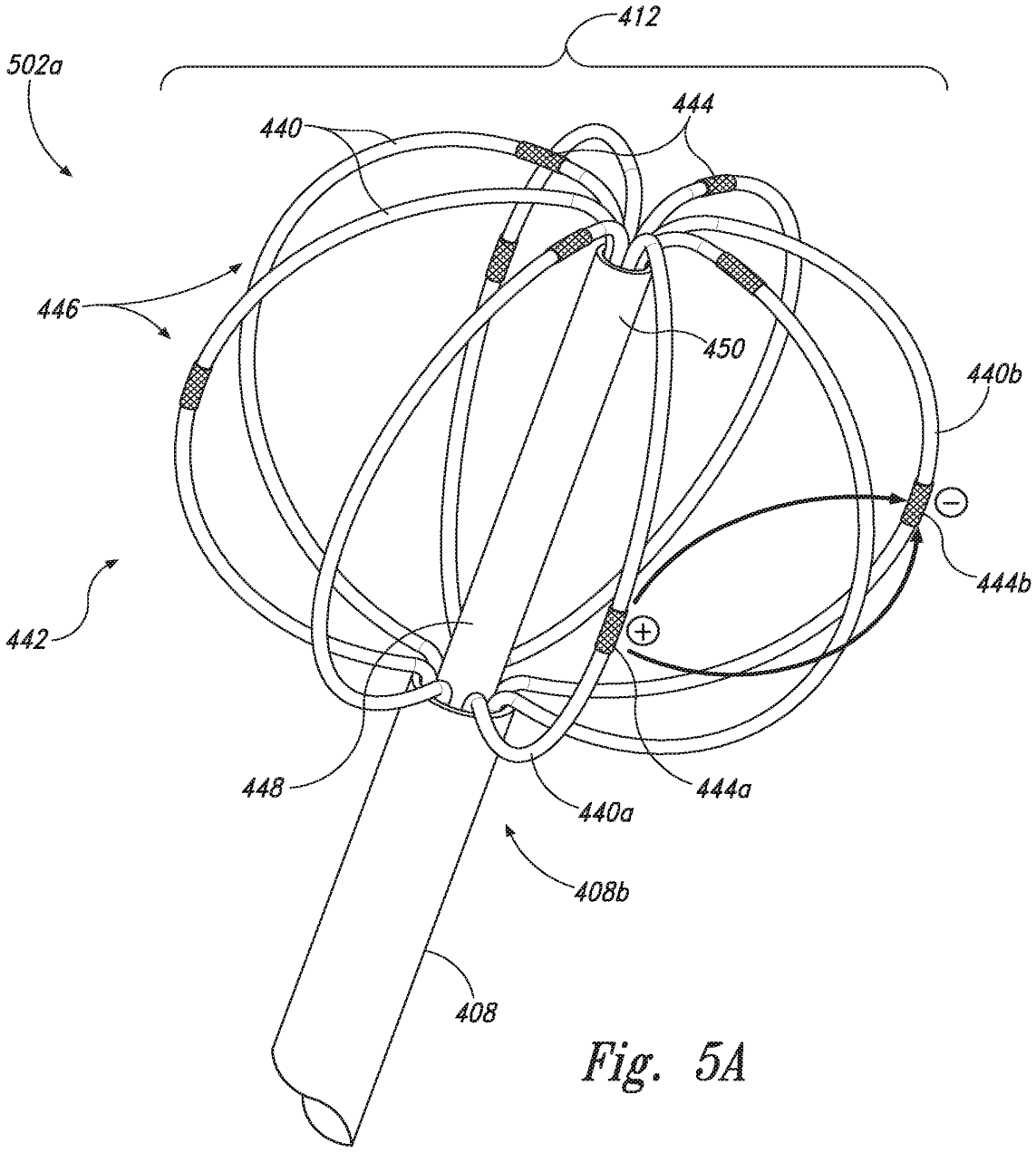


Fig. 5A

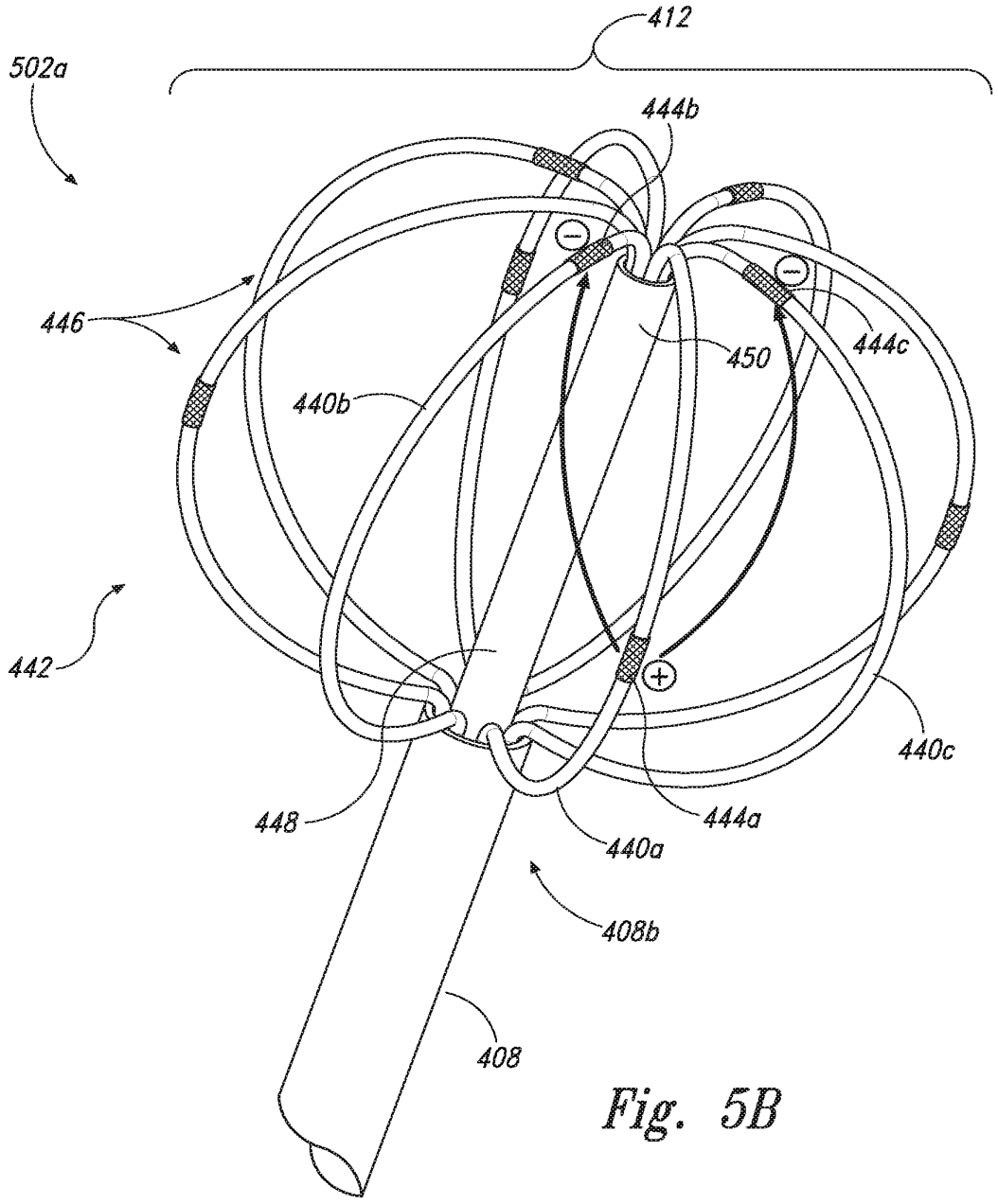

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444c
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440c
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444a
440a
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408

Fig. 5B

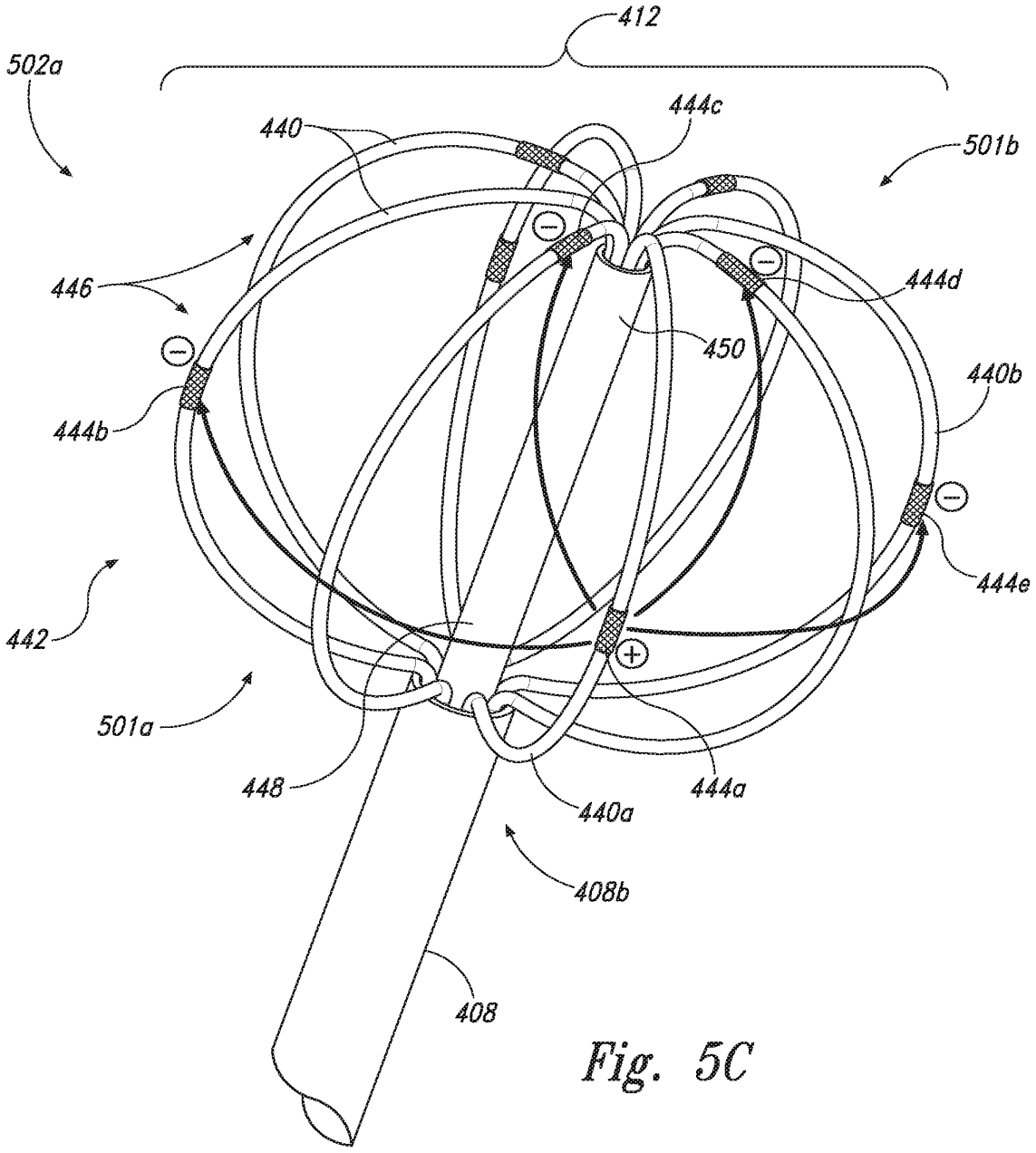

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Fig. 5C

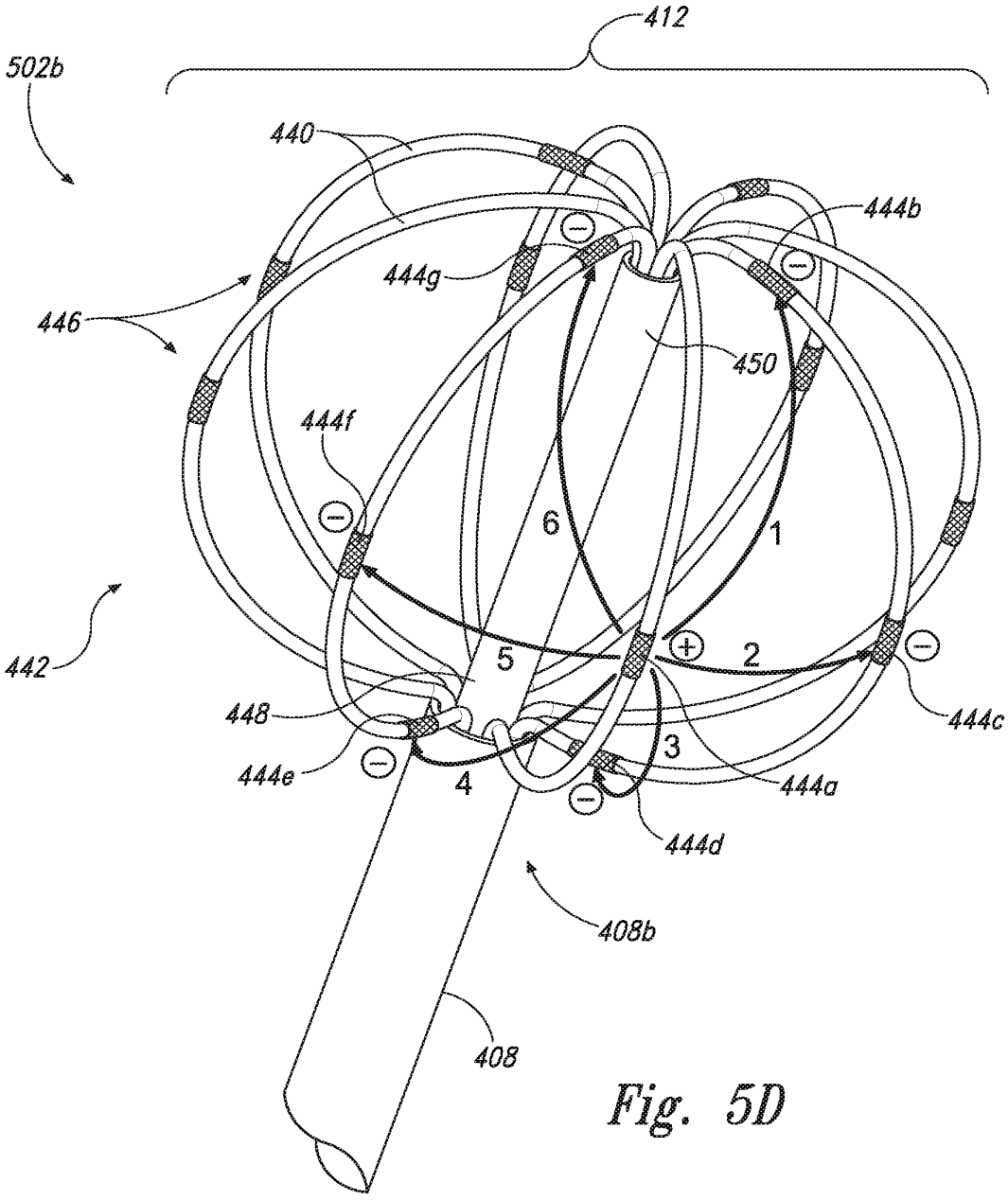

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Fig. 5D

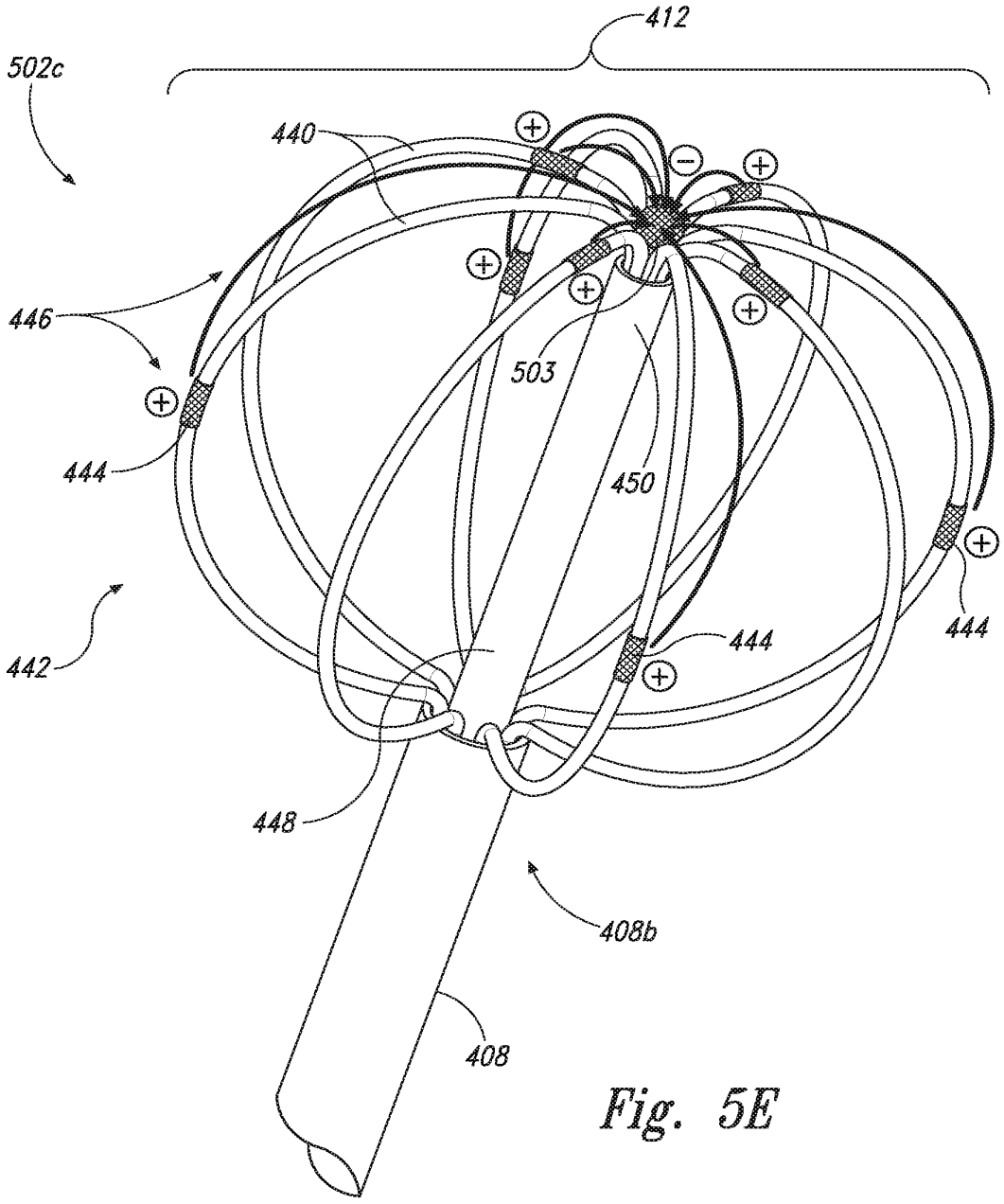


Fig. 5E

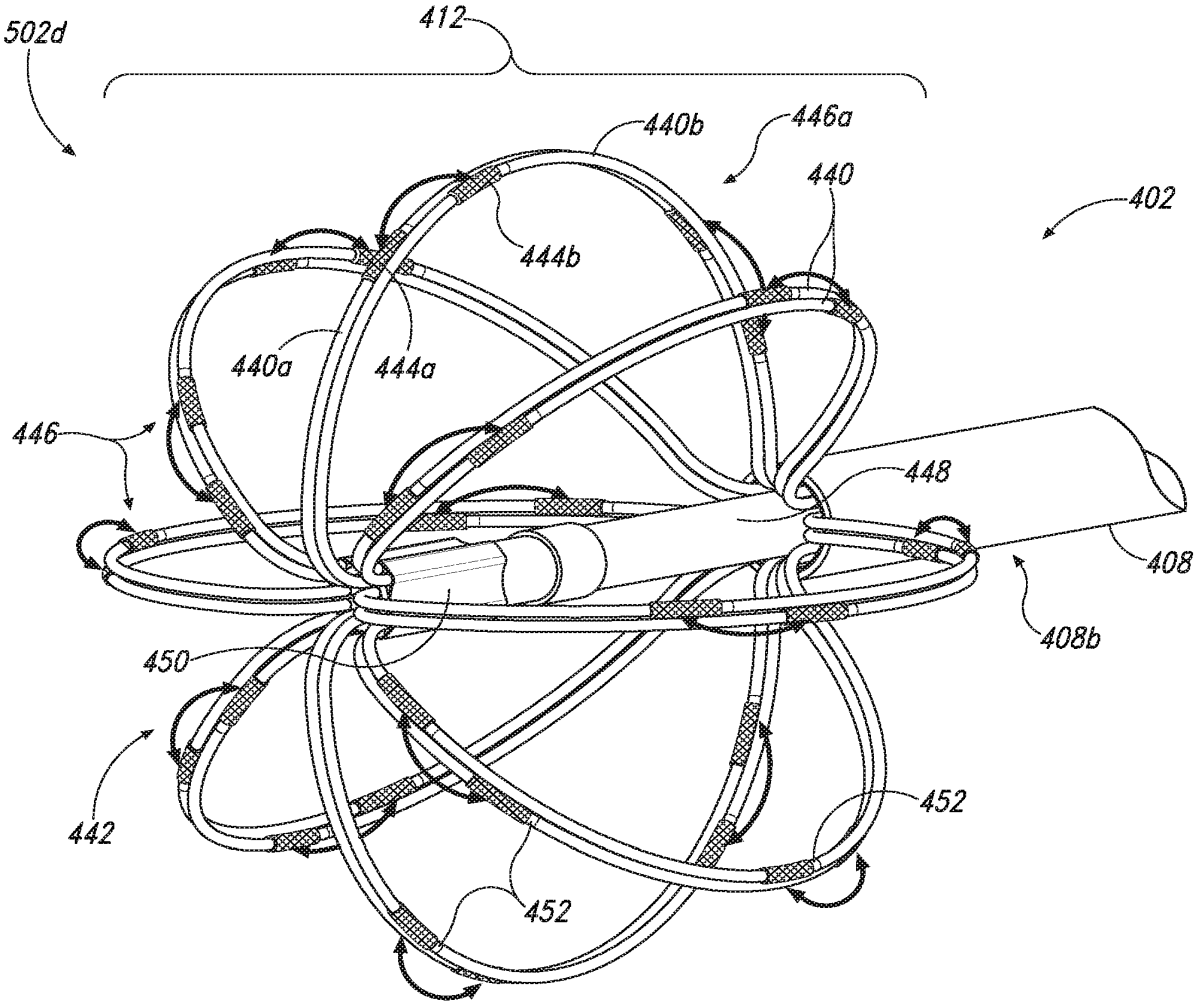

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Fig. 5F

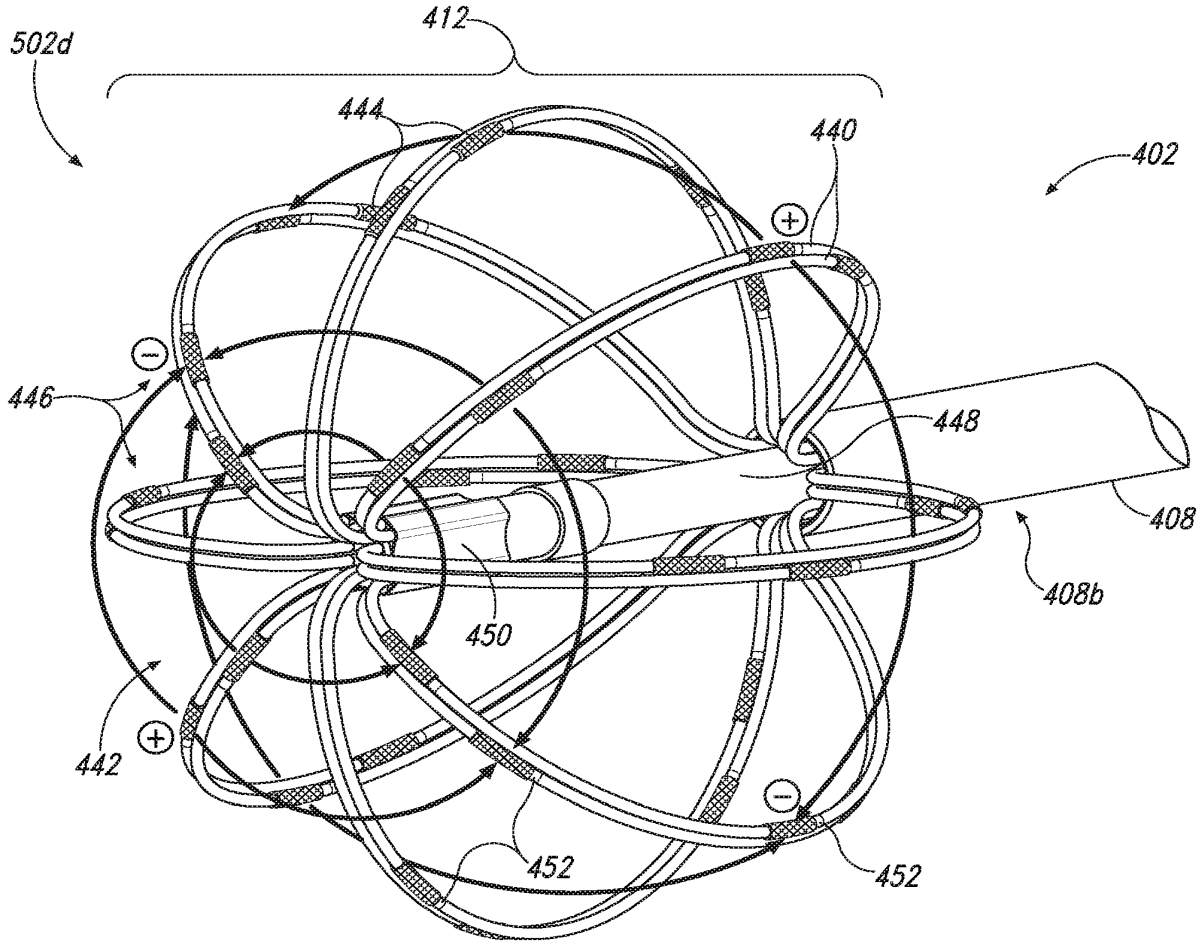


Fig. 5G

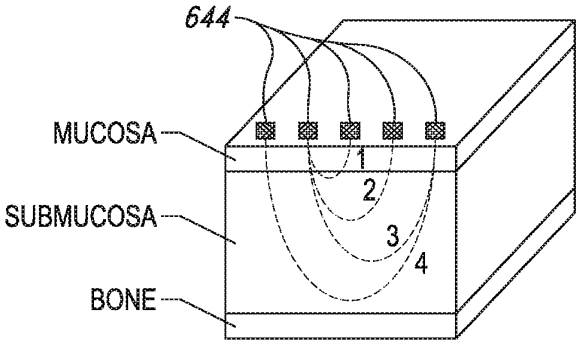


Fig. 6A

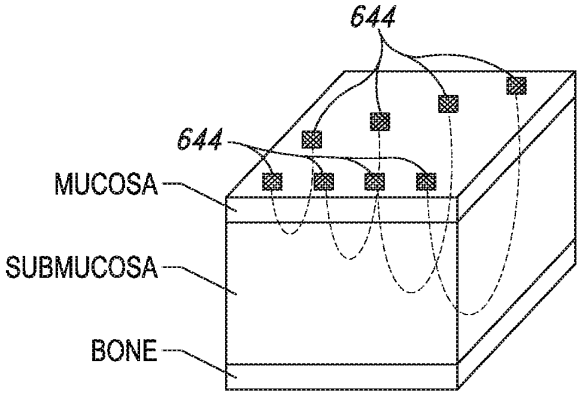


Fig. 6B

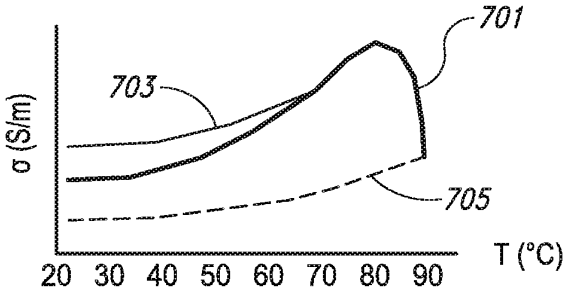


Fig. 7

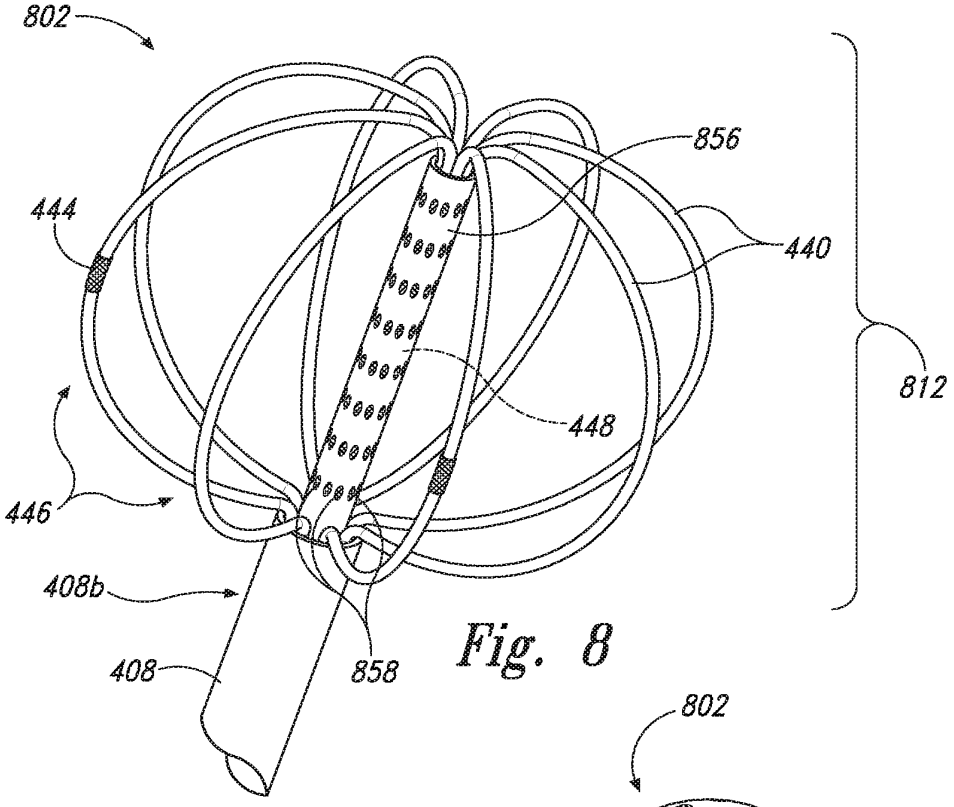

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Fig. 8

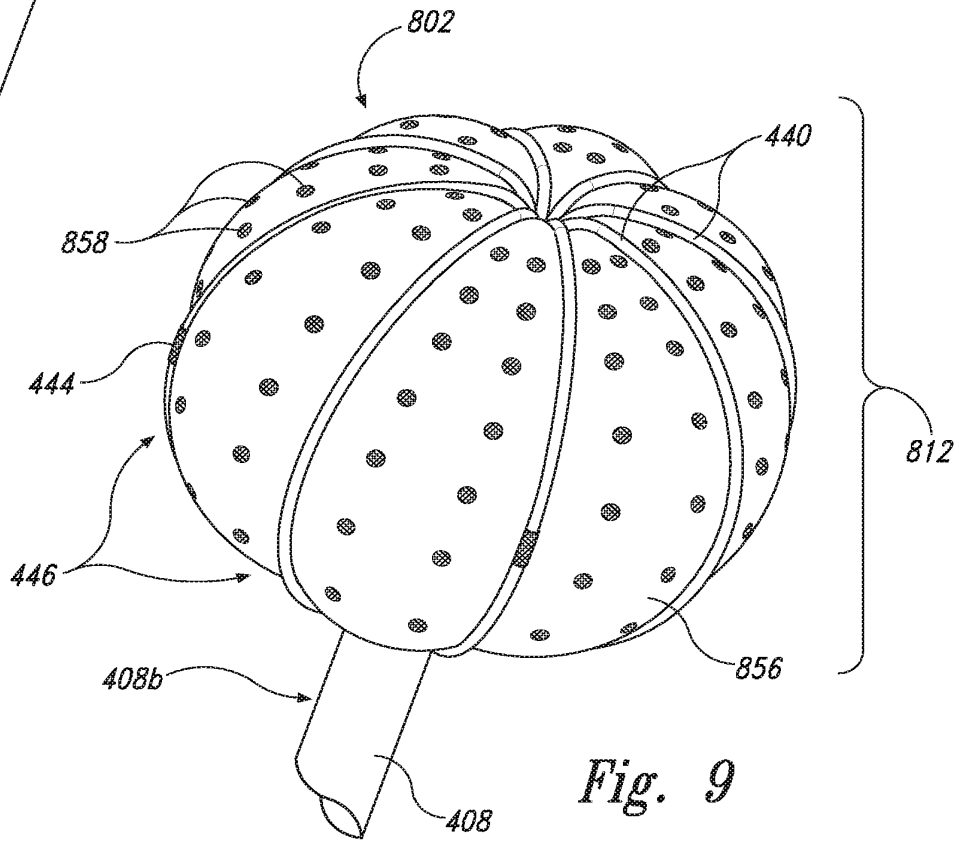

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Fig. 9

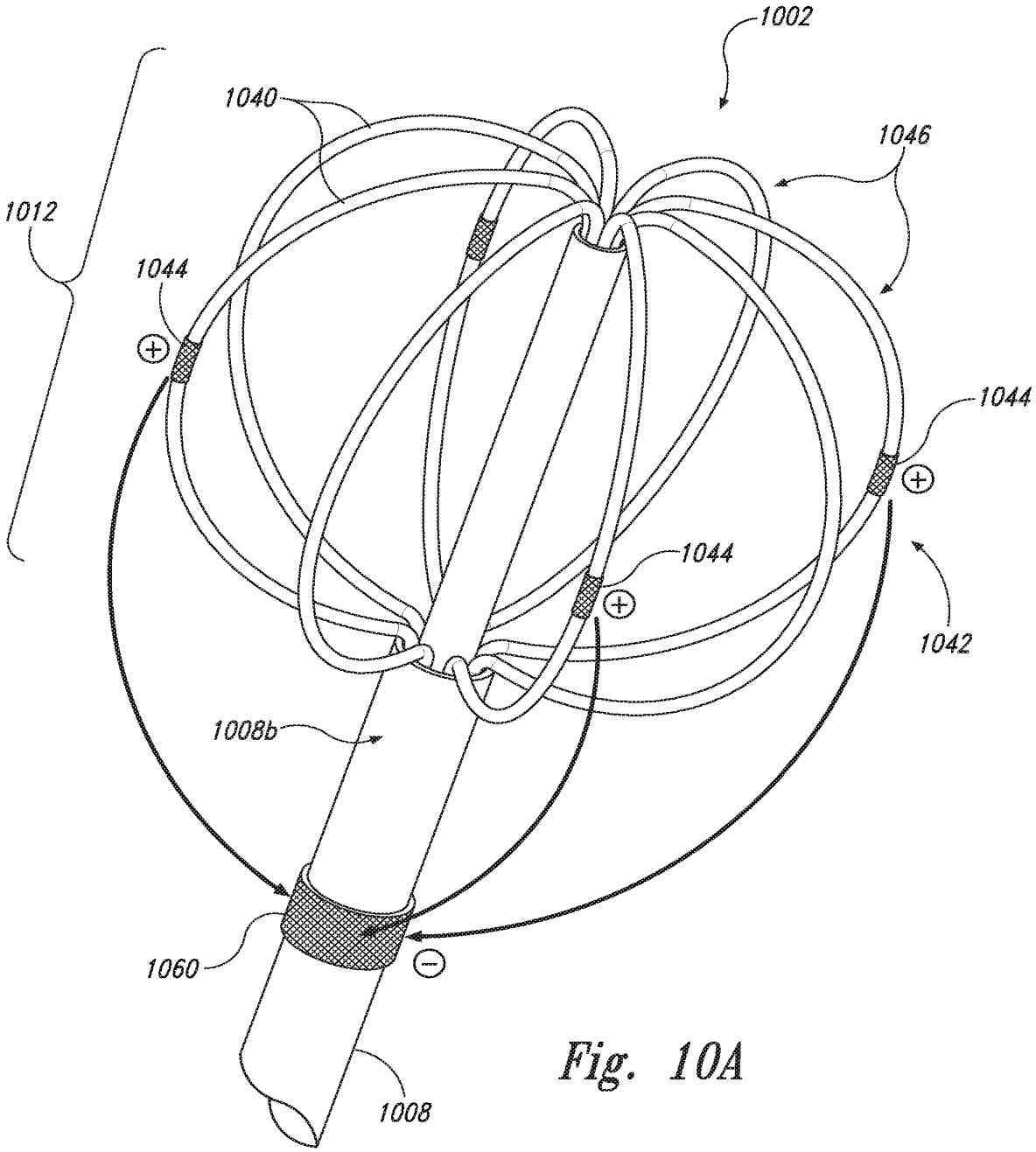


Fig. 10A

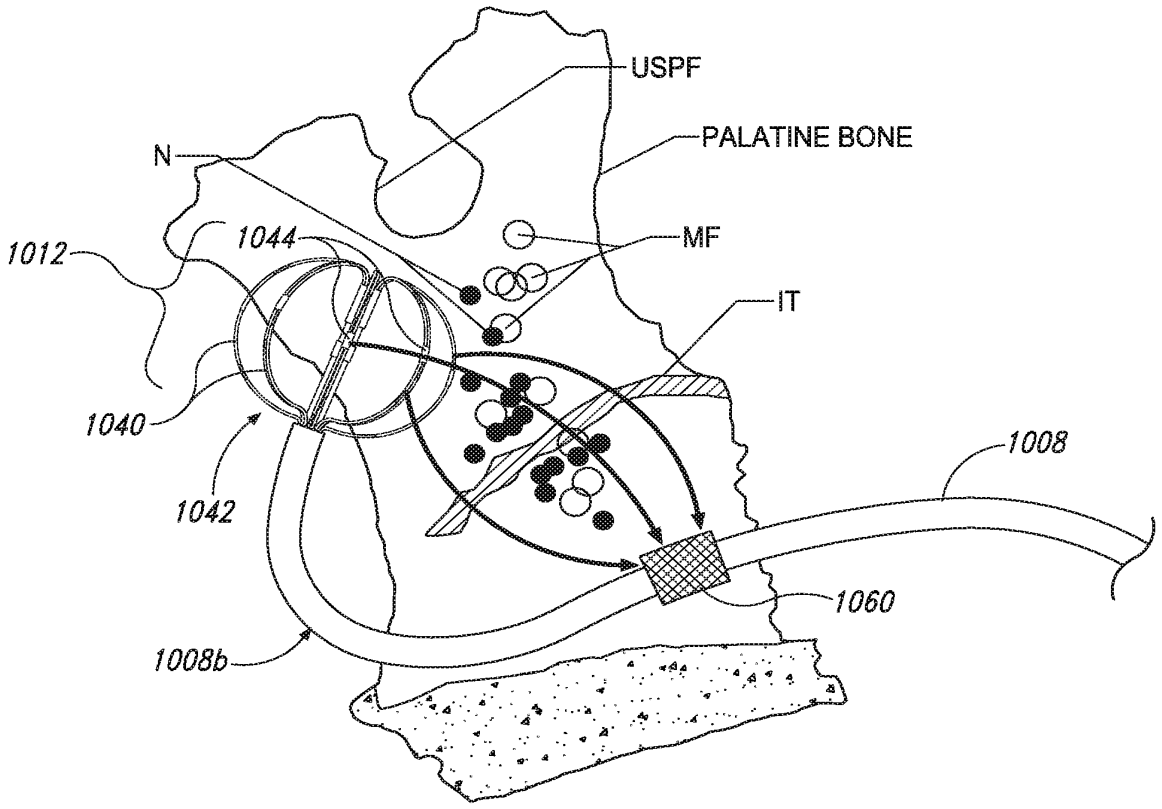

USPF
PALATINE BONE
N
1044
MF
1012
IT
1040
1008
1042
1060
1008b

Fig. 10B

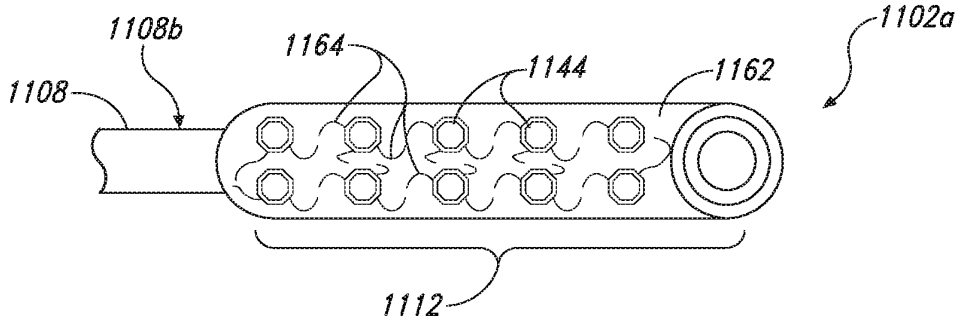


Fig. 11A

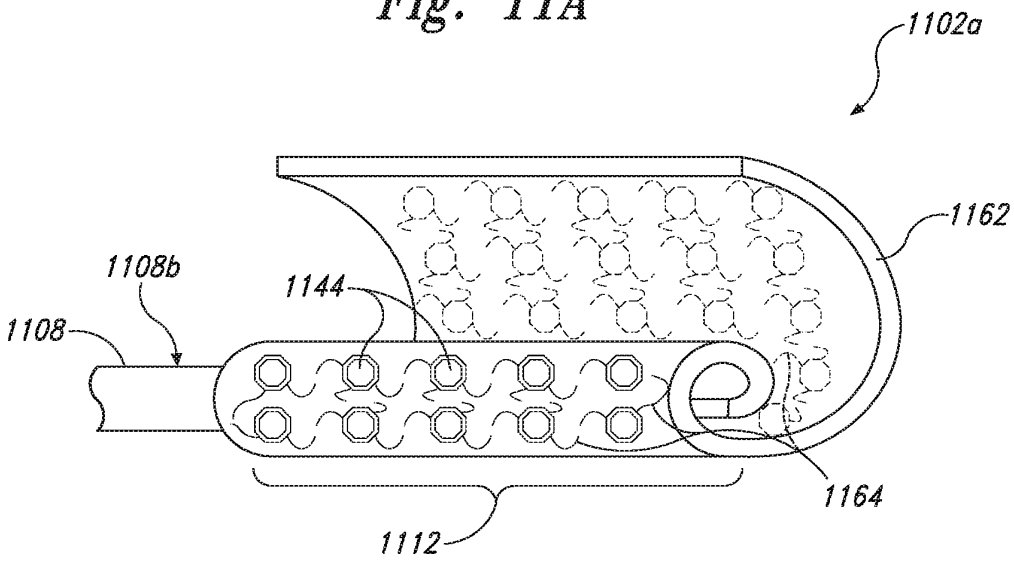


Fig. 11B

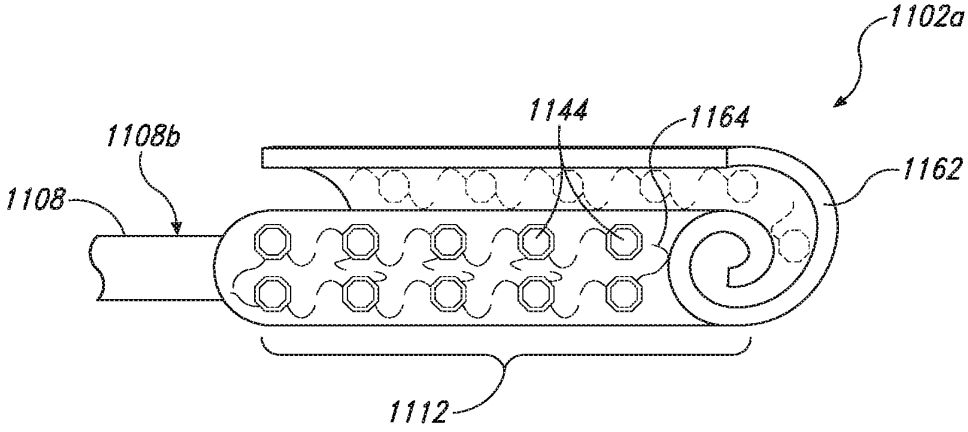


Fig. 11C

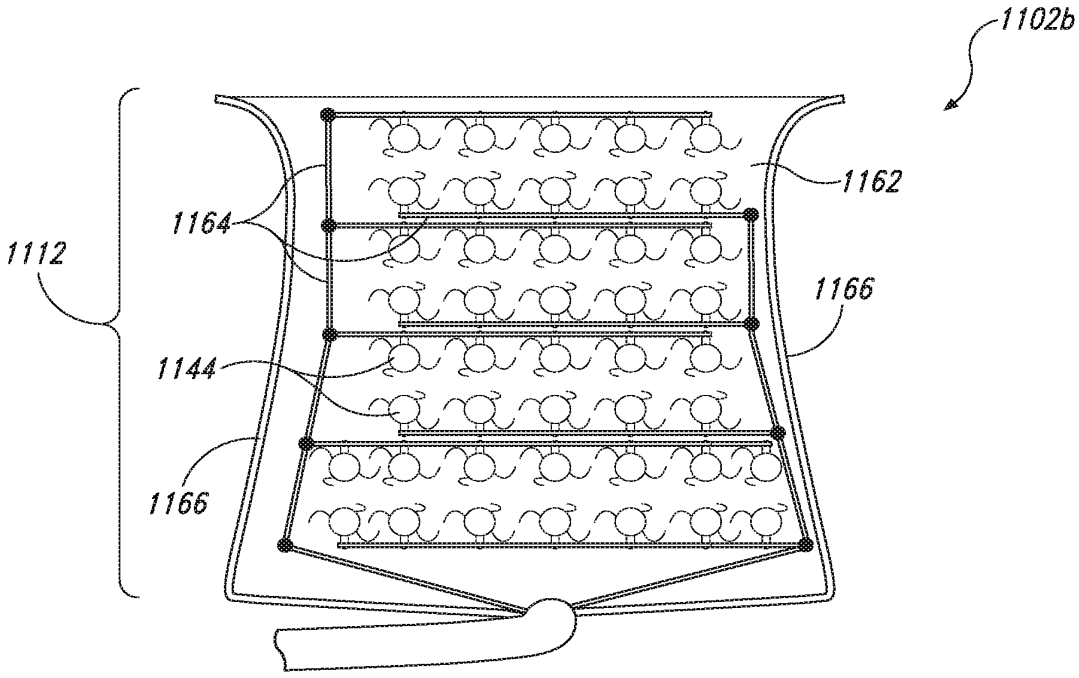


Fig. 11D

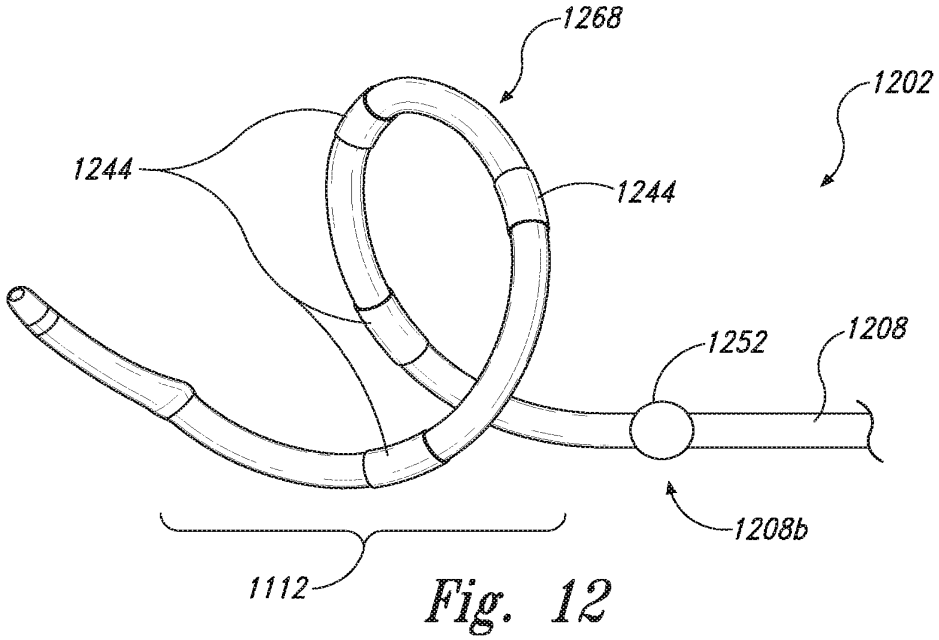


Fig. 12

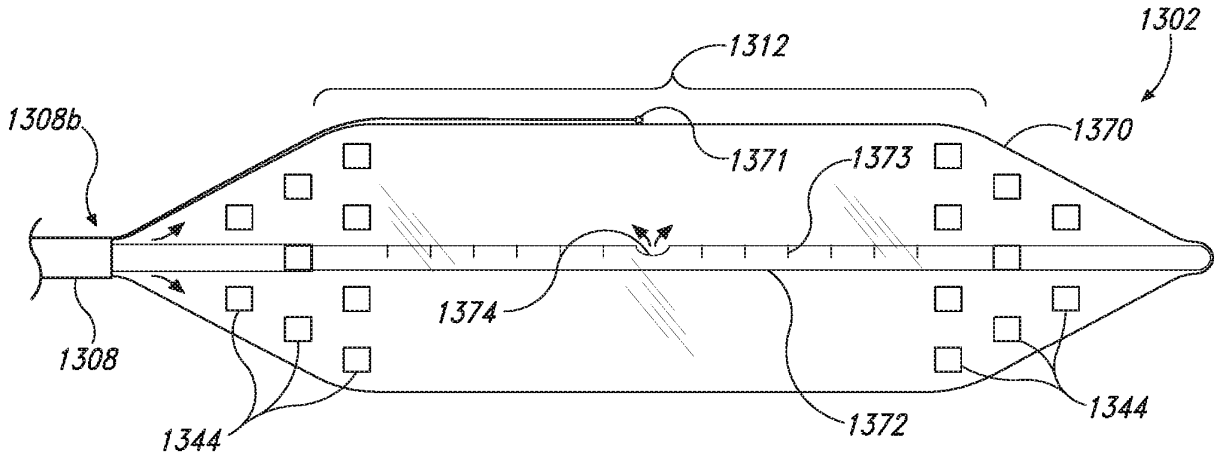

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Fig. 13

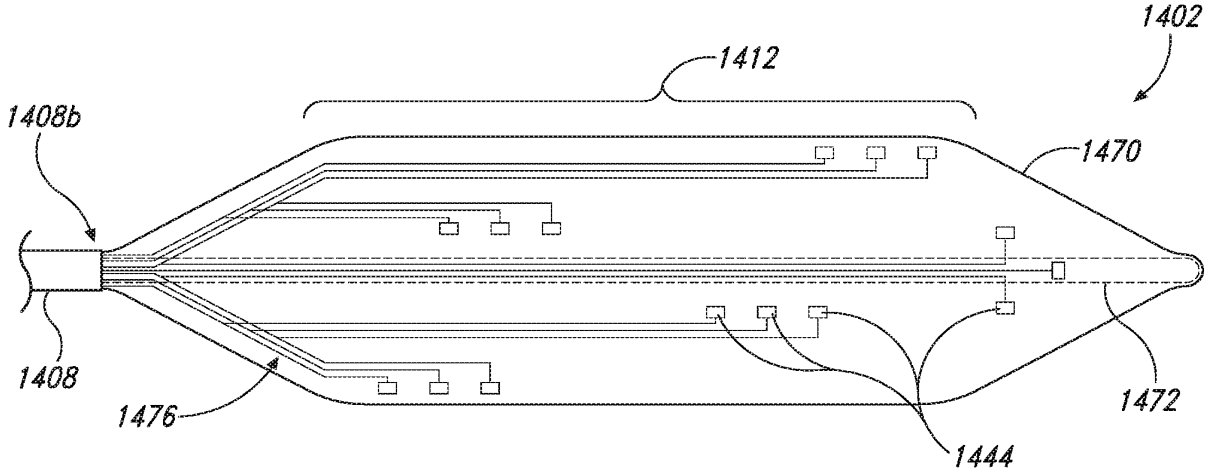

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Fig. 14

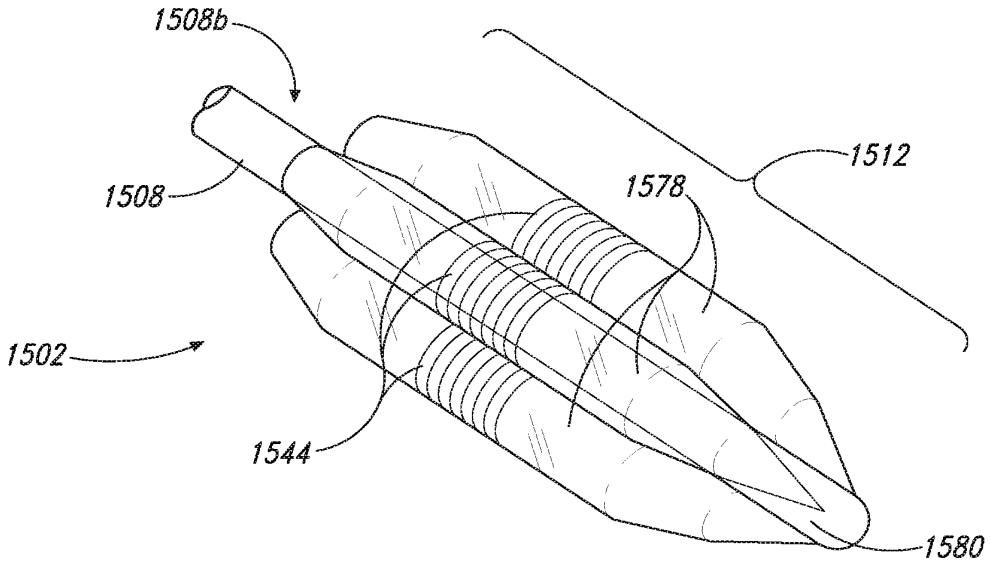

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Fig. 15

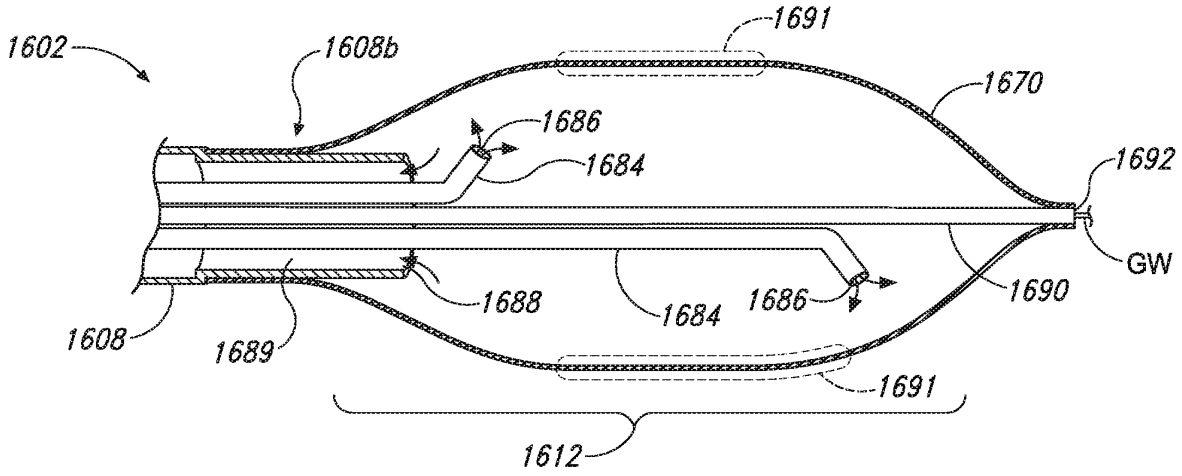

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Fig. 16

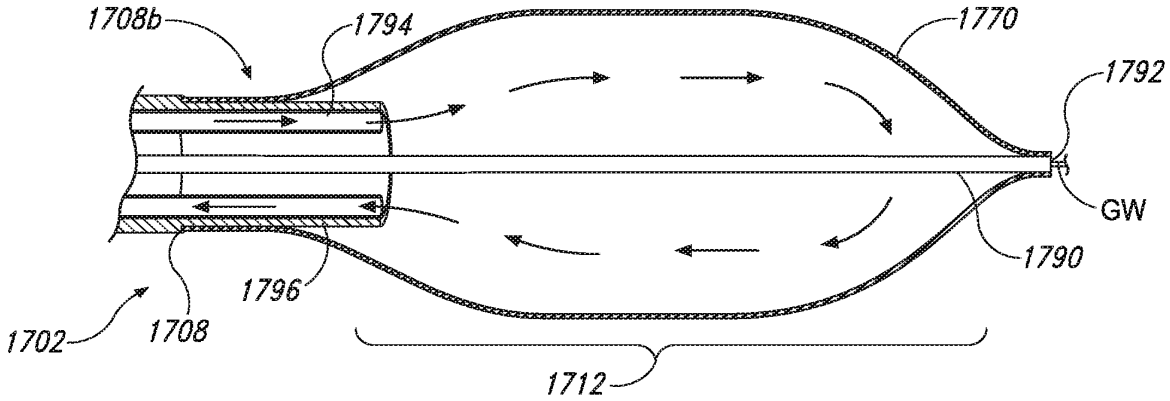

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Fig. 17

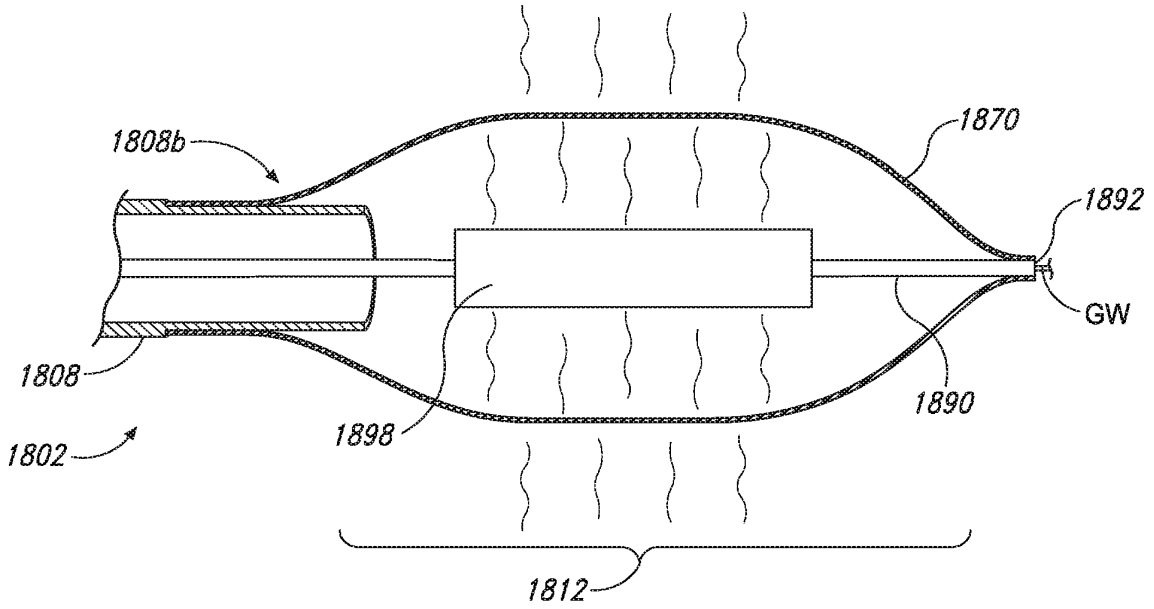

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Fig. 18

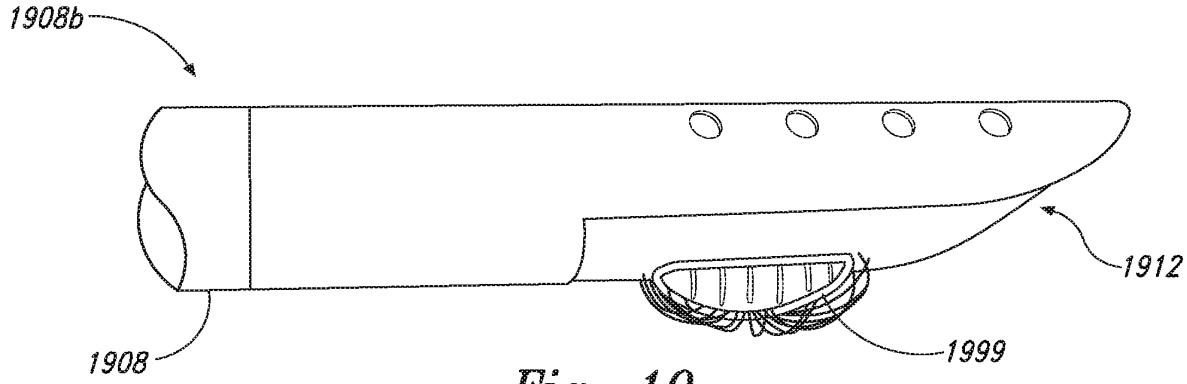

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Fig. 19

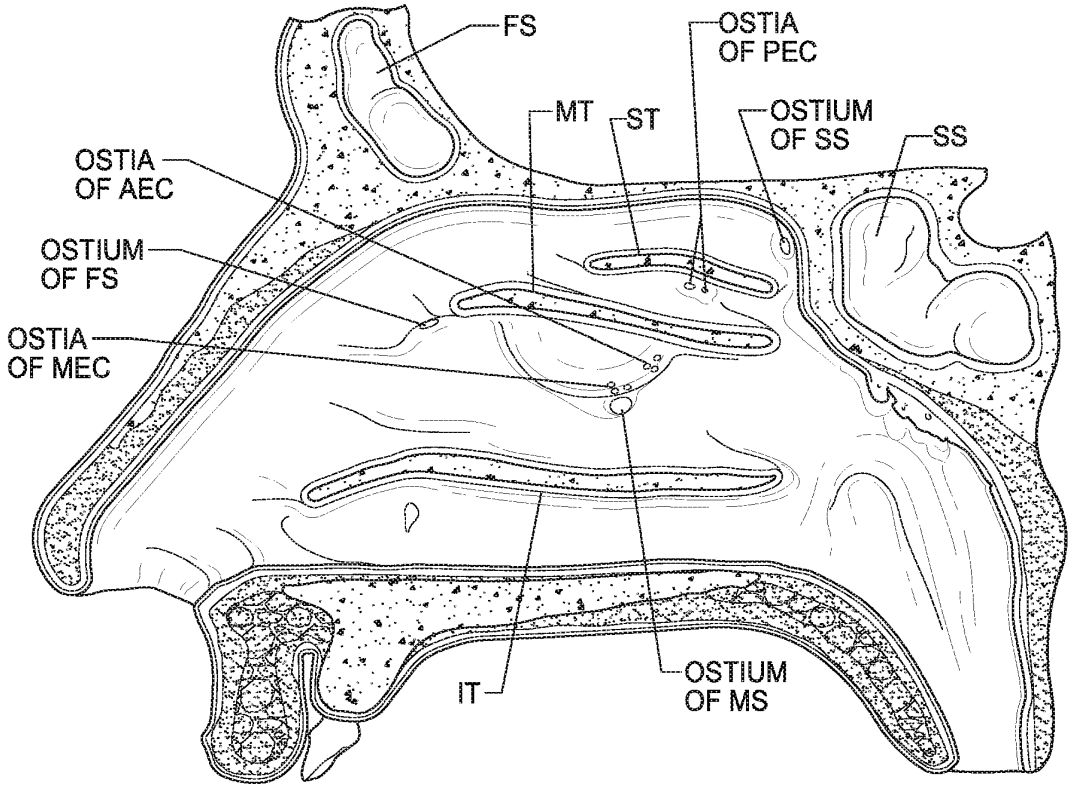

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Fig. 20

Espacenet

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DEVICES, SYSTEMS, AND METHODS FOR SPECIALIZING, MONITORING, AND/OR EVALUATING THERAPEUTIC NASAL NEUROMODULATION

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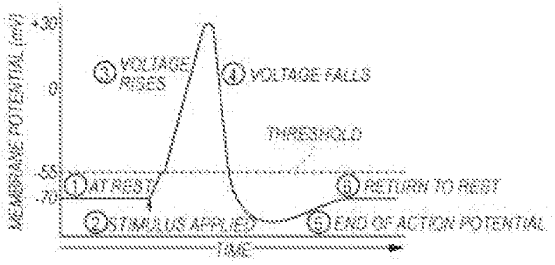
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Abstract of WO2018087601 (A1)

Devices, systems, and methods for specializing, monitoring, and/or evaluating therapeutic nasal neuromodulation are disclosed herein. A targeted neuromodulation system configured in accordance with embodiments of the present technology can include, for example, an evaluation/modulation assembly at a distal portion of a shaft and including a plurality of electrodes. The electrodes are configured to emit stimulating energy at frequencies for identifying and locating target neural structures and detect the

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Aerin Medical Inc. v. Neurent Medical Ltd.
IPR2025-01124

resultant bioelectric properties of the tissue. The system can also include a console that maps locations of the target neural structures. The evaluation/modulation assembly can then apply therapeutic neuromodulation energy in a highly tailored neuromodulation pattern based on the mapped locations of the target neural structures. Accordingly, the system provides therapeutic neuromodulation to highly specific target structures while avoiding non-target structures to reduce collateral effects.



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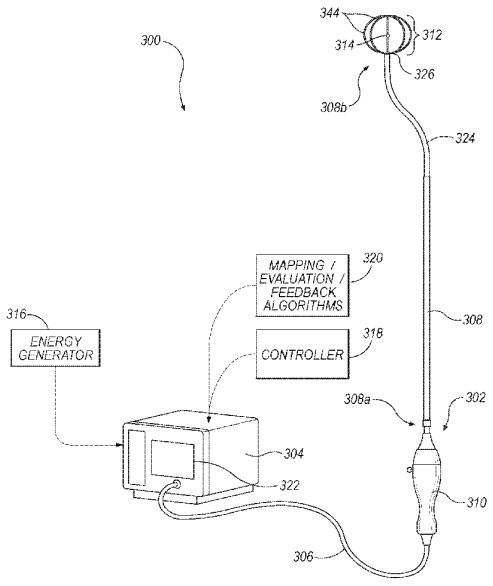


Fig. 3A

(57) Abstract: Devices, systems, and methods for specializing, monitoring, and/or evaluating therapeutic nasal neuromodulation are disclosed herein. A targeted neuromodulation system configured in accordance with embodiments of the present technology can include, for example, an evaluation/modulation assembly at a distal portion of a shaft and including a plurality of electrodes. The electrodes are configured to emit stimulating energy at frequencies for identifying and locating target neural structures and detect the resultant bioelectric properties of the tissue. The system can also include a console that maps locations of the target neural structures. The evaluation/modulation assembly can then apply therapeutic neuromodulation energy in a highly tailored neuromodulation pattern based on the mapped locations of the target neural structures. Accordingly, the system provides therapeutic neuromodulation to highly specific target structures while avoiding non-target structures to reduce collateral effects.

[Continued on next page]

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DEVICES, SYSTEMS, AND METHODS FOR SPECIALIZING, MONITORING, AND/OR EVALUATING THERAPEUTIC NASAL NEUROMODULATION

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] The present application claims priority to U.S. Provisional Patent Application No. 62/421,135, filed November 11, 2016, which is incorporated by reference herein in its entirety.

TECHNICAL FIELD

[0002] The present technology relates generally to devices, systems, and methods for mapping, monitoring, and/or evaluation of anatomical structures, including neural structures, in or associated with a nasal region of a patient. In particular, various embodiments of the present technology are related to devices, systems, and methods for specializing, monitoring, and/or evaluating therapeutic nasal neuromodulation.

BACKGROUND

[0003] Rhinosinusitis is characterized as an inflammation of the mucous membrane of the nose and refers to a group of conditions, including allergic rhinitis, non-allergic rhinitis, chronic rhinitis, chronic sinusitis, and medical resistant rhinitis. Symptoms of rhinosinusitis include nasal blockage, obstruction, congestion, nasal discharge (e.g., rhinorrhea and/or posterior nasal drip), facial pain, facial pressure, and/or reduction or loss of smell. Allergic rhinitis can include further symptoms, such as sneezing, watery rhinorrhea, nasal itching, and itchy or watery eyes. Severe rhinitis can lead to exacerbation of coexisting asthma, sleep disturbances, and impairment of daily activities. Depending on the duration and type of systems, rhinosinusitis can fall within four subtypes: acute rhinosinusitis, recurrent rhinosinusitis, chronic rhinosinusitis with nasal polyposis (i.e., soft, non-cancerous growths on the lining of the nasal passages or sinuses), and chronic rhinosinusitis without nasal polyposis. Acute rhinosinusitis refers to symptoms lasting for less than twelve weeks, whereas chronic rhinosinusitis (with and without nasal polyposis) refers to symptoms lasting longer than twelve weeks. Recurrent rhinosinusitis refers to four or more episodes of acute rhinosinusitis within a twelve-month period, with resolution of symptoms between each episode.

[0004] There are numerous environmental and biological causes of rhinosinusitis. Non-allergic rhinosinusitis, for example, can be caused by environmental irritants (e.g., exhaust fumes, cleaning solutions, latex, perfume, dust, etc.), medications (e.g., NSAIDs, oral contraceptives, blood pressure medications including ACE inhibitors, antidepressants, etc.), foods (e.g., alcoholic beverages, spicy foods, etc.), hormonal changes (e.g., pregnancy and menstruation), and/or nasal septum deviation. Triggers of allergic rhinitis can include exposure to seasonal allergens (e.g., exposure to environmental allergens at similar times each year), perennial allergens that occur any time of year (e.g., dust mites, animal dander, molds, etc.), and/or occupational allergens (e.g., certain chemicals, grains, latex, etc.).

[0005] The treatment of rhinosinusitis can include a general avoidance of rhinitis triggers, nasal irrigation with a saline solution, and/or drug therapies. Pharmaceutical agents prescribed for rhinosinusitis include, for example, oral H1 antihistamines, topical nasal H1 antihistamines, topical intranasal corticosteroids, systemic glucocorticoids, injectable corticosteroids, anti-leukotrienes, nasal or oral decongestants, topical anticholinergic, chromoglycate, and/or anti-immunoglobulin E therapies. However, these pharmaceutical agents have limited efficacy (e.g., 17% higher than placebo or less) and undesirable side effects, such as sedation, irritation, impairment to taste, sore throat, dry nose, epistaxis (i.e., nose bleeds), and/or headaches. Immunotherapy, including sublingual immunotherapy ("SLIT"), has also been used to treat allergic rhinitis by desensitizing the patient to particular allergens by repeated administration of an allergen extract. However, immunotherapy requires an elongated administration period (e.g., 3-5 years for SLIT) and may result in numerous side effects, including pain and swelling at the site of the injection, urticarial (i.e., hives), angioedema, asthma, and anaphylaxis.

[0006] Surgical interventions have also been employed in an attempt to treat patients with drug therapy resistant, severe rhinitis symptoms. In the 1960's through 1980's, surgeries were performed to sever parasympathetic nerve fibers in the vidian canal to decrease parasympathetic tone in the nasal mucosa. More recent attempts at vidian neurectomies were found to be 50-88% effective for the treatment of rhinorrhea, with other ancillary benefits including improvements in symptoms of sneezing and nasal obstruction. These symptomatic improvements have also been correlated to histologic mucosal changes with reductions in stromal edema, eosinophilic cellular infiltration, mast cell levels, and histamine concentrations in denervated mucosa. However, despite the clinical and histologic efficacy of vidian neurectomy, resecting the vidian nerve failed to gain widespread acceptance largely

due to the morbidities associated with its lack of anatomic and autonomic selectivity. For example, the site of neurectomy includes preganglionic secretomotor fibers to the lacrimal gland, and therefore the neurectomy often resulted in the loss of reflex tearing, i.e., lacrimation, which in severe cases can cause vision loss. Due to such irreversible complications, this technique was not more widely adopted. Further, due passage of postganglionic pterygopalatine fibers through the retro-orbital plexus, the position of the vidian neurectomy relative to the target end organ (i.e., the nasal mucosa) may result in re-innervation via the autonomic plexus and otic ganglion projections traveling with the accessory meningeal artery, thereby negating the clinical benefits of the neurectomy.

[0007] The complications associated with vidian neurectomies are generally attributed to the nonspecific site of autonomic denervation. Consequently, surgeons have recently shifted the site of the neurectomy to postganglionic parasympathetic rami that may have the same physiologic effect as a vidian neurectomy, while avoiding collateral injury to the lacrimal and sympathetic fibers. For example, surgeons in Japan have performed transnasal inferior turbinate submucosal resections in conjunction with resections of the posterior nasal nerves ("PNN"), which are postganglionic neural pathways located further downstream than the vidian nerve. (*See*, Kobayashi T, Hyodo M, Nakamura K, Komobuchi H, Honda N, Resection of peripheral branches of the posterior nasal nerve compared to conventional posterior neurectomy in severe allergic rhinitis. *Auris Nasus Larynx.* 2012 Feb 15;39:593-596.) The PNN neurectomies are performed at the sphenopalatine foramen, where the PNN is thought to enter the nasal region. These neurectomies are highly complex and laborious because of a lack of good surgical markers for identifying the desired posterior nasal nerves and, even if the desired nerves are located, resection of the nerves is very difficult because the nerves must be separated from the surrounding vasculature (e.g., the sphenopalatine artery).

BRIEF DESCRIPTION OF THE DRAWINGS

[0008] Many aspects of the present technology can be better understood with reference to the following drawings. The components in the drawings are not necessarily to scale. Instead, emphasis is placed on illustrating clearly the principles of the present technology. For ease of reference, throughout this disclosure identical reference numbers may be used to identify identical or at least generally similar or analogous components or features.

[0009] Figure 1 is a graph illustrating an action potential of a nerve.

[0010] Figure 2A is a graph illustrating neural cell membrane potential in relation to the opening of various ion channels opening, and Figure 2B is a graph illustrating relative neural cell membrane permeability.

[0011] Figure 3A is a partially schematic view of a neuromodulation and mapping system configured in accordance with embodiments of the present technology.

[0012] Figure 3B is an enlarged isometric view of a distal portion of a neuromodulation and mapping device of the neuromodulation and mapping system of Figure 3A configured in accordance with embodiments of the present technology.

[0013] Figures 4A-4C are three dimensional views of projected electrode ablation patterns of a neuromodulation device configured in accordance with embodiments of the present technology.

[0014] Figure 5 is an illustration of a projected neuromodulation zone in relation to anatomical structures in a zone of interest in accordance with embodiments of the present technology.

[0015] Figure 6 is an illustration of neural mapping configured in accordance with embodiments of the present technology.

[0016] Figure 7 is a block diagram illustrating a method of anatomical mapping and therapeutic neuromodulation in accordance with embodiments of the present technology.

[0017] Figures 8A and 8B are enlarged isometric views of a distal portion of a neuromodulation and mapping device configured in accordance with some embodiments of the present technology.

[0018] Figure 9 is an enlarged isometric view of a distal portion of a neuromodulation and mapping device configured in accordance with some embodiments of the present technology.

DETAILED DESCRIPTION

[0019] The devices, systems, and methods of the present technology are configured to determine one or more physiological parameters before, during, and/or after therapeutic nasal neuromodulation for (1) identifying a treatment location, (2) tailoring the treatment to a particular patient's anatomy and/or physiology, (3) adjusting ongoing treatment in real-time, and/or (4) evaluating treatment efficacy. The targeted neural ablation provided by the

systems and methods described herein are expected to enhance the efficacy of the neuromodulation therapy and avoid undesired collateral effects. In several embodiments, the devices, systems, and methods disclosed herein are configured to measure the functional/pathophysiological-specific electric, and/or dielectric properties (i.e., bioelectrical properties or parameters) of shallow heterogeneous tissue, individual cellular components, and/or constituents therein on a high resolution spatial grid.

[0020] Specific details of several embodiments of the present technology are described herein with reference to Figures 1-9. Although many of the embodiments are described with respect to devices, systems, and methods for mapping, evaluating, and therapeutically modulating neural structures in the nasal region for the treatment of rhinitis, other applications and other embodiments in addition to those described herein are within the scope of the present technology. For example, at least some embodiments of the present technology may be useful for neural mapping and evaluation at other anatomical sites and/or the treatment of other indications (e.g., chronic sinusitis and epistaxis). It should be noted that other embodiments in addition to those disclosed herein are within the scope of the present technology. Further, embodiments of the present technology can have different configurations, components, and/or procedures than those shown or described herein. Moreover, a person of ordinary skill in the art will understand that embodiments of the present technology can have configurations, components, and/or procedures in addition to those shown or described herein and that these and other embodiments can be without several of the configurations, components, and/or procedures shown or described herein without deviating from the present technology. The headings provided herein are for convenience only and should not be construed as limiting the subject matter disclosed.

Definitions

[0021] As used herein, the terms "distal" and "proximal" define a position or direction with respect to a clinician or a clinician's control device (e.g., a handle of a neuromodulation catheter). The terms, "distal" and "distally" refer to a position distant from or in a direction away from a clinician or a clinician's control device along the length of device. The terms "proximal" and "proximally" refer to a position near or in a direction toward a clinician or a clinician's control device along the length of device.

[0022] As used herein, "physiological parameters" refer to, at least in part, one or more of the following: cellular composition, tissue type, anatomical landscape, bioelectrical

properties or parameters, electric and dielectric measurements, impedance, resistance, voltage, current density, current frequency, membrane potential, temperature, pressure, ion concentration, neurotransmitter concentration, action potential, muscle response to stimulation, and any derivative (e.g., change in any of the foregoing, rate of change of any of the foregoing, etc.) and/or combination of the foregoing and/or as detailed herein. Bioelectrical properties or parameters refer to any measurable quantity or quality of a material (e.g., tissue) to describe the interaction between that material and an electrical or magnetic source. For example, bioelectrical parameters can include, among other parameters, resistance, reactance, complex impedance, capacitance, inductance, permittivity, conductivity, voltage, current density, current frequency, and/or derivations thereof.

[0023] As used herein, "treatment parameters" refer to one or more of the following: x, y, and/or z position of the treatment device and/or electrodes relative to the treated nerves; x, y, and/or z position of the electrodes relative to one another; shape and/or layout of the activated electrode array (e.g., ring-shaped, rectangular, etc.); shape and/or size of electrodes themselves; number of electrodes; number of treatments (within same procedure or different procedure); timing and/or activation sequence of energy delivery from a plurality of electrodes; energy delivery parameters (discussed below); polarity of electrodes; grouping of electrodes; and phase angles between voltage sources driving the electrodes.

[0024] As used herein, "energy delivery parameters" refer to amplitude, frequency, waveform, phase angle, pulse-repetition frequency, and pulse width of the applied treatment energy.

[0025] As used herein, "treatment site" refers to an anatomical location at or proximate to neural structures, such as parasympathetic fibers, sympathetic fibers, sensory fibers, A-group nerve fibers, B-group nerve fibers, C-group nerve fibers, and/or other neural structures, that are eventually targeted for neuromodulation. It will be appreciated that in certain embodiments of the present technology, the neural structures that are targeted for neuromodulation must first be identified and located by the present technology. Thus, "treatment site" refers to the anatomical location including or adjacent to the treated neural structures (e.g., within about 5 mm to about 10 mm, within about 2 mm to about 5 mm, within about 2 mm, etc.). The treatment site can also include other anatomical structures (e.g., glands) and/or avoid certain structures (e.g., vessels).

[0026] As used herein, the term "neural structure" refers to the structures associated with nerves or groups of nerves including, among other structures, neuronal bundles, axons, dendrites, cell bodies, parasympathetic fibers, sympathetic fibers, sensory fibers, A-group nerve fibers, B-group nerve fibers, and/or C-group nerve fibers.

Relevant Anatomy and Physiology

[0027] The cell bodies, dendrites, and axons of a neuron are bounded by a cell membrane. The cell membrane includes various means for pumping sodium ions outwards. This allows the concentration of potassium ions to build up within the neuron. Because of the unequal distribution of these and other ions, the neuronal cell membrane carries an electrical charge typically up to 50 to 70 millivolts, or even greater than 70 millivolts in certain instances, with the negative charge on the inner face of the cell membrane. If the membrane is briefly short-circuited by a change in its ionic permeability, sodium ions rush inwards and potassium ions rush outwards for a brief instant. This rapid movement of ions short-circuits an adjacent region of the cell membrane so that the cycle is propagated along the membrane. This self-propagating ionic and electrical change is known as an action potential. An example of an action potential is shown in Figure 1, and the effect of various ions channels and/or transporters opening during the compound action potential is shown in Figure 2A. Further, Figure 2B illustrates the effects of the compound action potential on the permeability of specific ion channels. As described in further detail below, the neuromodulation and mapping systems described herein can be used to selectively target certain ion channels to map the ensuing action potential cascade and/or neuromodulate the specific ion channel to stop the subsequent action potentials (e.g., by transmitting a stimulating or modulating signal having a threshold frequency associated with the target). Once an action potential has passed a region of a membrane, an equilibrium is restored so that the neuron is ready for the next action potential. During this brief restoration period (known as the refractory period) the membrane does not respond to any further stimuli. Action potentials are normally carried in only one direction, which is away from the origin of the action potential. All action potentials are identical after initiation. Thus, the information carried by the neurons is coded by the number and frequency pattern of the action potentials.

[0028] F wave is phenomena defined by the second of two voltage changes observed after electrical stimulation is applied to a nerve and can be used to measure nerve conduction velocity and/or other physiological parameters. For example, an electrical stimulus can be applied at a distal portion of a nerve so that the impulse travels both distally (orthodromic,

i.e., towards a muscle fiber) and proximally (antidromic, i.e., back to ganglionic bodies of the motor neurons of the central nervous system (CNS)). When the orthodromic stimulus reaches the muscle fiber, it elicits a first, strong response (muscle contraction). When the antidromic stimulus reaches the motor neuron cell bodies, some of the motor neurons backfire to cause a counterflow orthodromic wave that travels distally down the nerve towards the muscle. This stimulus evokes a small, second compound muscle action potential that defines the F wave.

[0029] Epithelia form a tight monolayer harboring a stable and sufficient transepithelial resistance. The active secretion or absorption of charged salts, such as sodium (Na^+) and chloride (Cl^-) ions, induces a potential difference across the epithelial surface that can be measured as a voltage. For example, the bioelectric potential can be measured by using a high-impedance voltmeter between two electrodes of a neuromodulation device, such as the neuromodulation device described below, or a separate voltage monitoring device.

[0030] In some embodiments, the incident electromagnetic field (e.g., detected via the electrodes) with soft and hard tissues within the nasal, paranasal space (e.g., the nasal mucosa, sub-mucosa composition, periosteum, and bony plates) depends on the local geometry and the dielectric properties of those systems. Due to the structures of the soft and hard tissues, large distinctions exist in both the relative conductivity and the relative permittivity of the soft and hard tissues. As such, a threshold level of frequency can be identified to differentiate the "deeper" mucosal tissue on the turbinates from the "shallow" tissue off the turbinates.

Selected Embodiments of Systems for Anatomical Mapping and Therapeutic Neuromodulation

[0031] Figure 3A is a partially schematic view of a system 300 for detecting anatomical structures and therapeutic nasal neuromodulation configured in accordance with an embodiment of the present technology, and Figure 3B is an enlarged isometric view of a distal portion of the system 300 configured in accordance with an embodiment of the present technology. As shown in Figure 3A, the system 300 includes a detection and modulation catheter or device 302 ("device 302"), a console 304, and a cable 306 extending therebetween. The device 302 includes a shaft 308 having a proximal portion 308a, a distal portion 308b, a handle 310 at a proximal portion 308a of the shaft 308, and an evaluation/modulation assembly or element 312 at the distal portion 308b of the shaft 308. The shaft 308 is configured to locate the distal portion 308b intraluminally at a treatment or

target site, such as within a nasal region proximate to postganglionic parasympathetic nerves that innervate the nasal mucosa. The target site may be a region, volume, or area in which the target nerves are located and may differ in size and shape depending upon the anatomy of the patient. For example, the target site may be a 3-5 cm^2 area inferior to the sphenopalatine foramen ("SPF"). In other embodiments, the target site may be larger, smaller, and/or located elsewhere in the nasal cavity to target the desired neural fibers. The evaluation/modulation assembly 312 can include at least one electrode 344 configured to therapeutically modulate postganglionic parasympathetic nerves via electromagnetic energy (e.g., RF energy). In certain embodiments, for example, the evaluation/modulation assembly 312 can therapeutically modulate the postganglionic parasympathetic nerves branching from the pterygopalatine ganglion and innervating the nasal region and nasal mucosa, such as parasympathetic nerves (e.g., the posterior nasal nerves) traversing the SPF, accessory foramen, and microforamina of a palatine bone. The electrodes 344 and/or other sensing elements of the evaluation/modulation assembly 312 can further be configured to detect one or more physiological parameters in an interest zone before, during, and/or after therapeutic neuromodulation for identifying the target site, targeting the treatment to the patient's anatomy, and/or evaluating the efficacy of the treatment.

[0032] In various embodiments, the evaluation/modulation assembly 312 can include one or more sensing elements 314, such as one or more of the following sensors: a pressure sensor, a temperature sensor (e.g., thermocouples, thermistors, etc.), a flow sensor (e.g., a Doppler velocity sensor, an ultrasonic flow meter, etc.), a flow rate sensor, a complex impedance sensor, a dielectric sensor, a chemical sensor, a bio-sensing element, a voltmeter, an electrochemical sensor, a hemodynamic sensor, an optical sensor, and/or other suitable sensing devices. The sensor(s) and/or the electrodes 344 can be connected to one or more wires (not shown; e.g., copper wires) extending through the shaft 308 to transmit signals to and from the electrodes 344 and/or the sensor(s). In some embodiments, the electrodes 344 and/or the sensor(s) can communicate wirelessly with various components of the system 300.

[0033] In some embodiments, the evaluation/modulation assembly 312 can include energy delivery elements configured to provide therapeutic neuromodulation using modalities other than RF energy, such as cryotherapeutic cooling, ultrasound energy (e.g., high intensity focused ultrasound ("HIFU") energy), microwave energy (e.g., via a microwave antenna), direct heating, high and/or low power laser energy, mechanical vibration, and/or optical power. In further embodiments, the evaluation/modulation assembly 312 can be configured

to deliver chemicals or drugs to the target site to chemically ablate or embolize the target nerves. For example, the evaluation/modulation assembly 312 can include a needle applicator extending through an access portion of the shaft 308 and/or a separate introducer, and the needle applicator can be configured to inject a chemical into the target site to therapeutically modulate the target nerves, such as botox, alcohol, guanethidine, ethanol, phenol, a neurotoxin, or another suitable agent selected to alter, damage, or disrupt nerves.

[0034] The device 302 can be operatively coupled to the console 304 via a wired connection (e.g., via the cable 306) and/or a wireless connection. The console 304 can be configured to control, monitor, supply, and/or otherwise support operation of device 302. The console 304 can further be configured to generate a selected form and/or magnitude of energy for delivery to tissue or nerves at the target site via the evaluation/modulation assembly 312, and therefore the console 304 may have different configurations depending on the treatment modality of the device 302. For example, when device 302 is configured for electrode-based, heat-element-based, and/or transducer-based treatment, the console 304 includes an energy generator 316 configured to generate RF energy (e.g., monopolar, bipolar, or multi-polar RF energy), pulsed electrical energy, microwave energy, optical energy, ultrasound energy (e.g., intraluminally-delivered ultrasound and/or HIFU), direct heat energy, radiation (e.g., infrared, visible, and/or gamma radiation), and/or another suitable type of energy. When the device 302 is configured for cryotherapeutic treatment, the console 304 can include a refrigerant reservoir (not shown), and can be configured to supply the device 302 with refrigerant. Similarly, when the device 302 is configured for chemical-based treatment (e.g., drug infusion), the console 304 can include a chemical reservoir (not shown) and can be configured to supply the device 302 with one or more chemicals.

[0035] In some embodiments, the device 302 can further include a channel 324 extending along at least a portion of the shaft 308 and a port 326 at the distal portion 308b of the shaft in communication with the port 326. In certain embodiments, the channel 324 is a fluid pathway to deliver a fluid to the distal portion 308b of the shaft 308 via the port 326. For example, the channel 324 can deliver saline solution or other fluids to rinse the intraluminal nasal pathway during delivery of the evaluation/modulation assembly 312, flush the target site before applying therapeutic neuromodulation to the target site, and/or deliver fluid to the target site during energy delivery to reduce heating or cooling of the tissue adjacent to the electrodes 344. In other embodiments, the channel 324 allows for drug delivery to the treatment site. For example, a needle (not shown) can project through the port

326 to inject or otherwise deliver a nerve block, a local anesthetic, and/or other pharmacological agent to tissue at the target site. In some embodiments, the channel 324 allows for vapor and/or smoke removal or evacuation from the treatment site.

[0036] As further shown in Figure 3A, the system 300 can include a controller 318 communicatively coupled to the device 302. In the illustrated embodiment, the controller 318 is housed in the console 304. In other embodiments, the controller 318 can be carried by the handle 310 of the device 302, the cable 306, an independent component, and/or another portion of the system 300. The controller 318 can be configured to initiate, terminate, and/or adjust operation of one or more components (e.g., the electrodes 344) of the device 302 directly and/or via the console 304. The controller 318 can be configured to execute an automated control algorithm and/or to receive control instructions from an operator (e.g., a clinician). For example, the controller 318 and/or other components of the console 304 (e.g., memory) can include a computer-readable medium carrying instructions, which when executed by the controller 318, cause the evaluation/modulation assembly 312 to perform certain functions (e.g., apply energy in a specific manner, detect impedance, detect temperature, detect nerve locations or anatomical structures, etc.). A memory includes one or more of various hardware devices for volatile and non-volatile storage, and can include both read-only and writable memory. For example, a memory can comprise random access memory (RAM), CPU registers, read-only memory (ROM), and writable non-volatile memory, such as flash memory, hard drives, floppy disks, CDs, DVDs, magnetic storage devices, tape drives, device buffers, and so forth. A memory is not a propagating signal divorced from underlying hardware; a memory is thus non-transitory.

[0037] The console 304 can also be configured to provide feedback to an operator before, during, and/or after a treatment procedure via mapping/evaluation/feedback algorithms 320. For example, the mapping/evaluation/feedback algorithms 320 can be configured to provide information associated with the location of nerves at the treatment site, the location of other anatomical structures (e.g., vessels) at the treatment site, the temperature at the treatment site during monitoring and modulation, and/or the effect of the therapeutic neuromodulation on the nerves at the treatment site. In certain embodiments, the mapping/evaluation/feedback algorithm 320 can include features to confirm efficacy of the treatment and/or enhance the desired performance of the system 300. For example, the mapping/evaluation/feedback algorithm 320, in conjunction with the controller 318 and the evaluation/modulation assembly 312, can be configured to monitor neural activity and/or

temperature at the treatment site during therapy and automatically shut off the energy delivery when the neural activity and/or temperature reaches a predetermined threshold (e.g., a threshold reduction in neural activity, a threshold maximum temperature when applying RF energy, or a threshold minimum temperature when applying cryotherapy). In other embodiments, the mapping/evaluation/feedback algorithm 320, in conjunction with the controller 318, can be configured to automatically terminate treatment after a predetermined maximum time, a predetermined maximum impedance or resistance rise of the targeted tissue (i.e., in comparison to a baseline impedance measurement), a predetermined maximum impedance of the targeted tissue), and/or other threshold values for biomarkers associated with autonomic function. This and other information associated with the operation of the system 300 can be communicated to the operator via a display 322 (e.g., a monitor, touchscreen, user interface, etc.) on the console 304 and/or a separate display (not shown) communicatively coupled to the console 304.

[0038] In various embodiments, the evaluation/modulation assembly 312 and/or other portions of the system 300 can be configured to detect various bioelectric-parameters of the tissue at the target site, and this information can be used by the mapping/evaluation/feedback algorithms 320 to determine the anatomy at the target site (e.g., tissue types, tissue locations, vasculature, bone structures, foramen, sinuses, etc.), locate neural structures, differentiate between different types of neural structures, map the anatomical and/or neural structure at the target site, and/or identify neuromodulation patterns of the evaluation/modulation assembly 312 with respect to the patient's anatomy. For example, the evaluation/modulation assembly 312 can be used to detect resistance, complex electrical impedance, dielectric properties, temperature, and/or other properties that indicate the presence of neural fibers and/or other anatomical structures in the target region. In certain embodiments, the evaluation/modulation assembly 312, together with the mapping/evaluation/feedback algorithms 320, can be used to determine resistance (rather than impedance) of the tissue (i.e., the load) to more accurately identify the characteristics of the tissue. The mapping/evaluation/feedback algorithms 320 can determine resistance of the tissue by detecting the actual power and current of the load (e.g., via the electrodes 344). In some embodiments, the system 300 provides resistance measurements with a high degree of accuracy and a very high degree of precision, such as precision measurements to the hundredths of an Ohm (e.g., 0.01 Ω) for the range of 1-50 Ω. The high degree of resistance detection accuracy provided by the system 300 allows for the detection sub-microscale structures, including the firing of neural structures, differences

between neural structures and other anatomical structures (e.g., blood vessels), and event different types of neural structures. This information can be analyzed by the mapping/evaluation/feedback algorithms and/or the controller 318 and communicated to the operator via a high resolution spatial grid (e.g., on the display 322) and/or other type of display to identify neural structures and other anatomy at the treatment site and/or indicate predicted neuromodulation regions based on the ablation pattern with respect to the mapped anatomy.

[0039] The device 302 provides access to target sites deep within the nasal region, such as at the immediate entrance of parasympathetic fibers into the nasal cavity to therapeutically modulate autonomic activity within the nasal cavity. In certain embodiments, for example, the device 302 can position the evaluation/modulation assembly 312 inferior to the SPF at the site of access foramen and/or microforamina as described in U.S. Patent Application No. 15/153,217, filed May 10, 2016, which is incorporated herein by reference in its entirety. By manipulating the proximal portion 308a of the shaft 308 from outside the entrance of the nose, a clinician may advance the shaft 308 through the tortuous intraluminal path through the nasal cavity and remotely manipulate the distal portion 308b of the shaft 308 via the handle 310 to position the evaluation/modulation assembly 312 at the target site. In certain embodiments, the shaft 308 can be a steerable device (e.g., a steerable catheter) with a small bend radius (e.g., a 5 mm bend radius, a 4 mm bend radius, a 3 mm bend radius or less) that allows the clinician to navigate through the tortuous nasal anatomy. The steerable shaft can further be configured to articulate in at least two different directions. For example, the steerable shaft 308 can include dual pull wire rings that allow a clinician to form the distal portion 308b of the shaft 308 into an "S"-shape to correspond to the anatomy of the nasal region. In other embodiments, the articulating shaft 308 can be made from a substantially rigid material (e.g., a metal material) and include rigid links at the distal portion 308b of the shaft 308 that resist deflection, yet allow for a small bend radius (e.g., a 5 mm bend radius, a 4 mm bend radius, a 3 mm bend radius or less). In further embodiments, the steerable shaft 308 may be a laser-cut tube made from a metal and/or other suitable material. The laser-cut tube can include one or more pull wires operated by the clinician to allow the clinician to deflect the distal portion 308b of the shaft 308 to navigate the tortuous nasal anatomy to the target site.

[0040] In various embodiments, the distal portion 308b of the shaft 308 is guided into position at the target site via a guidewire (not shown) using an over-the-wire (OTW) or a

rapid exchange (RX) technique. For example, the distal end of the evaluation/modulation assembly 312 can include a channel for engaging the guidewire. Intraluminal delivery of the evaluation/modulation assembly 312 can include inserting the guide wire into an orifice in communication with the nasal cavity (e.g., the nasal passage or mouth), and moving the shaft 308 and/or the evaluation/modulation assembly 312 along the guide wire until the evaluation/modulation assembly 312 reaches a target site (e.g., inferior to the SPF). In further embodiments, the device 302 can be configured for delivery via a guide catheter or introducer sheath (not shown) with or without using a guide wire. Image guidance (e.g., via an endoscope, computed tomography (CT), fluoroscopy, ultrasound, optical coherence tomography (OCT), and/or combinations thereof) may be used to aid the clinician's positioning and manipulation of the distal portion 308b of the shaft 308 and the evaluation/modulation assembly 312.

[0041] During delivery to the target site, the evaluation/modulation assembly 312 can be arranged in a low-profile delivery state and, once at the target site, the evaluation/modulation assembly 312 can be transformed to an expanded state (shown in Figures 3A and 3B) via manipulation of the handle 310 such that the evaluation/modulation assembly 312 contacts tissue at the target site for physiological parameter detection and/or neural modulation. As shown in the enlarged view of the evaluation/modulation assembly 312 in Figure 3B, the evaluation/modulation assembly 312 can include a plurality of struts 340 that are spaced apart from each other to form a frame or basket 342 when the evaluation/modulation assembly 312 is in the expanded state. The struts 340 can carry one or more of the electrodes 344 and/or other energy delivery elements. In the expanded state, the struts 340 can position at least two of the electrodes 344 against tissue at a target site or zone of interest within the nasal region (e.g., proximate to the palatine bone inferior to the SPF). The electrodes 344 can apply bipolar or multi-polar radiofrequency (RF) energy to the target site to detect bioelectric properties of the treatment site and/or to therapeutically modulate postganglionic parasympathetic nerves that innervate the nasal mucosa proximate to the target site. In various embodiments, the electrodes 344 can be configured to apply pulsed RF energy with a desired duty cycle (e.g., 1.00 second on/0.50 seconds off), varying power levels, and/or varying pulse durations and frequency to regulate the temperature increase in the target tissue. As shown in Figure 3B, the distal end portion of the basket includes a double inflection to enhance or maximize the contact surface area of the strut 340 to adjacent tissue (e.g., a mucosal wall).

[0042] In the embodiment illustrated in Figure 3B, the basket 342 includes eight branches 346 spaced radially apart from each other to form at least a generally spherical structure, and each of the branches 346 includes two struts 340 positioned adjacent to each other. In other embodiments, however, the basket 342 can include fewer than eight branches 346 (e.g., two, three, four, five, six, or seven branches) or more than eight branches 346. In further embodiments, each branch 346 of the basket 342 can include a single strut 340, more than two struts 340, and/or the number of struts 340 per branch 346 can vary. In still further embodiments, the branches 346 and struts 340 can form baskets or frames having other suitable shapes for placing the electrodes 344 in contact with tissue at the target site. For example, when in the expanded state, the struts 340 can form an ovoid shape, a hemispherical shape, a cylindrical structure, a pyramid structure, and/or other suitable shapes. The structural shape of the basket 342 can also be segmented, replicated, and/or miniaturized duplications of one or more suitable shapes.

[0043] As shown in Figure 3B, the evaluation/modulation assembly 312 can further include an internal or interior support member 348 that extends distally from the distal portion 308b of the shaft 308. A distal end portion 350 of the support member 348 can support the distal end portions of the struts 340 to form the desired basket shape. For example, as shown in Figure 3, the struts 340 can extend distally from the distal potion 308b of the shaft 308 and the distal end portions of the struts 340 can attach to the distal end portion 350 of the support member 348. In certain embodiments, the support member 348 can include an internal channel (not shown) through which flexible electrical connectors (e.g., wires) coupled to the electrodes 344 and/or other electrical features of the evaluation/modulation assembly 312 can run. In various embodiments, the internal support member 348 can also carry an electrode (not shown) at the distal end portion 350 and/or along the length of the support member 348.

[0044] The individual struts 340 can be made from a resilient material, such as a shape-memory material (e.g., Nitinol), that allows the struts 340 to self-expand into the desired shape of the basket 342 when in the expanded state. The struts 340 can also be made from composite wire structures with enhanced core materials for conductivity and resistivity performance to enhance the signals detected by the electrodes 344. In other embodiments, the struts 340 can be made from other suitable materials and/or the evaluation/modulation assembly 312 can be mechanically expanded via a balloon or by proximal movement of the support member 348. The basket 342 and the associated struts 340 can have sufficient

rigidity to support the electrodes 344 and position or press the electrodes 344 against tissue at the target site. In addition, the expanded basket 342 can press against surrounding anatomical structures proximate to the target site (e.g., the turbinates, the palatine bone, etc.) and the individual struts 340 can at least partially conform to the shape of the adjacent anatomical structures to anchor the therapeutic element 312 at the treatment site during energy delivery. This expansion and conformability of the struts 340 can facilitate placing the electrodes 344 in contact with the surrounding tissue at the target site.

[0045] Each strut 340 can include one or more electrodes 344 (e.g., two electrodes 344, three electrodes 344, four electrodes 344, five electrodes 344, more than five electrodes 344), and/or the number of electrodes 344 on the different struts 340 can vary. In some embodiments, for example, each strut 340 can include five electrodes 344 such that each branch 346 includes ten electrodes 344 that can define five adjacent electrode pairs, although the electrodes 344 may be independently activated and paired with different electrodes 344 of the branch 346 and/or other branches 346. For example, the electrodes 344 can have a length of 0.25-2.25 mm (e.g., 0.75 mm), a spacing along each strut 340 of about 0.5-3.5 mm (e.g., 1.5 mm), and an inter-pairing spacing of about 1.5-4.0 mm(e.g., 2 mm). In other embodiments the electrode sizing and spacing can differ. In some embodiments, it may be beneficial to have the electrodes positioned or spaced differently along the struts 340 than shown in Figure 3B and/or asymmetrically positioned electrodes on one or more of the struts 340. For example, a mid-portion of the struts 340 may include a higher density of electrodes 344 than the proximal or distal portions of the struts 340. Such an asymmetric distribution of electrodes 344 may be particularly advantageous for mapping functions. This may be achieved through the placing of the electrode array in a known spatial configuration, and mapping electro-anatomical characteristics in a composition of multiple (high-density) activation sequence mappings in multiple planes and/or multiple or varying depths that incorporates variations in the impedance of different tissue types, including different cellular or functional constructs, and at different waveform frequencies (as described in greater detail below).

[0046] In certain embodiments, each electrode 344 can be operated independently of the other electrodes 344. For example, each electrode can be individually activated and the polarity and amplitude of each electrode can be selected by an operator or a control algorithm executed by the controller 318 (Figure 3A). The selective independent control of the electrodes 344 allows the evaluation/modulation assembly 312 to detect information and

deliver RF energy to highly customized regions. For example, a select portion of the electrodes 344 can be activated to target specific neural fibers in a specific region while the other electrodes 344 remain inactive. In certain embodiments, for example, electrodes 344 may be activated across the portion of the basket 342 that is adjacent to tissue at the target site, and the electrodes 344 that are not proximate to the target tissue can remain inactive to avoid applying energy to non-target tissue. In addition, the electrodes 344 can be individually activated to stimulate or therapeutically modulate certain regions in a specific pattern at different times (e.g., via multiplexing), which facilitates detection of anatomical parameters across a zone of interest and/or regulated therapeutic neuromodulation.

[0047] The electrodes 344 can be electrically coupled to the energy generator 316 (Figure 3B) via wires (not shown) that extend from the electrodes 344, through the shaft 308, and to the energy generator 316. When each of the electrodes 344 is independently controlled, each electrode 344 couples to a corresponding wire that extends through the shaft 308. This allows each electrode 344 to be independently activated for stimulation or neuromodulation to provide precise ablation patterns and/or individually detected via the console 304 (Figure 3A) to provide information specific to each electrode 344 for neural or anatomical detection and mapping. In other embodiments, multiple electrodes 344 can be controlled together and, therefore, multiple electrodes 344 can be electrically coupled to the same wire extending through the shaft 308. The energy generator 316 (Figure 3A) and/or components (e.g., a control module) operably coupled thereto can include custom algorithms to control the activation of the electrodes 344. For example, the RF generator can deliver RF power at about 200-300 W to the electrodes 344, and do so while activating the electrodes 344 in a predetermined pattern selected based on the position of the evaluation/modulation assembly 312 relative to the treatment site and/or the identified locations of the target nerves. In other embodiments, the energy generator 316 delivers power at lower levels (e.g., less than 1 W, 1-5 W, 5-15 W, 15-50 W, 50-150 W, etc.) for stimulation and/or higher power levels. For example, the energy generator 316 can be configured to delivery stimulating energy pulses of 1-3 W via the electrodes 344 to stimulate specific targets in the tissue.

[0048] As shown in Figure 3B, the evaluation/modulation assembly 312 can further include one or more temperature sensors 352 disposed on the struts 340 and/or other portions of the evaluation/modulation assembly 312 and electrically coupled to the console 304 (Figure 3A) via wires (not shown) that extend through the shaft 308. In various embodiments, the temperature sensors 352 can be positioned proximate to the electrodes 344

to detect the temperature at the interface between tissue at the target site and the electrodes 344. In other embodiments, the temperature sensors 352 can penetrate the tissue at the target site (e.g., a penetrating thermocouple) to detect the temperature at a depth within the tissue. The temperature measurements can provide the operator or the system with feedback regarding the effect of the therapeutic neuromodulation on the tissue. For example, in certain embodiments the operator may wish to prevent or reduce damage to the tissue at the treatment site (e.g., the nasal mucosa), and therefore the temperature sensors 352 can be used to determine if the tissue temperature reaches a predetermined threshold for irreversible tissue damage. Once the threshold is reached, the application of therapeutic neuromodulation energy can be terminated to allow the tissue to remain intact and avoid significant tissue sloughing during wound healing. In certain embodiments, the energy delivery can automatically terminate based on an the mapping/evaluation/feedback algorithm 320 (Figure 3A) stored on the console 304 (Figure 3A) operably coupled to the temperature sensors 352.

[0049] In other embodiments, the evaluation/modulation assembly 312 can have different configurations than that shown in Figure 3B. For example, the evaluation/modulation assembly 312 can include structures and components similar to those described in U.S. Patent Application No. 15/153,217, filed May 10, 2016, and incorporated herein in its entirety. In various embodiments, for example, the evaluation/modulation assembly 312 may include an expandable balloon that has plurality of electrodes disposed thereon with spacing selected to enhance sensing resolution. The balloon can be positioned within the basket 342 and/or be a standalone structure. The balloon may also be configured to act as a heat sink by being configured to receive a cooling agent or media to reduce the heating of tissue adjacent to the electrodes 344 during preventing the surfaces electrodes from contributing to thermal damage from ablation.

[0050] Referring to Figure 3A and 3B together, when the evaluation/modulation assembly 312 is positioned at the target site, therapeutic modulation may be applied via the electrodes 344 and/or other features of the evaluation/modulation assembly 312 to precise, localized regions of tissue to induce one or more desired therapeutic neuromodulating effects to disrupt parasympathetic motor sensory function. The evaluation/modulation assembly 312 can selectively target postganglionic parasympathetic fibers that innervate the nasal mucosa at a target or treatment site proximate to or at their entrance into the nasal region. For example, evaluation/modulation assembly 312 can be positioned to apply therapeutic neuromodulation at least proximate to the SPF to therapeutically modulate nerves entering

the nasal region via the SPF, accessory foramen and/or microforamina (e.g., in the palatine bone). The purposeful application of the energy at the target site may achieve therapeutic neuromodulation along all or at least a portion of posterior nasal neural fibers entering the nasal region. The therapeutic neuromodulating effects are generally a function of, at least in part, power, time, and contact between the energy delivery elements and the adjacent tissue. For example, in certain embodiments therapeutic neuromodulation of autonomic neural fibers are produced by applying RF energy in pulsed or constant waveforms at a power of about 2-20 W (e.g., 5 W, 7 W, 10 W, etc.) for a time period of about 1-20 seconds (e.g., 5-10 seconds, 8-10 seconds, 10-12 seconds, etc.).

[0051] The therapeutic neuromodulating effects may include partial or complete denervation via thermal ablation and/or non-ablative thermal alteration or damage (e.g., via sustained heating and/or resistive heating). Desired thermal heating effects may include raising the temperature of target neural fibers above a desired threshold to achieve non-ablative thermal alteration, or above a higher temperature to achieve ablative thermal alteration. For example, the target temperature may be above the 45°C isotherm in which the applicants have identified that modulations of parasympathetic nerves begin to occur. It is expected that therapeutic neuromodulation can be achieved at the 45°C isotherm, the 55°C isotherm, at the 60°C, isotherms between 45°C and 60°C, and/or higher isotherms. Accordingly, the system 300 can be configured to apply therapeutic neuromodulation until the temperature at the target site reaches a threshold of 45°C, 55°C, 60°C, a value between 45°C and 60°C, or higher than 60°C. In various embodiments, delivering the neuromodulation energy creates an electric field-depth that causes ionic agitation to disrupt neural activity and/or tissue temperatures resulting in a lesion size for changing the conductive/impedance/electrical properties of the tissue types within the region of interest.

[0052] Hypothermic effects may also provide neuromodulation. For example, a cryotherapeutic applicator may be used to cool tissue at a target site to provide therapeutically-effective direct cell injury (e.g., necrosis), vascular injury (e.g., starving the cell from nutrients by damaging supplying blood vessels), and sublethal hypothermia with subsequent apoptosis. Exposure to cryotherapeutic cooling can cause acute cell death (e.g., immediately after exposure) and/or delayed cell death (e.g., during tissue thawing and subsequent hyperperfusion). Embodiments of the present technology can include cooling a structure positioned at or near tissue such that the tissue is effectively cooled to a depth where the targeted postganglionic parasympathetic nerves reside. For example, the cooling

structure is cooled to the extent that it causes therapeutically effective, cryogenic posterior nasal nerve modulation.

[0053] In certain embodiments, the system 300 can determine the locations and/or morphology of neural structures and/or other anatomical structures before therapy such that the therapeutic neuromodulation can be applied to precise regions including target neural structures, while avoiding negative effects on non-target structures, such as blood vessels. As described in further detail below, the system 300 can detect various bioelectrical parameters in an interest zone (e.g., within in the nasal cavity) to determine the location and morphology of various neural structures (e.g., different types of neural structures, neuronal directionality, etc.) and/or other tissue (e.g., glandular structures, vessels, bony regions, etc.). In some embodiments, the system 300 is configured to measure bioelectric potential. To do so, one or more of the electrodes 344 is placed in contact with an epithelial surface at a region of interest (e.g., a treatment site). Electrical stimuli (e.g., constant or pulsed currents at one or more frequencies) are applied to the tissue by one or more electrodes 344 at or near the treatment site, and the voltage and/or current differences at various different frequencies between various pairs of electrodes 344 of the evaluation/modulation assembly 312 may be measured to produce a spectral profile or map of the detected bioelectric potential, which can be used to identify different types of tissues (e.g., vessels, neural structures, and/or other types of tissue) in the region of interest. For example, current (i.e., direct or alternating current) can be applied to a pair of electrodes 344 adjacent to each other and the resultant voltages and/or currents between other pairs of adjacent electrodes 344 are measured. It will be appreciated that the current injection electrodes 344 and measurement electrodes 344 need not be adjacent, and that modifying the spacing between the two current injection electrodes 344 can affect the depth of the recorded signals. For example, closely-spaced current injection electrodes 344 provided recorded signals associated with tissue deeper from the surface of the tissue than further spaced apart current injection electrodes 344 that provide recorded signals associated with tissue at shallower depths. Recordings from electrode pairs with different spacings may be merged to provide additional information on depth and localization of anatomical structures.

[0054] Further, complex impedance and/or resistance measurements of the tissue at the region of interest can be detected directly from current-voltage data provided by the bioelectric potential measurements while differing levels of frequency currents are applied to the tissue (e.g., via the evaluation/modulation assembly 312), and this information can be

used to map the neural and anatomical structures by the use of frequency differentiation reconstruction. Applying the stimuli at different frequencies will target different stratified layers or cellular bodies or clusters. At high signal frequencies (e.g., electrical injection or stimulation), for example, cell membranes of the neural structures do not impede current flow, and the current passes directly through the cell membranes. In this case, the resultant measurement (e.g., impedance, resistance, capacitance, and/or induction) is a function of the intracellular and extracellular tissue and liquids. At low signal frequencies, the membranes impede current flow to provide different defining characteristics of the tissues, such as the shapes of the cells or cell spacing. The stimulation frequencies can be in the megahertz range, in the kilohertz range (e.g., 400-500 kHz, 450-480 kHz, etc.), and/or other frequencies attuned to the tissue being stimulated and the characteristics of the device being used. The detected complex impedance or resistances levels from the zone of interest can be displayed to the user (e.g., via the display 322) to visualize certain structures based on the stimulus frequency. For example, Figure 6 is an illustration of neural impedance mapping at three different regions of tissue and at five different depths, with the neural structures 609 being identified by a different color or shading so that the clinician can locate suitable neural targets. Similar complex impedance mapping can be provided for different structures (e.g., vessels).

[0055] Further, the inherent morphology and composition of the anatomical structures in the nasal region react differently to different frequencies and, therefore, specific frequencies can be selected to identify very specific structures. For example, the morphology or composition of targeted structures for anatomical mapping may depend on whether the cells of tissue or other structure are membranonic, stratified, and/or annular. In various embodiments, the applied stimulation signals can have predetermined frequencies attuned to specific neural structures, such as the level of myelination and/or morphology of the myelination. For example, second axonal parasympathetic structures are poorly myelinated than sympathetic nerves or other structures and, therefore, will have a distinguishable response (e.g., complex impedance, resistance, etc.) with respect to a selected frequency than sympathetic nerves. Accordingly, applying signals with different frequencies to the target site can distinguish the targeted parasympathetic nerves from the non-targeted sensory nerves, and therefore provide highly specific target sites for neural mapping before or after therapy and/or neural evaluation post-therapy. In some embodiments, the neural and/or anatomical mapping includes measuring data at a region of interest with at least two different

frequencies to identify certain anatomical structures such that the measurements are taken first based on a response to an injection signal having a first frequency and then again based on an injection signal having a second frequency different from the first. For example, there are two frequencies at which hypertrophied (i.e., disease-state characteristics) sub-mucosal targets have a different electrical conductivity or permittivity compared to "normal" (i.e., healthy) tissue. Complex conductivity may be determined based on one or more measured physiological parameters (e.g., complex impedance, resistance, dielectric measurements, dipole measurements, etc.) and/or observance of one or more confidently known attributes or signatures. Furthermore, the system 300 can also apply neuromodulation energy via the electrodes 344 at one or more predetermined frequencies attuned to a target neural structure to provide highly targeted ablation of the selected neural structure associated with the frequency(ies). This highly targeted neuromodulation also reduces the collateral effects of neuromodulation therapy to non-target sites/structures (e.g., blood vessels) because the targeted signal (having a frequency tuned to a target neural structure) will not have the same modulating effects on the non-target structures.

[0056] Accordingly, bioelectric properties, such as complex impedance and resistance, can be used by the system 300 before, during, and/or after neuromodulation therapy to guide one or more treatment parameters.. For example, before, during, and/or after treatment, impedance or resistance measurements may be used to confirm and/or detect contact between one or more electrodes 344 and the adjacent tissue. The impedance or resistance measurements can also be used to detect whether the electrodes 344 are placed appropriately with respect to the targeted tissue type by determining whether the recorded spectra have a shape consistent with the expected tissue types and/or whether serially collected spectra were reproducible. In some embodiments, impedance or resistance measurements may be used to identify a boundary for the treatment zone (e.g., specific neural structures that are to be disrupted), anatomical landmarks, anatomical structures to avoid (e.g., vascular structures or neural structures that should not be disrupted), and other aspects of delivering energy to tissue.

[0057] The bioelectric information can be used to produce a spectral profile or map of the different anatomical features tissues at the target site, and the anatomical mapping can be visualized in a 3D or 2D image via the display 322 and/or other user interface to guide the selection of a suitable treatment site. This neural and anatomical mapping allows the system 300 to accurately detect and therapeutically modulate the postganglionic parasympathetic

neural fibers that innervate the mucosa at the numerous neural entrance points into the nasal cavity. Further, because there are not any clear anatomical markers denoting the location of the SPF, accessory foramen, and microforamina, the neural mapping allows the operator to identify and therapeutically modulate nerves that would otherwise be unidentifiable without intricate dissection of the mucosa. In addition, anatomical mapping also allows the clinician to identify certain structures that the clinician may wish to avoid during therapeutic neural modulation (e.g., certain arteries). The neural and anatomical bioelectric properties detected by the system 300 can also be used during and after treatment to determine the real-time effect of the therapeutic neuromodulation on the treatment site. For example, the mapping/evaluation/feedback algorithms 320 can also compare the detected neural locations and/or activity before and after therapeutic neuromodulation, and compare the change in neural activity to a predetermined threshold to assess whether the application of therapeutic neuromodulation was effective across the treatment site.

[0058] In various embodiments, the system 300 can also be configured to map the expected therapeutic modulation patterns of the electrodes 344 at specific temperatures and, in certain embodiments, take into account tissue properties based on the anatomical mapping of the target site. For example, the system 300 can be configured to map the ablation pattern of a specific electrode ablation pattern at the 45°C isotherm, the 55°C isotherm, the 65°C isotherm, and/or other temperature/ranges (e.g., temperatures ranging from 45°C to 70°C or higher) depending on the target site and/or structure.

[0059] Figures 4A-4C illustrate three-dimensional views of such projected ablation patterns of the electrodes 344 of the evaluation/modulation assembly 312 (Figure 3A) configured in accordance with embodiments of the present technology. The ablation pattern mapping defines a region of influence 405 (shown in broken lines) that each electrode 344 has on the surrounding tissue. The region of influence 405 may correspond to the region of tissue that would be exposed to therapeutically modulating energy based on a defined electrode activation pattern. In the illustrated embodiment, the ablation pattern mapping corresponds to a device that includes five activated electrodes 344 on each strut 340 (Figure 3B), but the ablation pattern mapping can be used to illustrate the ablation pattern of any number of electrodes 344, any geometry of the electrode layout, and/or any ablation activation protocol (e.g., pulsed activation, multi-polar/sequential activation, etc.).

[0060] Referring to Figure 4A, in some embodiments the ablation pattern may be configured such that each electrode 344 has a region of influence 405 surrounding only the

individual electrode 344 (i.e., a "dot" pattern). In other embodiments, the ablation pattern may be such that two or more electrodes 344 may link together to form a sub-grouped regions of influence 405 (Figure 4B) that define peanut-like or linear shapes between two or more electrodes 344. In further embodiments, the ablation pattern can result in a more expansive or contiguous pattern in which the region of influence 405 extends along multiple electrodes 344 (e.g., along each strut 340 (Figure 3B)). In still further embodiments, the ablation pattern may result in different regions of influence depending upon the electrode activation pattern, phase angle, target temperature, pulse duration, device structure, and/or other treatment parameters. The three-dimensional views of the ablation patterns (e.g., as shown in Figures 4A-4C) can be output to the display 322 (Figure 3A) and/or other user interfaces to allow the clinician to visualize the changing regions of influence 405 based on different durations of energy application, different electrode activation sequences (e.g., multiplexing), different pulse sequences, different temperature isotherms, and/or other treatment parameters. This information can be used to determine the appropriate ablation algorithm for a patient's specific anatomy (as determined via the system 300 of Figure 3A). In other embodiments, the three-dimensional visualization of the regions of influence 405 can be used to illustrate the regions from which the electrodes 344 detect data when measuring bioelectrical properties for anatomical mapping. In this embodiment, the three dimensional visualization can be used to determine which electrode activation pattern should be used to determine the desired properties (e.g., impedance, resistance, etc.) in the desired area. In certain embodiments, it may be better to use dot assessments (e.g., Figure 4A), whereas in other embodiments it may be more appropriate to detect information from linear or larger contiguous regions (e.g., Figures 4B and 4C).

[0061] In some embodiments, the mapped ablation pattern is superimposed on the anatomical mapping to identify what structures (e.g., neural structures, vessels, etc.) will be therapeutically modulated or otherwise affected by the therapy. Figure 5, for example, is an illustration of a predicted or planned neuromodulation zone 507 (shown in broken lines) in relation to previously identified anatomical structures in a zone of interest in accordance with embodiments of the present technology. For example, the illustration shows numerous neural structures 509a-b and, based on the predicted neuromodulation zone 507, identifies which neural structures are expected to be therapeutically modulated. As shown in Figure 5, the expected therapeutically modulated neural structures 509a are shaded to differentiate them from the non-affected neural structures 509b. In other embodiments, the expected

therapeutically modulated neural structures 509a can be differentiated from the non-affected neural structures 509b using different colors and/or other indicators. In further embodiments, the predicted neuromodulation zone 507 and surrounding anatomy (based on anatomical mapping) can be shown in a three dimensional view (e.g., similar to Figures 4A-4C) and/or include different visualization features (e.g., color-coding to identify certain anatomical structures, bioelectric properties of the target tissue, etc.). The combined predicted ablation pattern and anatomical mapping (e.g., as shown in Figure 5) can be output to the display 322 (Figure 3A) and/or other user interfaces to allow the clinician to select the appropriate ablation algorithm for a patient's specific anatomy.

[0062] The imaging provided by the system 300 and shown in Figures 4A-6 allows the clinician to visualize the ablation pattern before therapy and adjust the ablation pattern to target specific anatomical structures while avoiding others to prevent collateral effects. For example, the clinician can select a treatment pattern to avoid blood vessels, thereby reducing exposure of the vessel to the therapeutic neuromodulation energy. This reduces the risk of damaging or rupturing vessels and, therefore, prevents immediate or latent bleeding. Further, the selective energy application provided by the neural mapping reduces collateral effects of the therapeutic neuromodulation, such as tissue sloughing off during wound healing (e.g., 1-3 weeks post ablation), thereby reducing the aspiration risk associated with the neuromodulation procedure.

[0063] The system 300 can be further configured to apply neuromodulation energy (via the electrodes 344) at specific frequencies attuned to the target neural structure and, therefore, specifically target desired neural structures over non-target structures. For example, the specific neuromodulation frequencies can correspond to the frequencies identified as corresponding to the target structure during neural mapping. As described above, the inherent morphology and composition of the anatomical structures react differently to different frequencies. Thus, frequency-tuned neuromodulation energy tailored to a target structure does not have the same modulating effects on non-target structures. More specifically, applying the neuromodulation energy at the target-specific frequency causes ionic agitation in the target neural structure, leading to differentials in osmotic potentials of the targeted neural structures and dynamic changes in neuronal membronic potentials (resulting from the difference in intra-cellular and extra-cellular fluidic pressure). This causes degeneration, possibly resulting in vacuolar degeneration and, eventually, necrosis at the target neural structure, but is not expected to functionally affect at least some non-target

structures (e.g., blood vessels). Accordingly, the system 300 can use the neural-structure specific frequencies to both (1) identify the locations of target neural structures to plan electrode ablation configurations (e.g., electrode geometry and/or activation pattern) that specifically focus the neuromodulation on the target neural structure; and (2) apply the neuromodulation energy at the characteristic neural frequencies to selectively ablate the neural structures responsive to the characteristic neural frequencies. For example, the evaluation/modulation assembly 312 of the system 300 may selectively stimulate and/or modulate parasympathetic fibers, sympathetic fibers, sensory fibers, alpha/beta/delta fibers, C-fibers, anoxic terminals of one or more of the foregoing, insulated over non-insulated fibers (regions with fibers), and/or other neural structures. In some embodiments, the system 300 may also selectively target specific cells or cellular regions during anatomical mapping and/or therapeutic modulation, such as smooth muscle cells, sub-mucosal glands, goblet cells, stratified cellular regions within the nasal mucosa. Therefore, the system 300 provides highly selective neuromodulation therapy specific to targeted neural structures, and reduces the collateral effects of neuromodulation therapy to non-target structures (e.g., blood vessels).

[0064] Figure 7 is a block diagram illustrating a method 700 of anatomical mapping and therapeutic neuromodulation in accordance with embodiments of the present technology. The method 700 is described below with respect to the system 300 described above with reference to Figures 3A-3B, but the method 700 may be implemented using other suitable systems for anatomical evaluation and neuromodulation therapy. As shown in Figure 7, the method 700 includes expanding an evaluation and modulation device at a zone of interest ("interest zone"), such as in a portion of the nasal cavity (block 705). For example, the evaluation/modulation assembly 312 can be expanded such that at least some of the electrodes 344 are placed in contact with mucosal tissue at the interest zone. The expanded device can then take bioelectric measurements via the electrodes 344 and/or other sensors to ensure that the desired electrodes are in proper contact with the tissue at the interest zone (block 710). In some embodiments, for example, the system 300 detects the impedance and/or resistance across pairs of the electrodes 344 to confirm that the desired electrodes have appropriate surface contact with the tissue and that all of the electrodes are 344 functioning properly.

[0065] The method 700 continues by optionally applying an electrical stimulus to the tissue (block 715), and detecting bioelectric properties of the tissue to establish baseline norms of the tissue (block 720). For example, the method 700 can include measuring

resistance, complex impedance, current, voltage, nerve firing rate, neuromagnetic field, muscular activation, and/or other parameters that are indicative of the location and/or function of neural structures and/or other anatomical structures (e.g., glandular structures, blood vessels, etc.). In some embodiments, the electrodes 344 send one or more stimulation signals (e.g., pulsed signals or constant signals) to the interest zone to stimulate neural activity and initiate action potentials (block 715). The stimulation signal can have a frequency attuned to a specific target structure (e.g., a specific neural structure, a glandular structure, a vessel) that allows for identification of the location of the specific target structure. The specific frequency of the stimulation signal is a function of the host permeability and, therefore, applying the unique frequency alters the tissue attenuation and the depth into the tissue the RF energy will penetrate. For example, lower frequencies typically penetrate deeper into the tissue than higher frequencies.

[0066] Pairs of the non-stimulating electrodes 344 of the evaluation/modulation assembly 312 can then detect one or more bioelectric properties of the tissue that occur in response to the stimulus, such as impedance or resistance. For example, an array of electrodes (e.g., the electrodes 344) can be selectively paired together an a desired pattern (e.g., multiplexing the electrodes 344) to detect the bioelectric properties at desired depths and/or across desired regions to provide a high level of spatial awareness at the interest zone. In certain embodiments, the electrodes 344 can be paired together in a time-sequenced manner according to an algorithm (e.g., provided by the mapping/evaluation/feedback algorithms 320). In various embodiments, stimuli can be injected into the tissue at two or more different frequencies, and the resultant bioelectric responses (e.g., action potentials) in response to each of the injected frequencies can be detected via various pairs of the electrodes 344. For example, an anatomical or neural mapping algorithm can cause the evaluation/modulation assembly 312 to deliver pulsed RF energy at specific frequencies between different pairs of the electrodes 344 and the resultant bioelectric response can be recorded in a time sequenced rotation until the desired interest zone is adequately mapped (i.e., "multiplexing"). For example, the evaluation/modulation assembly 312 can deliver stimulation energy at a first frequency via adjacent pairs of the electrodes 344 for a predetermined time period (e.g., 1-50 milliseconds), and the resultant bioelectric activity (e.g., resistance) can be detected via one or more other pairs of electrodes 344 (e.g., spaced apart from each other to reach varying depths within the tissue). The evaluation/modulation assembly 312 can then apply stimulation energy at a second frequency different from the first

frequency, and the resultant bioelectric activity can be detected via the other electrodes. This can continue when the interest zone has been adequately mapped at the desired frequencies. As described in further detail below, in some embodiments the baseline tissue bioelectric properties (e.g., nerve firing rate) are detected using static detection methods (without the injection of a stimulation signal).

[0067] After detecting the baseline bioelectric properties, the information can be used to map anatomical structures and/or functions at the interest zone (block 725). For example, the bioelectric properties detected by the electrodes 344 can be amazed via the mapping/evaluation/feedback algorithms 320, and an anatomical map can be output to a user via the display 322. In some embodiments, complex impedance, dielectric, or resistance measurements can be used to map parasympathetic nerves and, optionally, identify neural structures in a diseased state of hyperactivity. The bioelectric properties can also be used to map other non-target structures and the general anatomy, such as blood vessels, bone, and/or glandular structures. The anatomical locations can be provided to a user (e.g., on the display 322) as a two-dimensional map (e.g., illustrating relative intensities as shown in Figure 6, illustrating specific sites of potential target structures as shown in Figure 5) and/or as a three-dimensional image. This information can be used to differentiate structures on a submicron, cellular level and identify very specific target structures (e.g., hyperactive parasympathetic nerves). The method 700 can also predict the ablation patterns of the evaluation/modulation assembly 312 based on different electrode neuromodulation protocol (e.g., as shown in Figures 4A-4C) and, optionally, superimpose the predicted neuromodulation patterns onto the mapped anatomy to indicate to the user which anatomical structures will be affected by a specific neuromodulation protocol (e.g., as shown in Figure 5). For example, when the predicted neuromodulation pattern is displayed in relation to the mapped anatomy, a clinician can determine whether target structures will be appropriately ablated and whether non-target structures (e.g., blood vessels) will be undesirably exposed to the therapeutic neuromodulation energy. Thus, the method 700 can be used for planning neuromodulation therapy to locate very specific target structures, avoid non-target structures, and select electrode neuromodulation protocols.

[0068] Once the target structure is located and a desired electrode neuromodulation protocol has been selected, the method 700 continues by applying therapeutic neuromodulation to the target structure (block 740). The neuromodulation energy can be applied to the tissue in a highly targeted manner that forms micro-lesions to selectively

modulate the target structure, while avoiding non-targeted blood vessels and allowing the surrounding tissue structure to remain healthy for effective wound healing. In some embodiments, the neuromodulation energy can be applied in a pulsed manner, allowing the tissue to cool between modulation pulses to ensure appropriate modulation without undesirably affecting non-target tissue. In some embodiments, the neuromodulation algorithm can deliver pulsed RF energy between different pairs of the electrodes 344 in a time sequenced rotation until neuromodulation is predicted to be complete (i.e., "multi-plexing"). For example, the evaluation/modulation assembly 312 can deliver neuromodulation energy (e.g., having a power of 5-10 W (e.g., 7 W, 8 W, 9W) and a current of about 50-100 mA) via adjacent pairs of the electrodes 344 until at least one of the following conditions is met: (a) load resistance reaches a predefined maximum resistance (e.g., 350 Ω); (b) a thermocouple temperature associated with the electrode pair reaches a predefined maximum temperature (e.g., 80°C); or (c) a predetermined time period has elapsed (e.g., 10 seconds). After the predetermined conditions are met, the evaluation/modulation assembly 312 can move to the next pair of electrodes in the sequence, and the neuromodulation algorithm can terminate when all of the load resistances of the individual pairs of electrodes is at or above a predetermined threshold (e.g., 300 Ω). In various embodiments, the RF energy can be applied at a predetermined frequency (e.g., 450-500 kHz) and is expected to initiate ionic agitation of the specific target structure, while avoiding functional disruption of non-target structures.

[0069] During and/or after neuromodulation therapy, the method continues by detecting and, optionally, mapping the post-therapy bioelectric properties of the target site (block 740). This can be performed in a similar manner as described above with respect to blocks 715-725. The post-therapy evaluation can indicate if the target structures (e.g., hyperactive parasympathetic nerves) were adequately modulated or ablated (block 745). If the target structures are not adequately modulated (i.e., if neural activity is still detected in the target structure and/or the neural activity has not decreased), the method 700 can continue by again applying therapeutic neuromodulation to the target (block 735). If the target structures were adequately ablated, the neuromodulation procedure can be completed (block 750).

Selected Embodiments of Detection of Anatomical Structures and Function

[0070] Various embodiments of the present technology can include features that measure bio-electric, dielectric, and/or other properties of tissue at target sites to determine the presence, location, and/or activity of neural structures and other anatomical structures

and, optionally, map the locations of the detected neural structures and/or other anatomical structures. For example, the present technology can be used to detect glandular structures and, optionally, their mucoserous functions and/or other functions. The present technology can also be configured to detect vascular structures (e.g., arteries) and, optionally, their arterial functions, volumetric pressures, and/or other functions. The mapping features discussed below can be incorporated into any the system 300 (Figures 3A and 3B) and/or any other devices disclosed herein to provide an accurate depiction of nerves at the target site.

[0071] Neural and/or anatomical detection can occur (a) before the application of a therapeutic neuromodulation energy to determine the presence or location of neural structures and other anatomical structures (e.g., blood vessels, glands, etc.) at the target site and/or record baseline levels of neural activity; (b) during therapeutic neuromodulation to determine the real-time effect of the energy application on the neural fibers at the treatment site; and/or (c) after therapeutic neuromodulation to confirm the efficacy of the treatment on the targeted structures (e.g., nerves glands, etc.). This allows for the identification of very specific anatomical structures (even to the micro-scale or cellular level) and, therefore, provides for highly targeted neuromodulation. This enhances the efficacy and efficiency of the neuromodulation therapy. In addition, the anatomical mapping reduces the collateral effects of neuromodulation therapy to non-target sites. Accordingly, the targeted neuromodulation inhibits damage or rupture of blood vessels (i.e., inhibits undesired bleeding) and collateral damage to tissue that may be of concern during wound healing (e.g., when damage tissue sloughs off of the wall of the nasal wall).

[0072] In certain embodiments, the systems disclosed herein can use bioelectric measurements, such as impedance, resistance, voltage, current density, and/or other parameters (e.g., temperature) to determine the anatomy, in particular the neural, glandular, and vascular anatomy, at the target site. The bioelectric properties can be detected after the transmission of a stimulus (e.g., an electrical stimulus, such as RF energy delivered via the electrodes 344 of Figures 3A-3B; i.e., "dynamic" detection) and/or without the transmission of a stimulus (i.e., "static" detection).

[0073] Dynamic measurements include various embodiments to excite and/or detect primary or secondary effects of neural activation and/or propagation. Such dynamic embodiments involve the heightened states of neural activation and propagation and use this dynamic measurement for nerve location and functional identification relative to the neighboring tissue types. For example, a method of dynamic detection can include: (1)

delivering stimulation energy to a treatment site via a treatment device (e.g., the evaluation/modulation assembly 312) to excite parasympathetic nerves at the treatment site; (2) measuring one or more physiological parameters (e.g., resistance, impedance, etc.) at the treatment site via a measuring/sensing array of the treatment device (e.g., the electrodes 344); (4) based on the measurements, identifying the relative presence and position of parasympathetic nerves at the treatment site; and (5) delivering ablation energy to the identified parasympathetic nerves to block the detected para-sympathetic nerves.

[0074] Static measurements include various embodiments associated with specific native properties of the stratified or cellular composition at or near the treatment site. The static embodiments are directed to inherent biologic and electrical properties of tissue types at or near the treatment site, the stratified or cellular compositions at or near the treatment site, and contrasting both foregoing measurements with tissue types adjacent the treatment site (and that are not targeted for neuromodulation). This information can be used to localize specific targets (e.g., parasympathetic fibers) and non-targets (e.g., vessels, sensory nerves, etc.). For example, a method of static detection can include: (1) before ablation, utilizing a measuring/sensing array of a treatment device (e.g., the electrodes 344) to determine one or more baseline physiological parameters; (2) geometrically identifying inherent tissue properties within a region of interest based on the measured physiological parameters (e.g., resistance, impedance, etc.); (3) delivering ablation energy to one or more nerves within the region of via treatment device interest; (4) during the delivery of the ablation energy, determining one or more mid-procedure physiological parameters via the measuring/sensing array; and (5) after the delivery of ablation energy, determining one or more post-procedure physiological parameters via the measurement/sensing array to determine the effectiveness of the delivery of the ablation energy on blocking the nerves that received the ablation energy.

[0075] After the initial static and/or dynamic detection of bioelectric properties, the location of anatomical features can be used to determine where the treatment site(s) should be with respect to various anatomical structures for therapeutically effective neuromodulation of the targeted parasympathetic nasal nerves. The bioelectric and other physiological properties discussed herein can be detected via electrodes (e.g., the electrodes 344 of the evaluation/modulation assembly 312 of Figures 3A and 3B), and the electrode pairings on a device (e.g., evaluation/modulation assembly 312) can be selected to obtain the bioelectric data at specific zones or regions and at specific depths of the targeted regions. The specific properties detected at or surrounding target neuromodulation sites and associated methods for

obtaining these properties are described below. These specific detection and mapping methods discussed below are described with reference to the system 300 of Figures 3A and 3B, although the methods can be implemented on other suitable systems and devices that provide for anatomical identification, anatomical mapping and/or neuromodulation therapy.

Neural Identification and Mapping

[0076] In many neuromodulation procedures, it is beneficial to identify the portions of the nerves that fall within a zone and/or region of influence (referred to as the "interest zone") of the energy delivered by a neuromodulation device 302 (Figure 3A), as well as the relative three-dimensional position of the neural structures relative to the neuromodulation device 302. Characterizing the portions of the neural structures within the interest zone and/or determining the relative positions of the neural structures within the interest zone enables the clinician to (1) selectively activate target neural structures over non-target structures (e.g., blood vessels), and (2) sub-select specific targeted neural structures (e.g., parasympathetic nerves) over non-target neural structures (e.g., sensory nerves, subgroups of neural structures, neural structures having certain compositions or morphologies). The target structures (e.g., parasympathetic nerves) and non-target structures (e.g., blood vessels, sensory nerves, etc.) can be identified based on the inherent signatures of specific structures, which are defined by the unique morphological compositions of the structures and the bioelectrical properties associated with these morphological compositions. For example, unique, discrete frequencies can be associated with morphological compositions and, therefore, be used to identify certain structures. The target and non-target structures can also be identified based on relative bioelectrical activation of the structures to sub-select specific neuronal structures. Further, target and non-target structures can be identified by the differing detected responses of the structures to a tailored injected stimuli. For example, the systems described herein can detect the magnitude of response of structures and the difference in the responses of anatomical structures with respect to differing stimuli (e.g., stimuli injected at different frequencies).

[0077] At least for purposes of this disclosure, a nerve can include the following portions that are defined based on their respective orientations relative to the interest zone: terminating neural structures (e.g., terminating axonal structures), branching neural structures (e.g., branching axonal structures), and travelling neural structures (e.g., travelling axonal structures). For example, terminating neural structures enter the zone but do not exit. As such, terminating neural structures are terminal points for neuronal signaling and activation. Branching neural structures are nerves that enter the interest zone and increase number of

nerves exiting the interest zone. Branching neural structures are typically associated with a reduction in relative geometry of nerve bundle. Travelling neural structures are nerves that enter the interest zone and exit the zone with no substantially no change in geometry or numerical value.

[0078] The system 300 can be used to detect voltage, current, complex impedance, resistance, permittivity, and/or conductivity, which are tied to the compound action potentials of nerves, to determine and/or map the relative positions and proportionalities of nerves in the interest zone. Neuronal cross-sectional area ("CSA") is expected to be due to the increase in axonic structures. Each axon is a standard size. Larger nerves (in cross-sectional dimension) have a larger number of axons than nerves having smaller cross-sectional dimensions. The compound action responses from the larger nerves, in both static and dynamic assessments, are greater than smaller nerves. This is at least in part because the compound action potential is the cumulative action response from each of the axons. When using static analysis, for example, the system 300 can directly measure and map impedance or resistance of nerves and, based on the determined impedance or resistance, determine the location of nerves and/or relative size of the nerves. In dynamic analysis, the system 300 can be used to apply a stimulus to the interest zone and detect the dynamic response of the neural structures to the stimulus. Using this information, the system 300 can determine and/or map impedance or resistance in the interest zone to provide information related to the neural positions or relative nerve sizes. Neural impedance mapping can be illustrated by showing the varying complex impedance levels at a specific location at differing cross-sectional depths (e.g., as shown in Figure 6). In other embodiments, neural impedance or resistance can be mapped in a three-dimensional display.

[0079] Identifying the portions and/or relative positions of the nerves within the interest zone can inform and/or guide selection of one or more treatment parameters (e.g., electrode ablation patterns, electrode activation plans, etc.) of the system 300 for improving treatment efficiency and efficacy. For example, during neural monitoring and mapping, the system 300 can identify the directionality of the nerves based at least in part on the length of the neural structure extending along the interest zone, relative sizing of the neural structures, and/or the direction of the action potentials. This information can then be used by the system 300 or the clinician to automatically or manually adjust treatment parameters (e.g., selective electrode activation, bipolar and/or multipolar activation, and/or electrode positioning) to target specific nerves or regions of nerves. For example, the system 300 can selectively

activate specific electrodes 344, electrode combinations (e.g., asymmetric or symmetric), and/or adjust the bi-polar or multi-polar electrode configuration. In some embodiments, the system 300 can adjust or select the waveform, phase angle, and/or other energy delivery parameters based on the nerve portion/position mapping and/or the nerve proportionality mapping. In some embodiments, structure and/or properties of the electrodes 344 themselves (e.g., material, surface roughening, coatings, cross-sectional area, perimeter, penetrating, penetration depth, surface-mounted, etc.) may be selected based on the nerve portion and proportionality mapping.

[0080] In various embodiments, treatment parameters and/or energy delivery parameters can be adjusted to target on-axis or near axis travelling neural structures and/or avoid the activation of traveling neural structures that are at least generally perpendicular to the evaluation/modulation assembly 312. Greater portions of the on-axis or near axis travelling neural structures are exposed and susceptible to the neuromodulation energy provided by the evaluation/modulation assembly 312 than a perpendicular travelling neural structure, which may only be exposed to therapeutic energy at a discrete cross-section. Therefore, the evaluation/modulation assembly 312 is more likely to have a greater effect on the on-axis or near axis travelling neural structures. The identification of the neural structure positions (e.g., via complex impedance or resistance mapping) can also allow targeted energy delivery to travelling neural structures rather than branching neural structures (typically downstream of the travelling neural structures) because the travelling neural structures are closer to the nerve origin and, therefore, more of the nerve is affected by therapeutic neuromodulation, thereby resulting in a more efficient treatment and/or a higher efficacy of treatment. Similarly, the identification of neural structure positions can be used to target travelling and branching neural structures over terminal neural structures. In some embodiments, the treatment parameters can be adjusted based on the detected neural positions to provide a selective regional effect. For example, a clinician can target downstream portions of the neural structures if only wanting to influence partial effects on very specific anatomical structures or positions.

[0081] In various embodiments, neural locations and/or relative positions of nerves can be determined by detecting the nerve-firing voltage and/or current over time. An array of the electrodes 344 can be positioned in contact with tissue at the interest zone, and the electrodes 344 can measure the voltage and/or current associated with nerve-firing. This information can optionally be mapped (e.g., on a display 322) to identify the location of nerves in a hyper

state (i.e., excessive parasympathetic tone). Rhinitis is at least in part the result of over-firing nerves because this hyper state drives the hyper-mucosal production and hyper-mucosal secretion. Therefore, detection of nerve firing rate via voltage and current measurements can be used to locate the portions of the interest region that include hyper-parasympathetic neural function (i.e., nerves in the diseased state). This allows the clinician to locate specific nerves (i.e., nerves with excessive parasympathetic tone) before neuromodulation therapy, rather than simply targeting all parasympathetic nerves (including non-diseased state parasympathetic nerves) to ensure that the correct tissue is treated during neuromodulation therapy. Further, nerve firing rate can be detected during or after neuromodulation therapy so that the clinician can monitor changes in nerve firing rate to validate treatment efficacy. For example, recording decreases or elimination of nerve firing rate after neuromodulation therapy can indicate that the therapy was effective in therapeutically treating the hyper/diseased nerves.

[0082] In various embodiments, the system 300 can detect neural activity using dynamic activation by injecting a stimulus signal (i.e., a signal that temporarily activates nerves) via one or more of the electrodes 344 to induce an action potential, and other pairs of electrodes 344 can detect bioelectric properties of the neural response. Detecting neural structures using dynamic activation involves detecting the locations of action potentials within the interest zone by measuring the discharge rate in neurons and the associated processes. The ability to numerically measure, profile, map, and/or image fast neuronal depolarization for generating an accurate index of activity is a factor in measuring the rate of discharge in neurons and their processes. The action potential causes a rapid increase in the voltage across nerve fiber and the electrical impulse then spreads along the fiber. As an action potential occurs, the conductance of a neural cell membrane changes, becoming about 40 times larger than it is when the cell is at rest. During the action potential or neuronal depolarization, the membrane resistance diminishes by about 80 times, thereby allowing an applied current to enter the intracellular space as well. Over a population of neurons, this leads to a net decrease in the resistance during coherent neuronal activity, such as chronic para-sympathetic responses, as the intracellular space will provide additional conductive ions. The magnitude of such fast changes has been estimated to have local resistivity changes with recording near DC is 2.8–3.7% for peripheral nerve bundles (e.g., including the nerves in the nasal cavity).

[0083] Detecting neural structures using dynamic activation includes detecting the locations of action potentials within the interest zone by measuring the discharge rate in neurons and the associated processes. The basis of each this discharge is the action potential, during which there is a depolarization of the neuronal membrane of up to 110 mV or more, lasting approximately 2 milliseconds, and due to the transfer of micromolar quantities of ions (e.g., sodium and potassium) across the cellular membrane. The complex impedance or resistance change due to the neuronal membrane falls from 1000 to 25 Ω cm. The introduction of a stimulus and subsequent measurement of the neural response can attenuate noise and improve signal to noise ratios to precisely focus on the response region to improve neural detection, measurement, and mapping.

[0084] In some embodiments, the difference in measurements of physiological parameters (e.g., complex impedance, resistance, voltage) over time, which can reduce errors, can be used to create a neural profiles, spectrums, or maps. For example, the sensitivity of the system 300 can be improved because this process provides repeated averaging to a stimulus. As a result, the mapping function outputs can be a unit-less ratio between the reference and test collated data at a single frequency and/or multiple frequencies and/or multiple amplitudes. Additional considerations may include multiple frequency evaluation methods that consequently expand the parameter assessments, such as resistivity, admittivity, center frequency, or ratio of extra- to intracellular resistivity.

[0085] In some embodiments, the system 300 may also be configured to indirectly measure the electrical activity of neural structures to quantify the metabolic recovery processes that accompany action potential activity and act to restore ionic gradients to normal. These are related to an accumulation of ions in the extracellular space. The indirect measurement of electrical activity can be approximately a thousand times larger (in the order of millimolar), and thus are easier to measure and can enhance the accuracy of the measured electrical properties used to generate the neural maps.

[0086] The system 300 can perform dynamic neural detection by detecting nerve-firing voltage and/or current and, optionally, nerve firing rate over time, in response to an external stimulation of the nerves. For example, an array of the electrodes 344 can be positioned in contact with tissue at the interest zone, one or more of the electrodes 344 can be activated to inject a signal into the tissue that stimulates the nerves, and other electrodes 344 of the electrode array can measure the neural voltage and/or current due to nerve firing in response to the stimulus. This information can optionally be mapped (e.g., on a display 322) to

identify the location of nerves and, in certain embodiments, identify parasympathetic nerves in a hyper state (e.g., indicative of Rhinitis or other diseased state). The dynamic detection of neural activity (voltage, current, firing rate, etc.) can be performed before neuromodulation therapy to detect target nerve locations to select the target site and treatment parameters to ensure that the correct tissue is treated during neuromodulation therapy. Further, dynamic detection of neural activity can be performed during or after neuromodulation therapy to allow the clinician to monitor changes in neural activity to validate treatment efficacy. For example, recording decreases or elimination of neural activity after neuromodulation therapy can indicate that the therapy was effective in therapeutically treating the hyper/diseased nerves.

[0087] As described in further detail below with respect to Figure 9, in some embodiments a stimulating signal can be delivered to the vicinity of the targeted nerve via one or more penetrating electrodes (e.g., microneedles that penetrate tissue) associated with the evaluation/modulation assembly 312 and/or a separate device. The stimulating signal generates an action potential, which causes smooth muscle cells or other cells to contract. The location and strength of this contraction can be detected via the penetrating electrode(s) and, thereby, indicate to the clinician the distance to the nerve and/or the location of the nerve relative to the stimulating needle electrode. In some embodiments, the stimulating electrical signal may have a voltage of typically 1-2 mA or greater and a pulse width of typically 100-200 microseconds or greater. Shorter pulses of stimulation result in better discrimination of the detected contraction, but may require more current. The greater the distance between the electrode and the targeted nerve, the more energy is required to stimulate. The stimulation and detection of contraction strength and/or location enables identification of how close or far the electrodes are from the nerve, and therefore can be used to localize the nerve spatially. In some embodiments, varying pulse widths may be used to measure the distance to the nerve. As the needle becomes closer to the nerve, the pulse duration required to elicit a response becomes less and less.

[0088] To localize nerves via muscle contraction detection, the system 300 can vary pulse-width or amplitude to vary the energy (Energy=pulse-width*amplitude) of the stimulus delivered to the tissue via the penetrating electrode(s). By varying the stimulus energy and monitoring muscle contraction via the penetrating electrodes and/or other type of sensor, the system 300 can estimate the distance to the nerve. If a large amount of energy is required to stimulate the nerve/contract the muscle, the stimulating/penetrating electrode is far from the

nerve. As the stimulating/penetrating electrode, moves closer to the nerve, the amount of energy required to induce muscle contraction will drop. For example, an array of penetrating electrodes can be positioned in the tissue at the interest zone and one or more of the electrodes can be activated to apply stimulus at different energy levels until they induce muscle contraction. Using an iterative process, localize the nerve (e.g., via the mapping/evaluation/feedback algorithm 320).

[0089] In some embodiments, the system 300 can measure the muscular activation from the nerve stimulus (e.g., via the electrodes 344) to determine neural positioning for neural mapping, without the use of penetrating electrodes. In this embodiment, the treatment device targets the smooth muscle cells' varicosities surrounding the submucosal glands and the vascular supply, and then the compound muscle action potential. This can be used to summate voltage response from the individual muscle fiber action potentials. The shortest latency is the time from stimulus artifact to onset of the response. The corresponding amplitude is measured from baseline to negative peak and measured in millivolts (mV). Nerve latencies (mean ± SD) in adults typically range about 2-6 milliseconds, and more typically from about 3.4 ± 0.8 to about 4.0 ± 0.5 milliseconds. A comparative assessment may then be made which compares the outputs at each time interval (especially pre- and post-energy delivery) in addition to a group evaluation using the alternative nasal cavity. This is expected to provide an accurate assessment of the absolute value of the performance of the neural functioning because muscular action/activation may be used to infer neural action/activation and muscle action/activation is a secondary effect or by-product whilst the neural function is the absolute performance measure.

[0090] In some embodiments, the system 300 can record a neuromagnetic field outside of the nerves to determine the internal current of the nerves without physical disruption of the nerve membrane. Without being bound by theory, the contribution to the magnetic field from the current inside the membrane is two orders of magnitude larger than that from the external current, and that the contribution from current within the membrane is substantially negligible. Electrical stimulation of the nerve in tandem with measurements of the magnetic compound action fields ("CAFs") can yield sequential positions of the current dipoles such that the location of the conduction change can be estimated (e.g., via the least-squares method). Visual representation (e.g., via the display 322) using magnetic contour maps can show normal or non-normal neural characteristics (e.g., normal can be equated with a

characteristic quadrupolar pattern propagating along the nerve), and therefore indicate which nerves are in a diseases, hyperactive state and suitable targets for neuromodulation.

[0091] During magnetic field detection, an array of the electrodes 344 can be positioned in contact with tissue at the interest zone and, optionally, one or more of the electrodes 344 can be activated to inject an electrical stimulus into the tissue. As the nerves in the interest zone fire (either in response to a stimulus or in the absence of it), the nerve generates a magnetic field (e.g., similar to a current carrying wire), and therefore changing magnetic fields are indicative of the nerve nerve-firing rate. The changing magnetic field caused by neural firing can induce a current detected by nearby sensor wire (e.g., the sensor 314) and/or wires associated with the nearby electrodes 344. By measuring this current, the magnetic field strength can be determined. The magnetic fields can optionally be mapped (e.g., on a display 322) to identify the location of nerves and select target nerves (nerves with excessive parasympathetic tone) before neuromodulation therapy to ensure that the desired nerves are treated during neuromodulation therapy. Further, the magnetic field information can be used during or after neuromodulation therapy so that the clinician can monitor changes in nerve firing rate to validate treatment efficacy.

[0092] In other embodiments, the neuromagnetic field is measured with a Hall Probe or other suitable device, which can be integrated into the evaluation/modulation assembly 312 and/or part of a separate device delivered to the interest zone. Alternatively, rather than measuring the voltage in the second wire, the changing magnetic field can be measured in the original wire (i.e. the nerve) using a Hall probe. A current going through the Hall probe will be deflected in the semi-conductor. This will cause a voltage difference between the top and bottom portions, which can be measured. In some aspects of this embodiments, three orthogonal planes are utilized.

[0093] In some embodiments, the system 300 can be used to induce electromotive force ("EMF") in a wire (i.e., a frequency-selective circuit, such as a tunable/LC circuit) that is tunable to resonant frequency of a nerve. In this embodiment, the nerve can be considered to be a current carrying wire, and the firing action potential is a changing voltage. This causes a changing current which, in turn, causes a changing magnetic flux (i.e., the magnetic field that is perpendicular to the wire). Under Faraday's Law of Induction/Faraday's Principle, the changing magnetic flux induces EMF (including a changing voltage) in a nearby sensor wire (e.g., integrated into the evaluation/modulation assembly 312, the sensor 314, and/or other structure), and the changing voltage can be measured via the system 300.

[0094] In further embodiments, the sensor wire (e.g., the sensor 314) is an inductor and, therefore, provides an increase of the magnetic linkage between the nerve (i.e., first wire) and the sensor wire (i.e., second wire), with more turns for increasing effect. (e.g., V2,rms = V1,rms (N2/N1)). Due to the changing magnetic field, a voltage is induced in the sensor wire, and this voltage can be measured and used to estimate current changes in the nerve. Certain materials can be selected to enhance the efficiency of the EMF detection. For example, the sensor wire can include a soft iron core or other high permeability material for the inductor.

[0095] During induced EMF detection, the evaluation/modulation assembly 312 and/or other device including a sensor wire is positioned in contact with tissue at the interest zone and, optionally, one or more of the electrodes 344 can be activated to inject an electrical stimulus into the tissue. As the nerves in the interest zone fire (either in response to a stimulus or in the absence of it), the nerve generates a magnetic field (e.g., similar to a current carrying wire) that induces a current in the sensor wire (e.g., the sensor 314). This information can be used to determine neural location and/or map the nerves (e.g., on a display 322) to identify the location of nerves and select target nerves (nerves with excessive parasympathetic tone) before neuromodulation therapy to ensure that the desired nerves are treated during neuromodulation therapy. EMF information can also be used during or after neuromodulation therapy so that the clinician can monitor changes in nerve firing rate to validate treatment efficacy.

[0096] In some embodiments, the system 300 can detect magnetic fields and/or EMF generated at a selected frequency that corresponds to a particular type of nerve. The frequency and, by extension, the associated nerve type of the detected signal can be selected based on an external resonant circuit. Resonance occurs on the external circuit when it is matched to the frequency of the magnetic field of the particular nerve type and that nerve is firing. In manner, the system 300 can be used to locate a particular sub-group/type of nerves.

[0097] In some embodiments, the system 300 can include a variable capacitor frequency-selective circuit to identify the location and/or map specific nerves (e.g., parasympathetic nerve, sensory nerve, nerve fiber type, nerve subgroup, etc.). The variable capacitor frequency-selective circuit can be defined by the sensor 314 and/or other feature of the evaluation/modulation assembly 312. Nerves have different resonant frequencies based on their function and structure. Accordingly, the system 300 can include a tunable LC circuit with a variable capacitor (C) and/or variable inductor (L) that can be selectively tuned to the

resonant frequency of desired nerve types. This allows for the detection of neural activity only associated with the selected nerve type and its associated resonant frequency. Tuning can be achieved by moving the core in and out of the inductor. For example, tunable LC circuits can tune the inductor by: (i) changing the number of coils around the core; (ii) changing the cross-sectional area of the coils around the core; (iii) changing the length of the coil; and/or (iv) changing the permeability of the core material (e.g., changing from air to a core material). Systems including such a tunable LC circuit provide a high degree of dissemination and differentiation not only as to the activation of a nerve signal, but also with respect to the nerve type that is activated and the frequency at which the nerve is firing.

Anatomical Mapping

[0098] In various embodiments, the system 300 is further configured to provide minimally-invasive anatomical mapping that uses focused energy current/voltage stimuli from a spatially localized source (e.g., the electrodes 344) to cause a change in the conductivity of the of the tissue at the interest zone and detect resultant biopotential and/or bioelectrical measurements (e.g., via the electrodes 344). The current density in the tissue changes in response to changes of voltage applied by the electrodes 344, which creates a change in the electric current that can be measured with the evaluation/modulation assembly 312 and/or other portions of the system 300. The results of the bioelectrical and/or biopotential measurements can be used to predict or estimate relative absorption profilometry to predict or estimate the tissue structures in the interest zone. More specifically, each cellular construct has unique conductivity and absorption profiles that can be indicative of a type of tissue or structure, such as bone, soft tissue, vessels, nerves, types of nerves, and/or certain neural structures. For example, different frequencies decay differently through different types of tissue. Accordingly, by detecting the absorption current in a region, the system 300 can determine the underlying structure and, in some instances, to a sub-microscale, cellular level that allows for highly specialized target localization and mapping. This highly specific target identification and mapping enhances the efficacy and efficiency of neuromodulation therapy, while also enhancing the safety profile of the system 300 to reduce collateral effects on non-target structures.

[0099] To detect electrical and dielectric tissue properties (e.g., resistance, complex impedance, conductivity, and/or, permittivity as a function of frequency), the electrodes 344 and/or another electrode array is placed on tissue at an interest region, and an internal or external source (e.g., the generator 316) applies stimuli (current/voltage) to the tissue. The

electrical properties of the tissue between the source and the receiver electrodes 344 are measured, as well as the current and/or voltage at the individual receiver electrodes 344. These individual measurements can then be converted into an electrical map/image/profile of the tissue and visualized for the user on the display 322 to identify anatomical features of interest and, in certain embodiments, the location of firing nerves. For example, the anatomical mapping can be provided as a color-coded or gray-scale three-dimensional or two-dimensional map showing differing intensities of certain bioelectric properties (e.g., resistance, impedance, etc.), or the information can be processed to map the actual anatomical structures for the clinician. This information can also be used during neuromodulation therapy to monitor treatment progression with respect to the anatomy, and after neuromodulation therapy to validate successful treatment. In addition, the anatomical mapping provided by the bioelectrical and/or biopotential measurements can be used to track the changes to non-target tissue (e.g., vessels) due to neuromodulation therapy to avoid negative collateral effects. For example, a clinician can identify when the therapy begins to ligate a vessel and/or damage tissue, and modify the therapy to avoid bleeding, detrimental tissue ablation, and/or other negative collateral effects.

[00100] Furthermore, the threshold frequency of electric current used to identify specific targets can subsequently be used when applying therapeutic neuromodulation energy. For example, the neuromodulation energy can be applied at the specific threshold frequencies of electric current that are target neuronal-specific and differentiated from other non-targets (e.g., blood vessels, non-target nerves, etc.). Applying ablation energy at the target-specific frequency results in an electric field that creates ionic agitation in the target neural structure, which leads to differentials in osmotic potentials of the targeted neural structures. These osmotic potential differentials cause dynamic changes in neuronal membronic potentials (resulting from the difference in intra-cellular and extra-cellular fluidic pressure) that lead to vacuolar degeneration of the targeted neural structures and, eventually, necrosis. Using the highly targeted threshold neuromodulation energy to initiate the degeneration allows the system 300 to delivery therapeutic neuromodulation to the specific target, while surrounding blood vessels and other non-target structures are functionally maintained.

[00101] In some embodiments, the system 300 can further be configured to detect bioelectrical properties of tissue by non-invasively recording resistance changes during neuronal depolarization to map neural activity with electrical impedance, resistance, bio-impedance, conductivity, permittivity, and/or other bioelectrical measurements. Without

being bound by theory, when a nerve depolarizes, the cell membrane resistance decreases (e.g., by approximately 80x) so that current will pass through open ion channels and into the intracellular space. Otherwise the current remains in the extracellular space. For non-invasive resistance measurements, tissue can be stimulated by applying a current of less than 100 Hz, such as applying a constant current square wave at 1 Hz with an amplitude less than 25% (e.g., 10%) of the threshold for stimulating neuronal activity, and thereby preventing or reducing the likelihood that the current does not cross into the intracellular space or stimulating at 2 Hz. In either case, the resistance and/or complex impedance is recorded by recording the voltage changes. A complex impedance or resistance map or profile of the area can then be generated (e.g., as shown in Figure 6).

[00102] For impedance/conductivity/permittivity detection, the electrodes 344 and/or another electrode array are placed on tissue at an interest region, and an internal or external source (e.g., the generator 316) applies stimuli to the tissue, and the current and/or voltage at the individual receiver electrodes 344 is measured. The stimuli can be applied at different frequencies to isolate different types of nerves. These individual measurements can then be converted into an electrical map/image/profile of the tissue and visualized for the user on the display 322 to identify anatomical features of interest. The neural mapping can also be used during neuromodulation therapy to select specific nerves for therapy, monitor treatment progression with respect to the nerves and other anatomy, and validate successful treatment.

[00103] In some embodiments of the neural and/or anatomical detection methods described above, the procedure can include comparing the mid-procedure physiological parameter(s) to the baseline physiological parameter(s) and/or other, previously-acquired mid-procedure physiological parameter(s) (within the same energy delivery phase). Such a comparison can be used to analyze state changes in the treated tissue. The mid-procedure physiological parameter(s) may also be compared to one or more predetermined thresholds, for example, to indicate when to stop delivering treatment energy. In some embodiments of the present technology, the measured baseline, mid-, and post-procedure parameters include a complex impedance. In some embodiments of the present technology, the post-procedure physiological parameters are measured after a pre-determined time period to allow the dissipation of the electric field effects (ionic agitation and/or thermal thresholds), thus facilitating accurate assessment of the treatment.

[00104] In some embodiments, the anatomical mapping methods described above can be used to differentiate the depth of soft tissues within the nasal mucosa. The depth of mucosa

on the turbinates is great whilst the depth off the turbinate is shallow and, therefore, identifying the tissue depth in the present technology also identifies positions within the nasal mucosa and where precisely to target. Further, by providing the micro-scale spatial impedance mapping of epithelial tissues as described above, the inherent unique signatures of stratified layers or cellular bodies can be used as identifying the region of interest. For example, different regions have larger or small populations of specific structures, such as submucosal glands, so target regions can be identified via the identification of these structures.

[00105] In some embodiments, the system 300 includes additional features that can be used to detect anatomical structures and map anatomical features. For example, the system 300 can include an ultrasound probe for identification of neural structures and/or other anatomical structures. Higher frequency ultrasound provides higher resolution, but less depth of penetration. Accordingly, the frequency can be varied to achieve the appropriate depth and resolution for neural/anatomical localization. Functional identification may rely on the spatial pulse length ("SPL") (wavelength multiplied by number of cycles in a pulse). Axial resolution (SPL/2) may also be determined to locate nerves.

[00106] In some embodiments, the system 300 can further be configured to emit stimuli with selective parameters that suppress rather than fully stimulate neural activity. for example, in embodiments where the strength–duration relationship for extracellular neural stimulation is selected and controlled, a state exists where the extracellular current can hyperpolarize cells, resulting in suppression rather than stimulation spiking behavior (i.e., a full action potential is not achieved). Both models of ion channels, HH and RGC, suggest that it is possible to hyperpolarize cells with appropriately designed burst extracellular stimuli, rather than extending the stimuli. This phenomenon could be used to suppress rather than stimulate neural activity during any of the embodiments of neural detection and/or modulation described herein.

Selected Embodiments of Evaluation and Neuromodulation Devices

[00107] Figures 8A and 8B are isometric views of a distal portion of a neuromodulation and mapping device 802 ("device 802") configured in accordance with an embodiment of the present technology. The device 802 can include various features generally similar to the features of the device 302 described above with reference to Figures 3A and 3B. For example, the device 802 includes an evaluation/modulation assembly 812 at the distal portion

308b of the shaft 308. The evaluation/modulation 812 includes a plurality of struts 340 that form branches 346 and define an expandable frame or basket 342, and optionally include one or more electrodes 344 disposed on one or more of the struts 340. As shown in Figures 8A and 8B, the device 802 can further include an expandable member 856 (e.g., a balloon) carried by the support member 348 and expandable within the basket 342. The expandable member 856 can include one or more electrodes 858 that extend in a circumferential pattern across the outer surface of the expandable member 856. For example, the one or more electrodes 858 can define a coil shape disposed on the expandable member 856. The electrodes 858 can be used for detection of bioelectric features (e.g., complex impedance, resistance, etc.) to allow for mapping of the anatomy at the interest zone before, during, and/or after therapeutic neuromodulation via the other electrodes 344. In other embodiments, the electrodes 858 can be configured to apply energy for therapeutic neuromodulation.

[00108] As shown in Figure 8B, the electrode(s) 858 can be positioned across a substantial portion of the expandable member 856 that proves an expansive area at which impedance and/or other properties can be detected across the tissue and, therefore, may provide a more detailed mapping of the tissue and nerves at the treatment site. The expandable member 856 can also closely conform to the adjacent tissue at the zone of interest and, therefore, facilitate contact between the electrode(s) 858 and the tissue. In other embodiments, the electrodes 858 can have different configurations on the outer surface of the expandable member 856. When there are multiple electrodes 358, the individual electrodes 858 can be selectively activated at a specific polarity, and therefore the electrode array can be configured in a variety of static configurations and a dynamically change sequences (e.g., sesquipolar application of current) that may be advantageous for mapping functions.

[00109] In operation, the expandable member 856 can be inflated or otherwise expanded (Figure 8B) to place at least a portion of the electrodes 858 into contact with tissue at the target site. The electrodes 858 can measure various bioelectric properties of the tissue (e.g., impedance, action potentials, etc.) to detect, locate, and/or map the neural structures and/or other anatomical structures at the interest zone. In certain embodiments, the electrodes 344 on the struts 340 and/or a portion of the electrodes 858 on the expandable member 856 can apply a stimulating pulse of RF energy, and the electrodes 858 can detect the resultant neural response. After mapping, the expandable member 856 can be deflated or collapsed (Figure 8A), and the electrodes 344 on the struts 340 can apply therapeutically effective neuromodulation energy to the target site. For example, the ablation pattern of the electrodes

344 can be based on the neural locations identified via the information detected from the sensing electrodes 858 on the expandable member 856. In other embodiments, the expandable member 856 may remain expanded during neuromodulation, and the electrodes 858 can detect neural activity during the neuromodulation procedure or the electrodes 858 can themselves be configured to apply neuromodulation energy to the treatment site. After applying the neuromodulation energy, the electrodes 858 on the expandable member 856 can again be placed into contact with tissue at the target site, and used to record bioelectric properties (e.g., impedance, resistance, voltage, etc.). The detected properties taken before, during, and/or after neuromodulation can be compared to each other to determine whether the neuromodulation was therapeutically effective. If not, the electrodes 344 can again apply therapeutic neuromodulation energy to the same treatment site, or the configuration of the active electrodes 344 can be changed to apply therapeutic neuromodulation energy in a different pattern or sequence, and/or the evaluation/modulation assembly 812 can be moved to a different treatment site.

[00110] Figure 9 is an enlarged isometric view of a distal portion of a neuromodulation and mapping device 902 ("device 902") configured in accordance with some embodiments of the present technology. The device 902 can include various features generally similar to the features of the device 802 described above with reference to Figures 8A and 8B. For example, the device 902 includes an evaluation/modulation assembly 912 that includes the plurality of struts 340 (optionally including electrodes 344 disposed thereon) that form the expandable frame or basket 342 and the expandable member 856 (e.g., a balloon) inflatable within the basket 342 via an inflation media (e.g., a fluid, coolant, etc.). As shown in Figure 9, the expandable member 856 includes one or more protruding or penetrating electrodes 960 that extend across the outer surface of the expandable member 856 in a circumferential pattern to define a three-dimensional microneedle array. The penetrating electrodes 960 can be very small needles and/or other structures with sharp end portions that penetrate a small depth into adjacent tissue when the expandable member 856 is expanded. For example, the needle electrodes 960 may have a tip diameter on the micron level (e.g., 1 micron diameter, 2 micron diameter, 3 micron diameter, 1-20 micron diameter, etc.), a length of 50-350 microns (e.g., 150 microns, 210 microns, 250 microns, etc.), and/or tips coated in platinum black and/or other suitable materials. In other embodiments, the protruding needle electrodes 960 have different sizes, different material composition, and/or are arranged in different patterns across the expandable member 856 (e.g., in an asymmetrical pattern) that facilitate

penetration into adjacent tissue and/or detection of desired tissue parameters. In some embodiments, for example, the penetrating electrodes 960 can be fabricated by selective vapor-liquid-solid growth of a silicon wire. In further embodiments, the penetrating electrodes 960 can define a microneedle array on a different portion of the device 902 (e.g., along the struts 340) and/or on a substrate separate from the evaluation/modulation assembly 912. For example, the penetrating electrodes 960 can be positioned on substrate (e.g., a paddle) that can be pressed into contact with tissue to drive the electrodes 960 a small depth into the tissue. The penetrating electrodes 960 may also be deployable and/or retractable. In some embodiments, the penetrating electrodes 960 can be integrated with the metal oxide semiconductor process for high-performance on-chip electronics configurations. In some embodiments, the electrodes 344 on the struts 340 and/or other electrodes on the evaluation/modulation assembly 912 can be replaced by deployable and/or protruding/retractable penetrating needle electrodes.

[00111] The electrodes 960 can be used for detection of bioelectric features (e.g., impedance, resistance, etc.) and/or other detectable parameters to allow for mapping of the neural and/or other anatomy at the interest zone before, during, and/or after therapeutic neuromodulation via the other electrodes 344. In other embodiments, the penetrating electrodes 960 can be configured to apply energy for therapeutic neuromodulation. The device 902 requires only a minimal level of invasiveness, but is expected to provide high spatial resolution and high level of accuracy due to the broad area covered by the penetrating electrodes, the high density of the electrodes 960 across the area, and the penetration into the tissue of interest. In some embodiments, for example, the output/input signal amplitude ratios may be > 90% at about 40 Hz to about 10 KHz. The device 902 can be used in chronic as well as acute cases.

[00112] In various embodiments, the expandable member 856 of the devices 802 and 902 described above with respect to Figures 8A-9 can be used as a drug delivery mechanism for delivering a local anesthetic pre- or post-procedurally, a neurotoxin (e.g., to stimulate or modulate nerves at the target site), and/or other drugs or chemicals. The expandable member 856 can be made from a porous material with a plurality of openings or voids for drug expulsion (e.g., eluding drugs disposed within the expandable member 856). The expandable member 856 can also include drugs loaded or embedded within the wall of the expandable member 856 such that pressure against the drug-loaded wall by the tissue causes drug

elusion. The neural and anatomical mapping systems and methods described above can be used to ensure precision and accuracy of the drug delivery.

[00113] Any of the therapeutic or detection assemblies and devices disclosed herein may be semi-permanently implanted rather than connected to a catheter shaft (for temporary delivery to the treatment site). For implanted embodiments, any of the devices and methods disclosed herein may be used to obtain feedback to locate the appropriate implant site, position the device for long-term implantation, confirm device functionality (e.g., for neural blocking) *in-situ* and in real-time, and/or to confirm the functionality of the implantable device over the lifetime of the device, the disease, and/or the patient.

[00114] In some embodiments, for example, the evaluation/modulation assembly 312 (Figure 3A) is part of an implantable device separate from the catheter shaft 308 to allow for continued use of the evaluation/modulation assembly 312 over an extended period of time (i.e., not only during the procedure). For example, the implantable device can include a micro-stimulator/modulator (e.g., the evaluation/modulation 312 with the electrodes 344) that is permanently or semi-permanently implanted at a treatment site and a hermetically- or mechanically-sealed controller coupled to the implantable device. In various embodiments, the implantable device can include a variable resistive element, a variable capacitive element, one or more electrodes, and/or fixation or anchoring elements that position the electrodes against tissue within the target site (e.g., within the nasal cavity).

[00115] In various embodiments, the implantable device is powered wirelessly by an external unit spaced apart from the monitoring and therapeutic assembly and the treatment site. For example, the external power unit can be worn by the patient , implanted within the patient (e.g., subdermally, within a cavity, etc.) apart from the monitoring and therapeutic assembly, and/or otherwise spaced apart from the treatment site. The device may have a power source that is not reliant on a battery to avoid additional clinical intervention. For example, the device may use capacitive coupling to charge/receive transient charge and/or generation of a magnetic field to couple to the power unit. In some embodiments, magnetic resonant coupling may be the connection mechanism regarding wireless/battery connectivity and coupling.

[00116] The implantable device treats conditions, such as rhinitis, by electrically modulating the parasympathetic nerve pathway to the nasal cavity in a similar manner as the system 300 described above with reference to Figures 3A-3B, but may provide neural

modulation and/or anatomical mapping over an extended period of time (e.g., outside of a procedure) and may be activated at the onset of a predefined sensed trigger (e.g., hyperactivity of the mucosal glad or the parasympathetic nerves). For example, in some embodiments, the modulation may be delivered in bursts in response to threshold levels of autonomic activity. In some embodiments, the modulation may be delivered by a patient in response to symptomatic conditions associated with the disease state (e.g., allergic symptoms as perceived by the patient such as hay fever triggers, sneezing, excessive rhinorrhea, congestion, etc.). The modulation provided by the implantable device may selectively stimulate or modulate parasympathetic fibers, sympathetic fibers, sensory fibers, alpha/beta/delta fibers, C-fibers, anoxic terminals of one or more of the foregoing, insulated over non-insulated fibers (regions with fibers), and/or other neural structures. In some embodiments, the implantable device may selectively target specific cells or cellular regions, such as smooth muscle cells, sub-mucosal glands, goblet cells, stratified cellular regions within the nasal mucosa. These target sites may be identified during anatomical mapping of neural structures and/or other tissues before implantation of the device, during implantation, and/or while the device is implanted.

[00117] The implantable device may be deployed at the target site via a delivery system (e.g., a catheter) using anatomical mapping (including neural mapping) for landmarks and positional accuracy as described above. For example, the delivery system may locate and eject the implantable device on, partially within, or fully into the nasal mucosa. The delivery system may be spring loaded, piston activated, hydraulically activated, and/or otherwise activated to deploy the implantable device from a distal end of the delivery system. When the implantable device is configured to be positioned or otherwise anchored at least partially under the surface of the nasal walls, the delivery system may include a suction tip, a needle tip, a dissection tip, a retractable blade with a rotational member/action, and/or other sharp structures that can form an opening and an insertion pathway into the soft tissue.

[00118] The implant delivery system may further include linkages or couplings that connect a distal end portion of the delivery system (including deployment and access components) to a proximal handle of the delivery system. Deployment of the implantable device from the delivery system may be driven by sliders, pistons, depression buttons, rotational elements, and/or other actuators at the proximal handle that advance or initiate implantation mechanisms of the delivery system. In some embodiments, the delivery system may have a range/stroke limiting mechanism and/or other restrictive features to limit

insertion depth. In some embodiments, the delivery system may have suction functionality to control tissue/device interface and the entry angulation of implant. In some embodiments, the delivery system has an angulated/circumferential orientation control to selectively position implant point of entry. The delivery system may also have micro-positional capabilities to fine-tune positional accuracy based on neural locations. In some embodiments, the distal tip of the implantable device is electrically coupled to the delivery system when the implantable device is in a delivery state (before deployment) and acts independently or in conjunction with other features of the delivery system to provide neural mapping and measuring features and refine positional accuracy. In various embodiments, the evaluation/modulation assembly 312 (Figure 3A) and the device 302 (Figure 3A) can include similar features as those described above with respect to the implantable device and the delivery system.

[00119] The neural and anatomical mapping systems, devices, and methods, disclosed herein can also be used with respect to anatomical structures outside of the nasal cavity and/or additional diseased states, including any peripheral nervous system acute or chronic disease state. The present technology may be used to assess and/or monitor (short-term and/or long-term) neural/neuro-muscular degenerative disease states, intraoperative neuroma-in-continuity, and the nerve regeneration and degenerative neuromuscular disorders. Other examples disease states treatable with the present technology include: acute inflammatory demyelinating polyneuropathy ("AIDP"), Multiple Sclerosis ("MS"), acute motor axonal neuropathy ("MAN"), Lambert-Eaton myasthenic syndrome ("LEMS"), myasthenia gravis ("MG"), neuromuscular transmission disorders ("NMTD"), peripheral neurophysiological examination ("PNE"), any neuromuscular transmission disorder of nerve terminal function, transmitter production, storage, and/or release, pre-/post-synaptic membrane structure and function, receptor dynamics, endplate potentials, propagated muscle action potentials, and others.

Additional Examples

[00120] Several aspects of the present technology are set forth in the following additional examples.

1. A system for detecting anatomical structures and therapeutic neuromodulation in a nasal region of a human patient, the system comprising:

a shaft having a proximal portion and a distal portion, wherein the shaft is configured to locate the distal portion intraluminally at a target site within a nasal cavity inferior to a sphenopalatine foramen of the human patient;

an evaluation/modulation assembly at the distal portion of the shaft, wherein the evaluation/modulation assembly comprises a plurality of electrodes configured to emit stimulating energy to tissue at the target site at frequencies for locating target neural structures and detect bioelectric properties in response to the stimulating energy; and

a console including a controller having a computer-readable medium carrying instructions, which when executed by the controller, causes the console to map locations of the target neural structures and causes the evaluation/modulation assembly to apply therapeutic neuromodulation energy in a predetermined neuromodulation pattern based on the locations of the target neural structures.

2. The system of example 1 wherein at least a portion of the plurality of electrodes are configured to apply RF energy at a predetermined frequency to initiate ionic agitation of the target neural structure to therapeutically modulate postganglionic parasympathetic nerves.

3. The system of example 1 or 2 wherein at least a portion of the plurality of electrodes are configured to apply RF energy at a predetermined frequency to initiate ionic agitation of sub mucosal structures to therapeutically modulate postganglionic parasympathetic tone.

4. The system of any one of examples 1-3 wherein at least a portion of the plurality of electrodes are configured to apply RF energy at a predetermined frequency to initiate vacuolar degeneration of the target neural structure to therapeutically modulate postganglionic parasympathetic nerves.

5. The system of any one of examples 1-4 wherein:

the plurality of electrodes are configured to detect bioelectric properties of non-target anatomical structures at the target site;

the computer-readable medium carrying instructions, which when executed by the controller, causes the console to map locations of non-target anatomical structures and causes the evaluation/modulation assembly to apply neuromodulation energy in the predetermined pattern to avoid the locations of the non-target anatomical structures.

6. The system of any one of examples 1-5, further comprising a display configured to visualize locations of the target neural structures with respect to a predicted neuromodulation zone defined by the predetermined neuromodulation pattern.

7. The system of any one of examples 1-6 wherein the plurality of electrodes are configured to detect bioelectric properties of tissue at the treatment site before therapeutic neuromodulation, during therapeutic neuromodulation, and/or after therapeutic neuromodulation.

8. The system of example 7 wherein the bioelectric properties include at least one of complex impedance, resistance, reactance, capacitance, inductance, permittivity, conductivity, nerve firing voltage, nerve firing current, magnetic field, and induced electromotive force.

9. The system of any one of examples 1-8 wherein the evaluation/modulation assembly comprises:

a basket transformable between a low-profile delivery state and an expanded state, wherein the basket includes plurality of struts spaced radially apart from each other when the basket is in the expanded state, wherein—

the plurality of electrodes are disposed on the struts,

the plurality of struts are configured to position at least two of the electrodes at the target site when the basket is in the expanded state, and

the electrodes are configured to apply radiofrequency (RF) energy to the target site to therapeutically modulate parasympathetic nerves proximate to the target site.

10. The system of example 9 wherein the evaluation/modulation assembly further comprises:

an expandable member within the basket and transformable between a low-profile delivery state to an expanded state, wherein at least a portion of the plurality of electrodes are disposed on an exterior surface of the expandable surface.

11. The system of example 10 wherein the balloon comprises a plurality of holes configured to allow perfusion of a drug through the balloon when the balloon is in the expanded state.

12. The system of example 9 wherein the evaluation/modulation assembly further comprises:

an expandable member within the basket and transformable between a low-profile delivery state to an expanded state; and

at least one sensing electrode disposed on the expandable member, wherein the sensing electrode defines a coiled shape extending around a circumferential portion of the expandable member.

13. The system of example 9 wherein the evaluation/modulation assembly further comprises:

an expandable member within the basket and transformable between a low-profile delivery state to an expanded state; and

a plurality of penetrating electrodes disposed on an exterior surface of the expandable member, wherein the expandable member is configured to position at least a portion of the penetrating electrodes a depth into tissue at the target site when the expandable member is in the expanded state.

14. The system of any one of examples 1-13 wherein the plurality of electrodes includes an array of penetrating electrodes configured to penetrate a depth into tissue at the target site when the expandable member is in the expanded state.

15. The system of example 14 wherein the penetrating electrodes are configured to detect muscle contraction in response to the stimulating energy.

16. The system of any one of examples 1-15 wherein the evaluation/modulation assembly comprises a balloon transformable between a low-profile delivery state to an expanded state, wherein at least a portion of the plurality of electrodes are disposed on the balloon.

17. The system of any one of examples 1-16 wherein the plurality of electrodes are configured to be independently activated and independently assigned a selective polarity to apply therapeutic neuromodulation across selected regions of the evaluation/modulation assembly.

18. A system for detecting anatomical structures and therapeutic neuromodulation in a nasal region of a human patient, the system comprising:

a shaft having a proximal portion and a distal portion, wherein the shaft is configured to locate the distal portion intraluminally at a target site, wherein the target site is at least one of proximate to the sphenopalatine foramen of a human patient or inferior to the sphenopalatine foramen; and

an evaluation/modulation assembly at the distal portion of the shaft and transformable between a low-profile delivery state and an expanded state, wherein the evaluation/modulation assembly comprises a plurality of electrodes configured to be placed into contact with tissue at the target site when the evaluation/modulation assembly is in the expanded state and measure bioelectric properties of tissue at the target site to identify and locate target anatomical structures and non-target structures; and

a console including a controller having a computer-readable medium carrying instructions, which when executed by the controller, causes the console to map locations of the target anatomical structures and non-target anatomical structures and causes the evaluation/modulation assembly to apply therapeutic neuromodulation energy in a predetermined neuromodulation pattern based on the locations of the target and non-target anatomical structures.

19. The system of example 18 wherein the instructions, when executed by the controller, causes the evaluation/modulation assembly to determine resistance at least proximate to the target site.

20. The system of example 18 or 19 wherein the bioelectric properties are detected before therapeutic neuromodulation, during therapeutic neuromodulation, and/or after therapeutic neuromodulation, and wherein the bioelectric properties include at least one of complex impedance, resistance, reactance, capacitance, inductance, permittivity, conductivity, nerve firing voltage, nerve firing current, magnetic field, and induced electromotive force.

21. The system of any one of examples 18-20 wherein at least a portion of the plurality of electrodes are configured to apply RF energy at a predetermined frequency to activate target anatomical structures for anatomical mapping and/or therapeutic neuromodulation.

22. The system of examples 18-21 wherein the evaluation/modulation assembly comprises:

a frame transformable between the low-profile delivery state and the expanded state, wherein the frame includes plurality of struts spaced radially apart from each other when the frame is in the expanded state, and wherein—

the plurality of electrodes are disposed on the struts, and

the plurality of struts are configured to position at least two of the electrodes at the target site when the frame is in the expanded state.

23. The system of examples 18-22 wherein the evaluation/modulation assembly comprises an expandable member transformable between the low-profile delivery state to the expanded state, wherein at least a portion of the plurality of electrodes are disposed on the expandable member.

24. A method of therapeutically modulating nerves in a nasal region of a human patient, the method comprising:

intraluminally advancing an evaluation/modulation assembly at a distal portion of a shaft of a therapeutic device to a target site within the nasal region, wherein the target site is proximate to parasympathetic nerves, and wherein the evaluation/modulation assembly includes a plurality of electrodes;

delivering stimulation energy to the target site to excite neural structures at the target site, wherein the stimulation energy is emitted at one or more frequencies for locating specific target neural structures;

detecting one or more bioelectric parameters at the target site via at least a portion of the plurality of electrodes of the evaluation/modulation assembly;

based on the detected bioelectric parameters, identifying relative presence and position of target neural structures at the target site; and

determining a neuromodulation pattern based on the locations of the target neural structures to block the detected target neural structures.

25. The method of example 24, further comprising delivering therapeutic neuromodulation energy based on the predetermined neuromodulation pattern.

26. The method of example 25 wherein delivering therapeutic neuromodulation energy further comprises delivering RF energy at a predetermined frequency to initiate ionic agitation of the target neural structure to therapeutically modulate postganglionic parasympathetic nerves.

27. The method of example 25 wherein delivering therapeutic neuromodulation energy further comprises delivering RF energy at a predetermined frequency to initiate ionic agitation of the submucosal structures to therapeutically modulate postganglionic parasympathetic nerves.

28. The method of example 25 wherein delivering therapeutic neuromodulation energy further comprises delivering RF energy at a predetermined frequency to initiate vacuolar degeneration of the target neural structure to therapeutically modulate postganglionic parasympathetic nerves.

29. The method of any one of examples 24-28 wherein detecting one or more bioelectric parameters comprises detecting resistance of the tissue.

30. The method of any one of examples 24-29 wherein detecting one or more bioelectric parameters comprises detecting at least one of nerve firing voltage and nerve firing current.

31. The method of any one of examples 24-30 wherein detecting one or more bioelectric parameters comprises detecting a neuromagnetic field at the target site.

32. The method of any one of examples 24-31 wherein detecting one or more bioelectric parameters comprises detecting induced electromotive force at the target site.

33. The method of any one of examples 24-32 wherein:

detecting one or more bioelectric parameters at the target site comprises detecting bioelectric parameters of non-target anatomical structures at the target site; and

the method further comprises identifying locations of non-target structures at the target site based on the detected bioelectric parameters.

34. The method of any one of examples 24-33, further comprising visually mapping locations of the target neural structures with respect to a predicted neuromodulation zone defined by the predetermined neuromodulation pattern.

35. The method of any one of examples 24-34, further comprising, before delivering stimulation energy, deploying an array of penetrating electrodes such that at least a portion of the penetrating electrodes penetrate a depth into the target tissue, the penetrating electrodes being at least a portion of the plurality of electrodes and disposed on the evaluation/modulation assembly.

36. The method of example 35 wherein:

detecting one or more bioelectric parameters at the target site via at least a portion of the plurality of electrodes of the evaluation/modulation assembly comprises detecting muscle contraction data in response to the stimulation energy via the penetrating electrodes; and

identifying relative presence and position of target neural structures at the target site comprises mapping locations of target neural structures based on the detected muscle contraction data.

37. A method of therapeutically modulating nerves in a nasal region of a human patient, the method comprising:

intraluminally advancing an evaluation/modulation assembly at a distal portion of a shaft of a therapeutic device to a target site within the nasal region, wherein the target site is proximate to parasympathetic nerves, and wherein the evaluation/modulation assembly includes a plurality of electrodes;

before therapeutic neuromodulation, detecting one or more baseline bioelectric parameters at the target site via at least a portion of the plurality of electrodes;

geometrically identifying inherent tissue properties within the target site based on the detected bioelectric parameters to identify locations of target structures and non-target structures;

determining a neuromodulation pattern based on the locations of the target structures and the non-target structures; and

delivering therapeutic neuromodulation energy to the target structures in accordance with the neuromodulation pattern.

38. The method of example 37, further comprising:

during the delivery of the therapeutic neuromodulation energy, determining one or more mid-procedure bioelectric parameters via the evaluation/modulation assembly; and

after the delivery of the therapeutic neuromodulation energy, determining one or more post-procedure bioelectric parameters via the evaluation/modulation assembly to determine the effectiveness of the delivery of the therapeutic neuromodulation energy in blocking the nerves that received the therapeutic neuromodulation energy.

39. The method of example 37 or 38 wherein geometrically identifying inherent tissue properties within the target site based on the detected bioelectric parameters comprises detecting nerve firing rate at the target site.

40. The method of any one of examples 37-39 wherein delivering therapeutic neuromodulation energy to the target structures in accordance with the neuromodulation pattern comprises delivering RF energy at a predetermined frequency to initiate ionic

agitation of the target structure to therapeutically modulate postganglionic parasympathetic nerves.

41. The method of any one of examples 37-40 wherein delivering therapeutic neuromodulation energy to the target structures in accordance with the neuromodulation pattern comprises delivering RF energy at a predetermined frequency to initiate ionic agitation of submucosal structures to therapeutically modulate postganglionic parasympathetic nerves.

42. The method of any one of examples 37-41 wherein delivering therapeutic neuromodulation energy to the target structures in accordance with the neuromodulation pattern comprises delivering RF energy at a predetermined frequency to initiate vacuolar degeneration of the target structures to therapeutically modulate postganglionic parasympathetic nerves.

43. A device for detecting anatomical structures and therapeutic neuromodulation in a nasal region of a human patient, the system comprising:

a shaft having a proximal portion and a distal portion, wherein the shaft is configured to locate the distal portion intraluminally at a target site within a nasal cavity inferior to a sphenopalatine foramen of the human patient;

an evaluation/modulation assembly at the distal portion of the shaft, wherein—

the evaluation/modulation assembly comprises a plurality of electrodes configured to emit stimulating energy to tissue at the target site at frequencies for locating target structures and non-target structures and detect bioelectric properties in response to the stimulating energy;

the bioelectric properties are used to map locations of the target structures and the non-target structures; and

at least a portion of the plurality of electrodes are configured to apply therapeutic neuromodulation energy in a predetermined neuromodulation pattern based on the locations of the target structures and the non-target structures.

44. The device of example 43 wherein at least a portion of the plurality of electrodes are configured to apply RF energy at a predetermined frequency to initiate ionic

agitation and/or vacuolar degeneration of the target structures to therapeutically modulate postganglionic parasympathetic nerves.

Conclusion

[00121] This disclosure is not intended to be exhaustive or to limit the present technology to the precise forms disclosed herein. Although specific embodiments are disclosed herein for illustrative purposes, various equivalent modifications are possible without deviating from the present technology, as those of ordinary skill in the relevant art will recognize. In some cases, well-known structures and functions have not been shown and/or described in detail to avoid unnecessarily obscuring the description of the embodiments of the present technology. Although steps of methods may be presented herein in a particular order, in alternative embodiments the steps may have another suitable order. Similarly, certain aspects of the present technology disclosed in the context of particular embodiments can be combined or eliminated in other embodiments. Furthermore, while advantages associated with certain embodiments may have been disclosed in the context of those embodiments, other embodiments can also exhibit such advantages, and not all embodiments need necessarily exhibit such advantages or other advantages disclosed herein to fall within the scope of the present technology. Accordingly, this disclosure and associated technology can encompass other embodiments not expressly shown and/or described herein.

[00122] Throughout this disclosure, the singular terms "a," "an," and "the" include plural referents unless the context clearly indicates otherwise. Similarly, unless the word "or" is expressly limited to mean only a single item exclusive from the other items in reference to a list of two or more items, then the use of "or" in such a list is to be interpreted as including (a) any single item in the list, (b) all of the items in the list, or (c) any combination of the items in the list. Additionally, the terms "comprising" and the like are used throughout this disclosure to mean including at least the recited feature(s) such that any greater number of the same feature(s) and/or one or more additional types of features are not precluded. Directional terms, such as "upper," "lower," "front," "back," "vertical," and "horizontal," may be used herein to express and clarify the relationship between various elements. It should be understood that such terms do not denote absolute orientation. Reference herein to "one embodiment," "an embodiment," or similar formulations means that a particular feature, structure, operation, or characteristic described in connection with the embodiment can be included in at least one embodiment of the present technology. Thus, the appearances of such phrases or formulations herein are not necessarily all referring to the same embodiment.

Furthermore, various particular features, structures, operations, or characteristics may be combined in any suitable manner in one or more embodiments.

CLAIMS

I/We claim:

1. A system for detecting anatomical structures and therapeutic neuromodulation in a nasal region of a human patient, the system comprising:

a shaft having a proximal portion and a distal portion, wherein the shaft is configured to locate the distal portion intraluminally at a target site within a nasal cavity inferior to a sphenopalatine foramen of the human patient;

an evaluation/modulation assembly at the distal portion of the shaft, wherein the evaluation/modulation assembly comprises a plurality of electrodes configured to emit stimulating energy to tissue at the target site at frequencies for locating target neural structures and detect bioelectric properties in response to the stimulating energy; and

a console including a controller having a computer-readable medium carrying instructions, which when executed by the controller, causes the console to map locations of the target neural structures and causes the evaluation/modulation assembly to apply therapeutic neuromodulation energy in a predetermined neuromodulation pattern based on the locations of the target neural structures.

2. The system of claim 1 wherein at least a portion of the plurality of electrodes are configured to apply RF energy at a predetermined frequency to initiate ionic agitation of the target neural structure to therapeutically modulate postganglionic parasympathetic nerves.

3. The system of claim 1 wherein at least a portion of the plurality of electrodes are configured to apply RF energy at a predetermined frequency to initiate ionic agitation of sub mucosal structures to therapeutically modulate postganglionic parasympathetic tone.

4. The system of claim 1 wherein at least a portion of the plurality of electrodes are configured to apply RF energy at a predetermined frequency to initiate vacuolar degeneration of the target neural structure to therapeutically modulate postganglionic parasympathetic nerves.

5. The system of claim 1 wherein:

the plurality of electrodes are configured to detect bioelectric properties of non-target anatomical structures at the target site;

the computer-readable medium carrying instructions, which when executed by the controller, causes the console to map locations of non-target anatomical structures and causes the evaluation/modulation assembly to apply neuromodulation energy in the predetermined pattern to avoid the locations of the non-target anatomical structures.

6. The system of claim 1, further comprising a display configured to visualize locations of the target neural structures with respect to a predicted neuromodulation zone defined by the predetermined neuromodulation pattern.

7. The system of claim 1 wherein the plurality of electrodes are configured to detect bioelectric properties of tissue at the treatment site before therapeutic neuromodulation, during therapeutic neuromodulation, and/or after therapeutic neuromodulation.

8. The system of claim 7 wherein the bioelectric properties include at least one of complex impedance, resistance, reactance, capacitance, inductance, permittivity, conductivity, nerve firing voltage, nerve firing current, magnetic field, and induced electromotive force.

9. The system of claim 1 wherein the evaluation/modulation assembly comprises:

a basket transformable between a low-profile delivery state and an expanded state, wherein the basket includes plurality of struts spaced radially apart from each other when the basket is in the expanded state, wherein—

the plurality of electrodes are disposed on the struts,

the plurality of struts are configured to position at least two of the electrodes at the target site when the basket is in the expanded state, and

the electrodes are configured to apply radiofrequency (RF) energy to the target site to therapeutically modulate parasympathetic nerves proximate to the target site.

10. The system of claim 9 wherein the evaluation/modulation assembly further comprises:

an expandable member within the basket and transformable between a low-profile delivery state to an expanded state, wherein at least a portion of the plurality of electrodes are disposed on an exterior surface of the expandable surface.

11. The system of claim 10 wherein the balloon comprises a plurality of holes configured to allow perfusion of a drug through the balloon when the balloon is in the expanded state.

12. The system of claim 9 wherein the evaluation/modulation assembly further comprises:

an expandable member within the basket and transformable between a low-profile delivery state to an expanded state; and

at least one sensing electrode disposed on the expandable member, wherein the sensing electrode defines a coiled shape extending around a circumferential portion of the expandable member.

13. The system of claim 9 wherein the evaluation/modulation assembly further comprises:

an expandable member within the basket and transformable between a low-profile delivery state to an expanded state; and

a plurality of penetrating electrodes disposed on an exterior surface of the expandable member, wherein the expandable member is configured to position at least a portion of the penetrating electrodes a depth into tissue at the target site when the expandable member is in the expanded state.

14. The system of claim 1 wherein the plurality of electrodes includes an array of penetrating electrodes configured to penetrate a depth into tissue at the target site when the expandable member is in the expanded state.

15. The system of claim 14 wherein the penetrating electrodes are configured to detect muscle contraction in response to the stimulating energy.

16. The system of claim 1 wherein the evaluation/modulation assembly comprises a balloon transformable between a low-profile delivery state to an expanded state, wherein at least a portion of the plurality of electrodes are disposed on the balloon.

17. The system of claim 1 wherein the plurality of electrodes are configured to be independently activated and independently assigned a selective polarity to apply therapeutic neuromodulation across selected regions of the evaluation/modulation assembly.

18. A system for detecting anatomical structures and therapeutic neuromodulation in a nasal region of a human patient, the system comprising:

a shaft having a proximal portion and a distal portion, wherein the shaft is configured to locate the distal portion intraluminally at a target site, wherein the target site is at least one of proximate to the sphenopalatine foramen of a human patient or inferior to the sphenopalatine foramen; and

an evaluation/modulation assembly at the distal portion of the shaft and transformable between a low-profile delivery state and an expanded state, wherein the evaluation/modulation assembly comprises a plurality of electrodes configured to be placed into contact with tissue at the target site when the evaluation/modulation assembly is in the expanded state and measure bioelectric properties of tissue at the target site to identify and locate target anatomical structures and non-target structures; and

a console including a controller having a computer-readable medium carrying instructions, which when executed by the controller, causes the console to map locations of the target anatomical structures and non-target anatomical structures and causes the evaluation/modulation assembly to apply therapeutic neuromodulation energy in a predetermined neuromodulation pattern based on the locations of the target and non-target anatomical structures.

19. The system of claim 18 wherein the instructions, when executed by the controller, causes the evaluation/modulation assembly to determine resistance at least proximate to the target site.

20. The system of claim 18 wherein the bioelectric properties are detected before therapeutic neuromodulation, during therapeutic neuromodulation, and/or after therapeutic

neuromodulation, and wherein the bioelectric properties include at least one of complex impedance, resistance, reactance, capacitance, inductance, permittivity, conductivity, nerve firing voltage, nerve firing current, magnetic field, and induced electromotive force.

21. The system of claim 18 wherein at least a portion of the plurality of electrodes are configured to apply RF energy at a predetermined frequency to activate target anatomical structures for anatomical mapping and/or therapeutic neuromodulation.

22. The system of claim 18 wherein the evaluation/modulation assembly comprises:

a frame transformable between the low-profile delivery state and the expanded state, wherein the frame includes plurality of struts spaced radially apart from each other when the frame is in the expanded state, and wherein—

the plurality of electrodes are disposed on the struts, and

the plurality of struts are configured to position at least two of the electrodes at the target site when the frame is in the expanded state.

23. The system of claim 18 wherein the evaluation/modulation assembly comprises an expandable member transformable between the low-profile delivery state to the expanded state, wherein at least a portion of the plurality of electrodes are disposed on the expandable member.

24. A method of therapeutically modulating nerves in a nasal region of a human patient, the method comprising:

intraluminally advancing an evaluation/modulation assembly at a distal portion of a shaft of a therapeutic device to a target site within the nasal region, wherein the target site is proximate to parasympathetic nerves, and wherein the evaluation/modulation assembly includes a plurality of electrodes;

delivering stimulation energy to the target site to excite neural structures at the target site, wherein the stimulation energy is emitted at one or more frequencies for locating specific target neural structures;

detecting one or more bioelectric parameters at the target site via at least a portion of the plurality of electrodes of the evaluation/modulation assembly;

based on the detected bioelectric parameters, identifying relative presence and position of target neural structures at the target site; and

determining a neuromodulation pattern based on the locations of the target neural structures to block the detected target neural structures.

25. The method of claim 24, further comprising delivering therapeutic neuromodulation energy based on the predetermined neuromodulation pattern.

26. The method of claim 25 wherein delivering therapeutic neuromodulation energy further comprises delivering RF energy at a predetermined frequency to initiate ionic agitation of the target neural structure to therapeutically modulate postganglionic parasympathetic nerves.

27. The method of claim 25 wherein delivering therapeutic neuromodulation energy further comprises delivering RF energy at a predetermined frequency to initiate ionic agitation of the submucosal structures to therapeutically modulate postganglionic parasympathetic nerves.

28. The method of claim 25 wherein delivering therapeutic neuromodulation energy further comprises delivering RF energy at a predetermined frequency to initiate vacuolar degeneration of the target neural structure to therapeutically modulate postganglionic parasympathetic nerves.

29. The method of claim 24 wherein detecting one or more bioelectric parameters comprises detecting resistance of the tissue.

30. The method of claim 24 wherein detecting one or more bioelectric parameters comprises detecting at least one of nerve firing voltage and nerve firing current.

31. The method of claim 24 wherein detecting one or more bioelectric parameters comprises detecting a neuromagnetic field at the target site.

32. The method of claim 24 wherein detecting one or more bioelectric parameters comprises detecting induced electromotive force at the target site.

33. The method of claim 24 wherein:

detecting one or more bioelectric parameters at the target site comprises detecting bioelectric parameters of non-target anatomical structures at the target site; and

the method further comprises identifying locations of non-target structures at the target site based on the detected bioelectric parameters.

34. The method of claim 24, further comprising visually mapping locations of the target neural structures with respect to a predicted neuromodulation zone defined by the predetermined neuromodulation pattern.

35. The method of claim 24, further comprising, before delivering stimulation energy, deploying an array of penetrating electrodes such that at least a portion of the penetrating electrodes penetrate a depth into the target tissue, the penetrating electrodes being at least a portion of the plurality of electrodes and disposed on the evaluation/modulation assembly.

36. The method of claim 35 wherein:

detecting one or more bioelectric parameters at the target site via at least a portion of the plurality of electrodes of the evaluation/modulation assembly comprises detecting muscle contraction data in response to the stimulation energy via the penetrating electrodes; and

identifying relative presence and position of target neural structures at the target site comprises mapping locations of target neural structures based on the detected muscle contraction data.

37. A method of therapeutically modulating nerves in a nasal region of a human patient, the method comprising:

intraluminally advancing an evaluation/modulation assembly at a distal portion of a shaft of a therapeutic device to a target site within the nasal region, wherein the target site is proximate to parasympathetic nerves, and wherein the evaluation/modulation assembly includes a plurality of electrodes;

before therapeutic neuromodulation, detecting one or more baseline bioelectric parameters at the target site via at least a portion of the plurality of electrodes;

geometrically identifying inherent tissue properties within the target site based on the detected bioelectric parameters to identify locations of target structures and non-target structures;

determining a neuromodulation pattern based on the locations of the target structures and the non-target structures; and

delivering therapeutic neuromodulation energy to the target structures in accordance with the neuromodulation pattern.

38. The method of claim 37, further comprising:

during the delivery of the therapeutic neuromodulation energy, determining one or more mid-procedure bioelectric parameters via the evaluation/modulation assembly; and

after the delivery of the therapeutic neuromodulation energy, determining one or more post-procedure bioelectric parameters via the evaluation/modulation assembly to determine the effectiveness of the delivery of the therapeutic neuromodulation energy in blocking the nerves that received the therapeutic neuromodulation energy.

39. The method of claim 37 wherein geometrically identifying inherent tissue properties within the target site based on the detected bioelectric parameters comprises detecting nerve firing rate at the target site.

40. The method of claim 37 wherein delivering therapeutic neuromodulation energy to the target structures in accordance with the neuromodulation pattern comprises delivering RF energy at a predetermined frequency to initiate ionic agitation of the target structure to therapeutically modulate postganglionic parasympathetic nerves.

41. The method of claim 37 wherein delivering therapeutic neuromodulation energy to the target structures in accordance with the neuromodulation pattern comprises delivering RF energy at a predetermined frequency to initiate ionic agitation of submucosal structures to therapeutically modulate postganglionic parasympathetic nerves.

42. The method of claim 37 wherein delivering therapeutic neuromodulation energy to the target structures in accordance with the neuromodulation pattern comprises

delivering RF energy at a predetermined frequency to initiate vacuolar degeneration of the target structures to therapeutically modulate postganglionic parasympathetic nerves.

43. A device for detecting anatomical structures and therapeutic neuromodulation in a nasal region of a human patient, the system comprising:

a shaft having a proximal portion and a distal portion, wherein the shaft is configured to locate the distal portion intraluminally at a target site within a nasal cavity inferior to a sphenopalatine foramen of the human patient;

an evaluation/modulation assembly at the distal portion of the shaft, wherein—

the evaluation/modulation assembly comprises a plurality of electrodes configured to emit stimulating energy to tissue at the target site at frequencies for locating target structures and non-target structures and detect bioelectric properties in response to the stimulating energy;

the bioelectric properties are used to map locations of the target structures and the non-target structures; and

at least a portion of the plurality of electrodes are configured to apply therapeutic neuromodulation energy in a predetermined neuromodulation pattern based on the locations of the target structures and the non-target structures.

44. The device of claim 43 wherein at least a portion of the plurality of electrodes are configured to apply RF energy at a predetermined frequency to initiate ionic agitation and/or vacuolar degeneration of the target structures to therapeutically modulate postganglionic parasympathetic nerves.

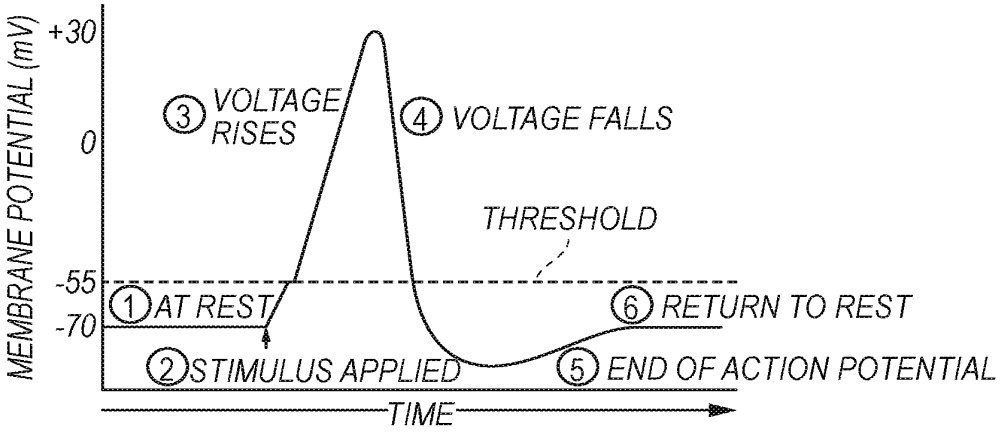


Fig. 1

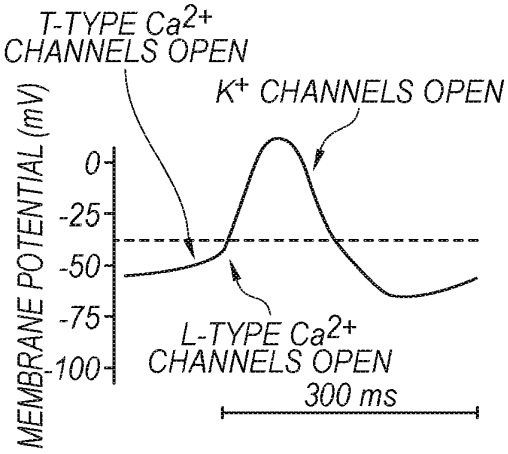


Fig. 2A

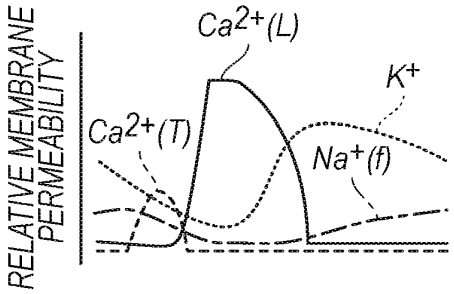


Fig. 2B

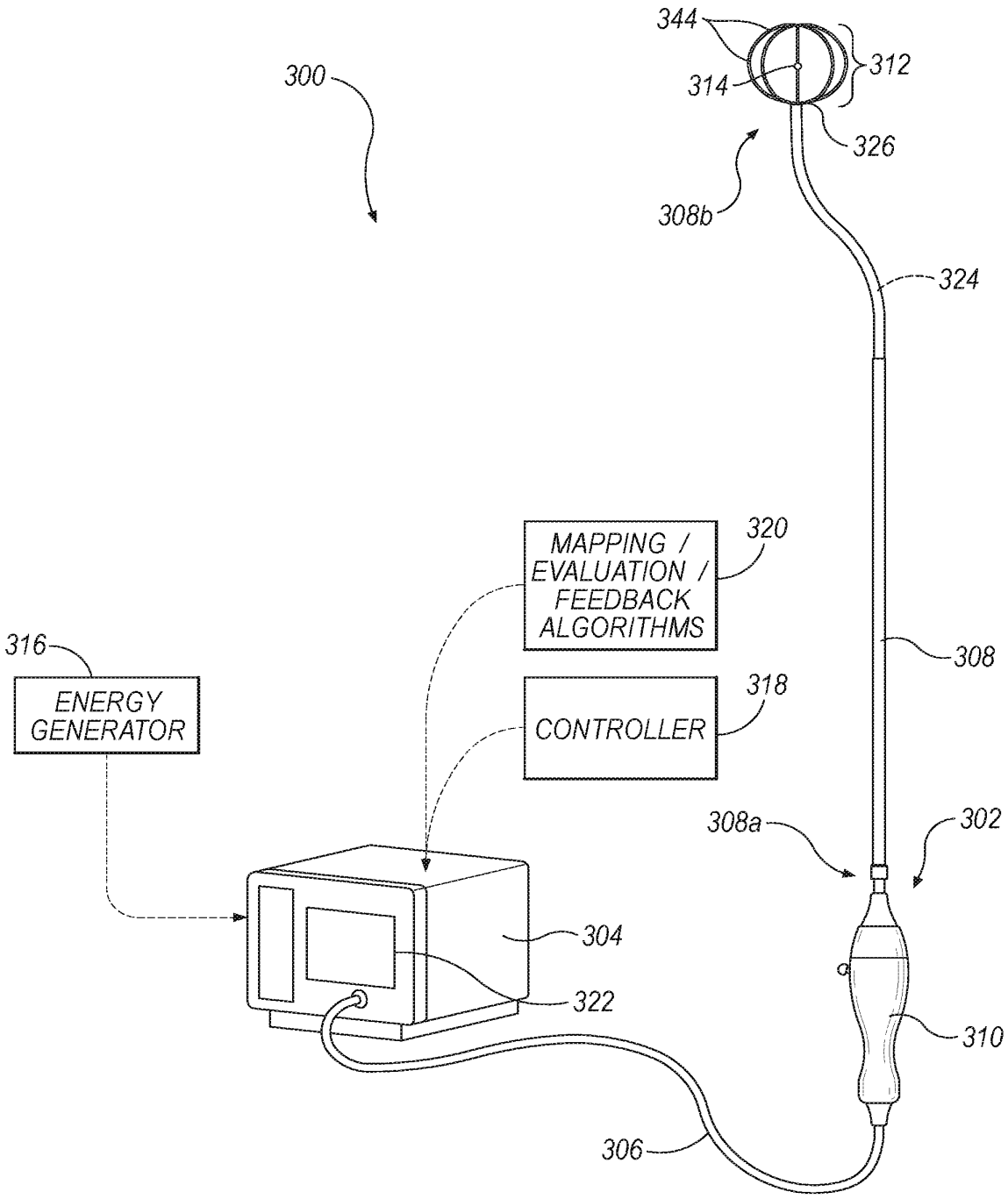

344
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MAPPING / EVALUATION / FEEDBACK ALGORITHMS
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316
308
ENERGY GENERATOR
CONTROLLER
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308a
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Fig. 3A

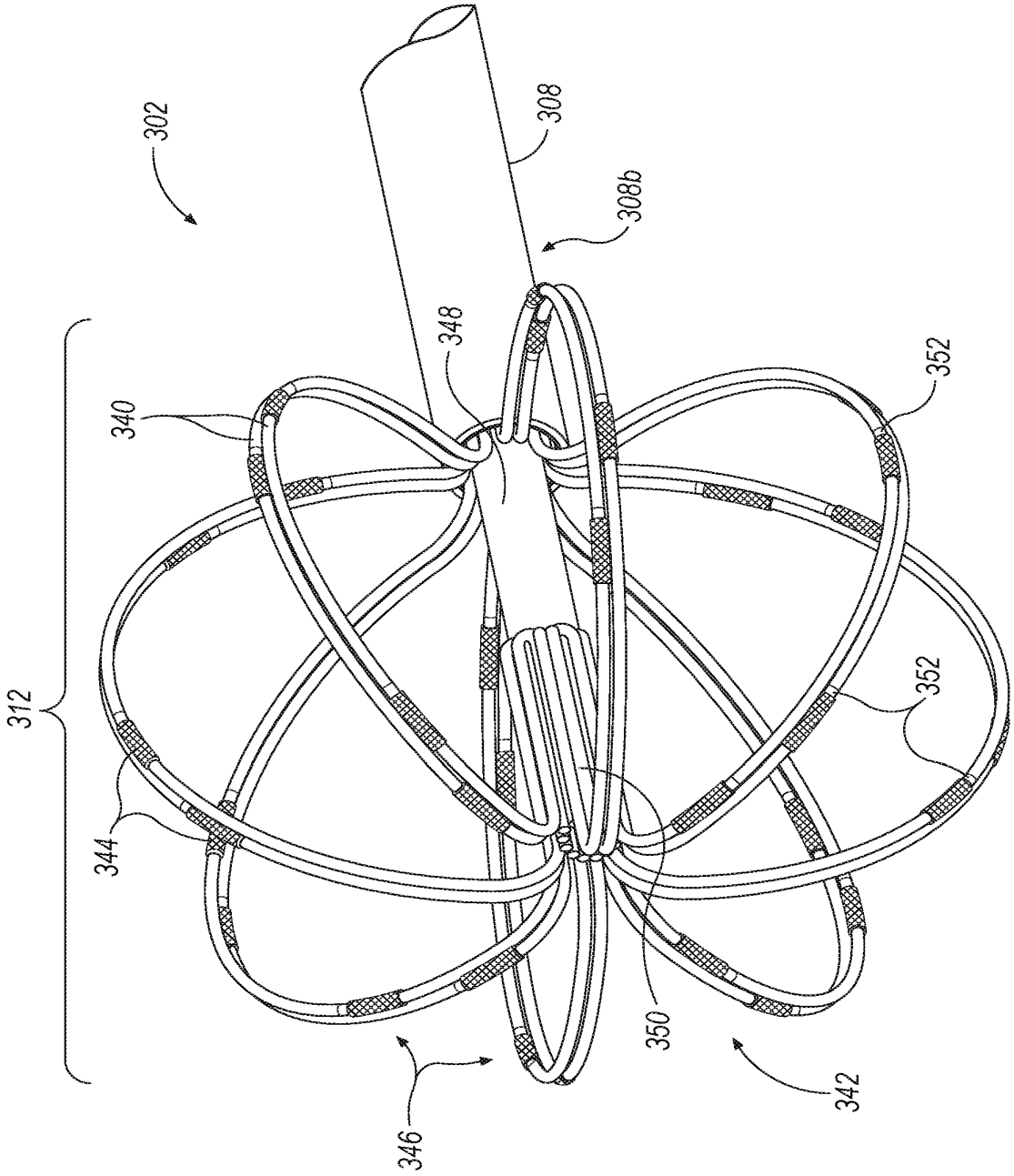


Fig. 3B

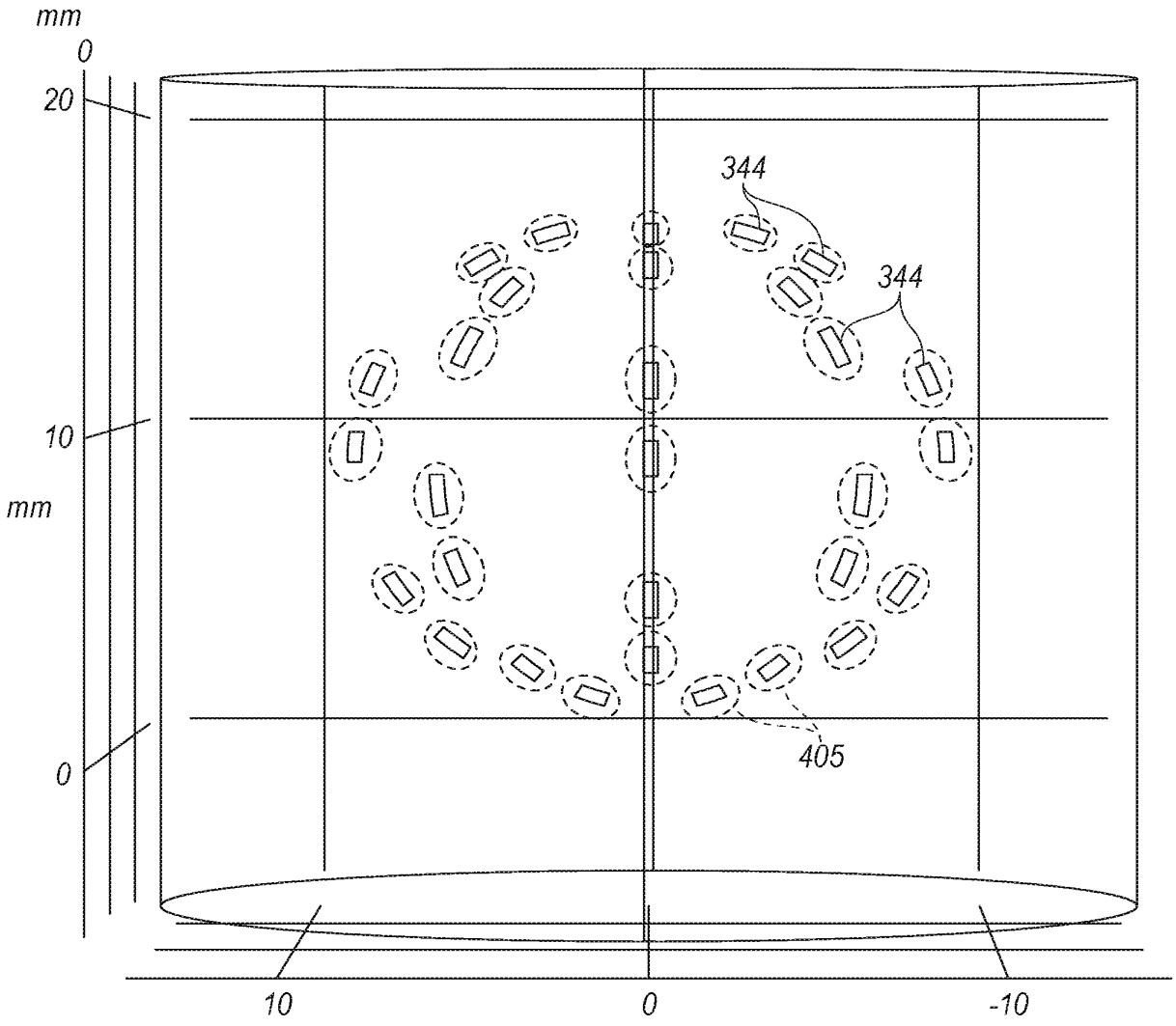


Fig. 4A

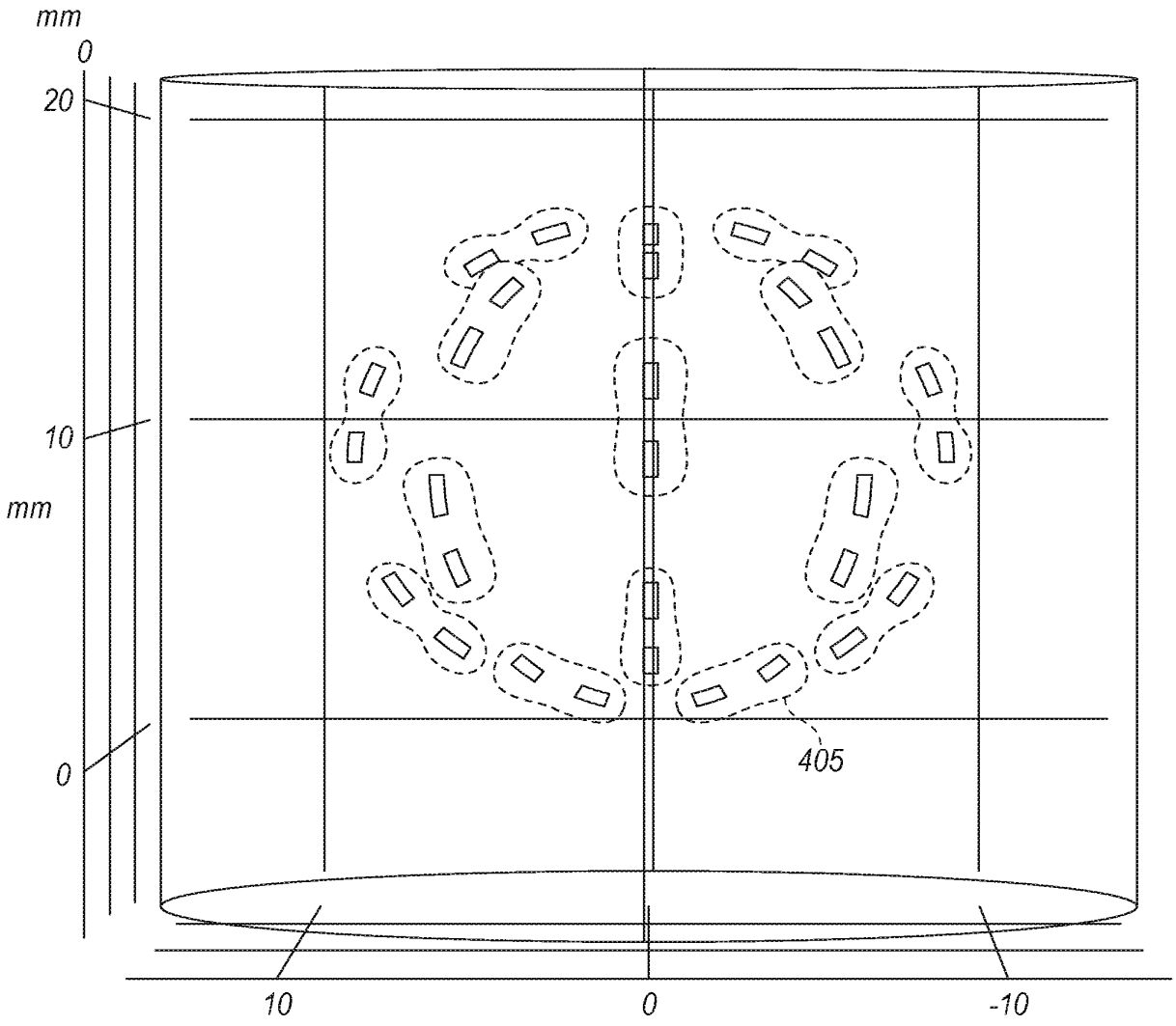


Fig. 4B

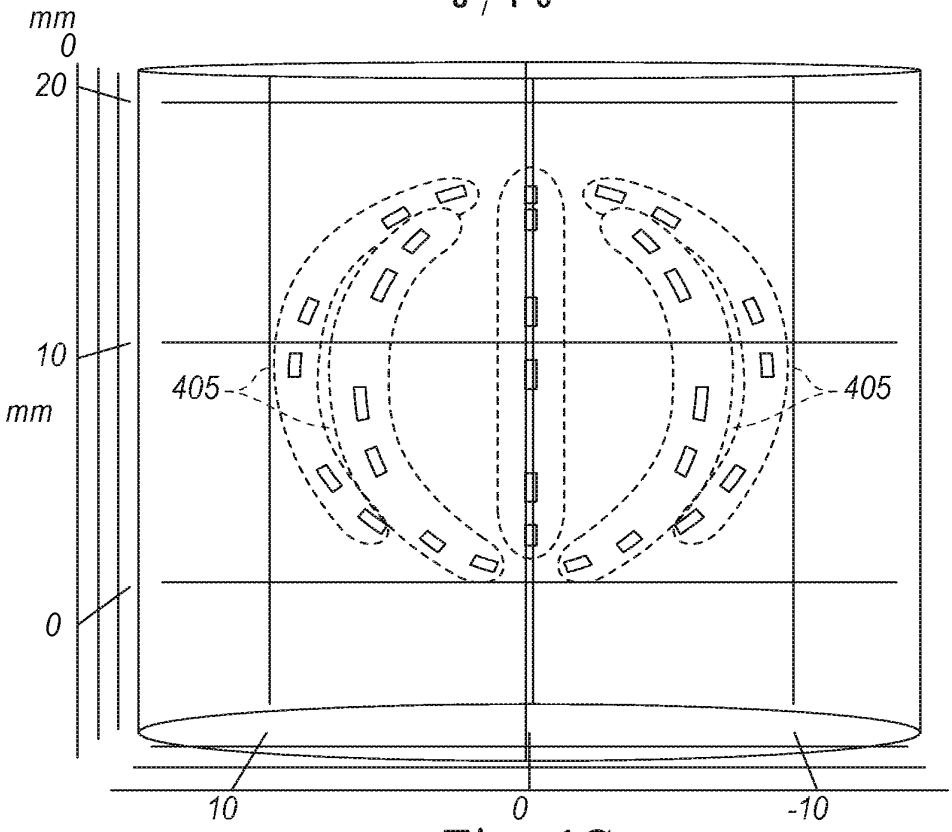


Fig. 4C

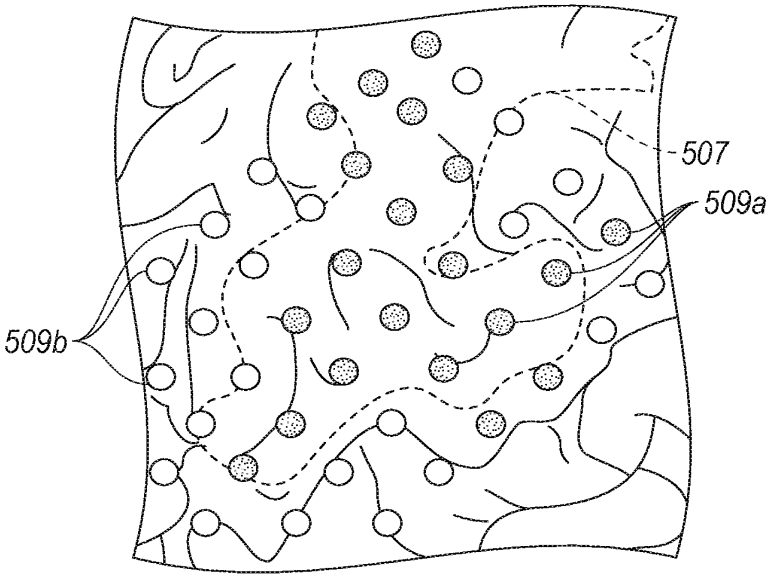


Fig. 5

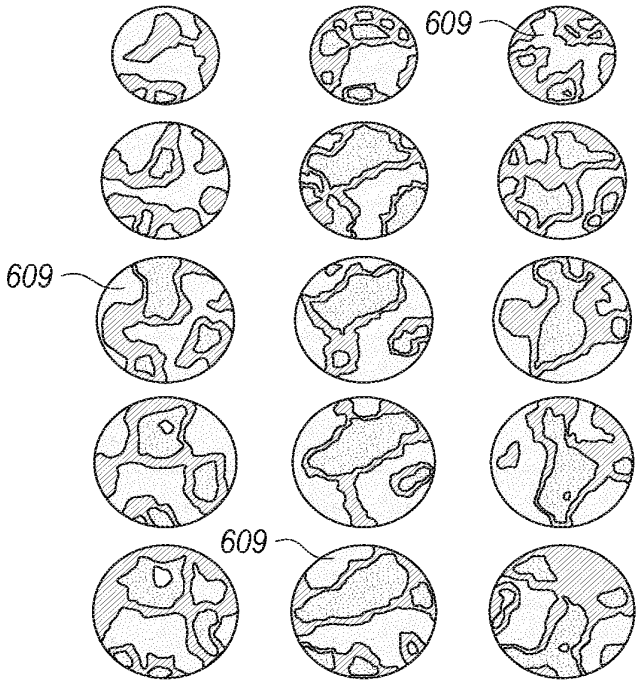


Fig. 6

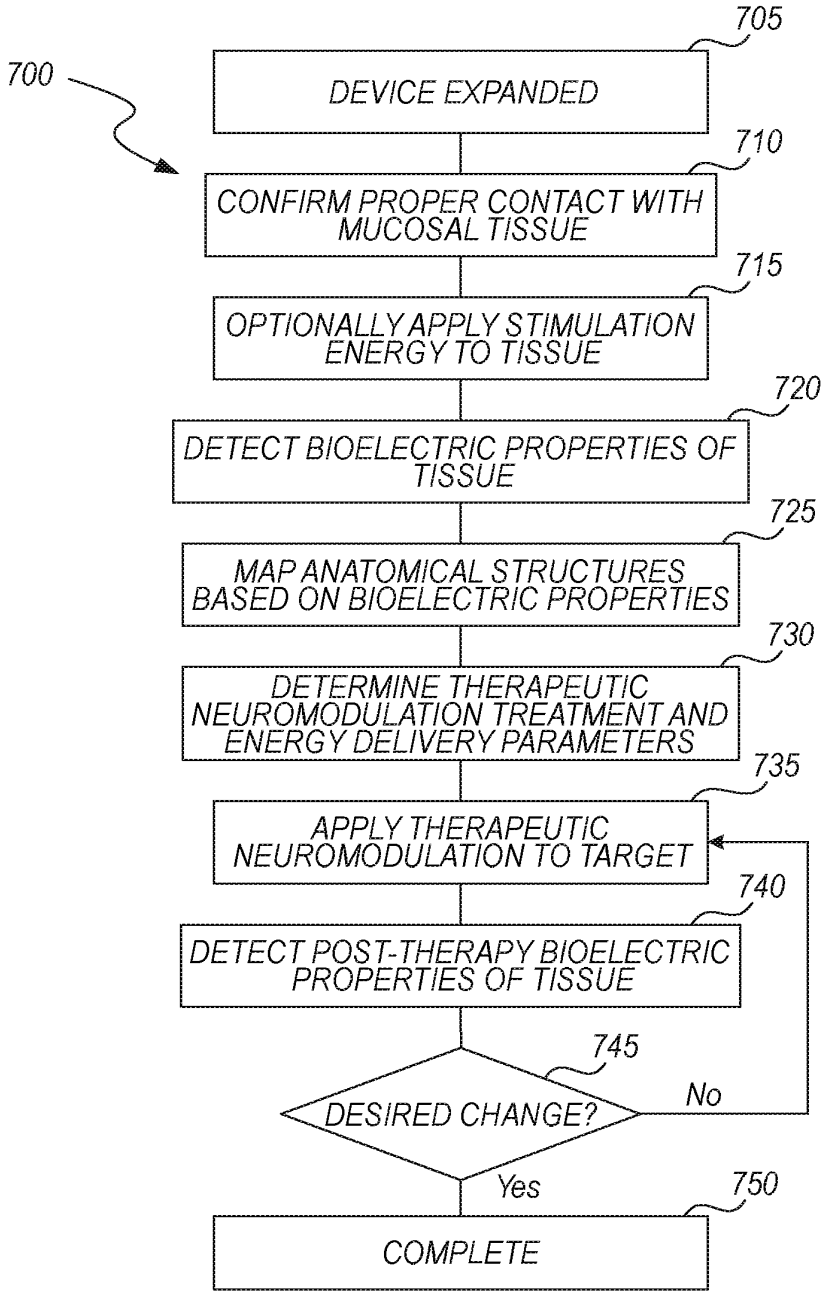

700
705
DEVICE EXPANDED
710
CONFIRM PROPER CONTACT WITH MUCOSAL TISSUE
715
OPTIONALLY APPLY STIMULATION ENERGY TO TISSUE
720
DETECT BIOELECTRIC PROPERTIES OF TISSUE
725
MAP ANATOMICAL STRUCTURES BASED ON BIOELECTRIC PROPERTIES
730
DETERMINE THERAPEUTIC NEUROMODULATION TREATMENT AND ENERGY DELIVERY PARAMETERS
735
APPLY THERAPEUTIC NEUROMODULATION TO TARGET
740
DETECT POST-THERAPY BIOELECTRIC PROPERTIES OF TISSUE
745
DESIRED CHANGE?
No
Yes
750
COMPLETE

Fig. 7

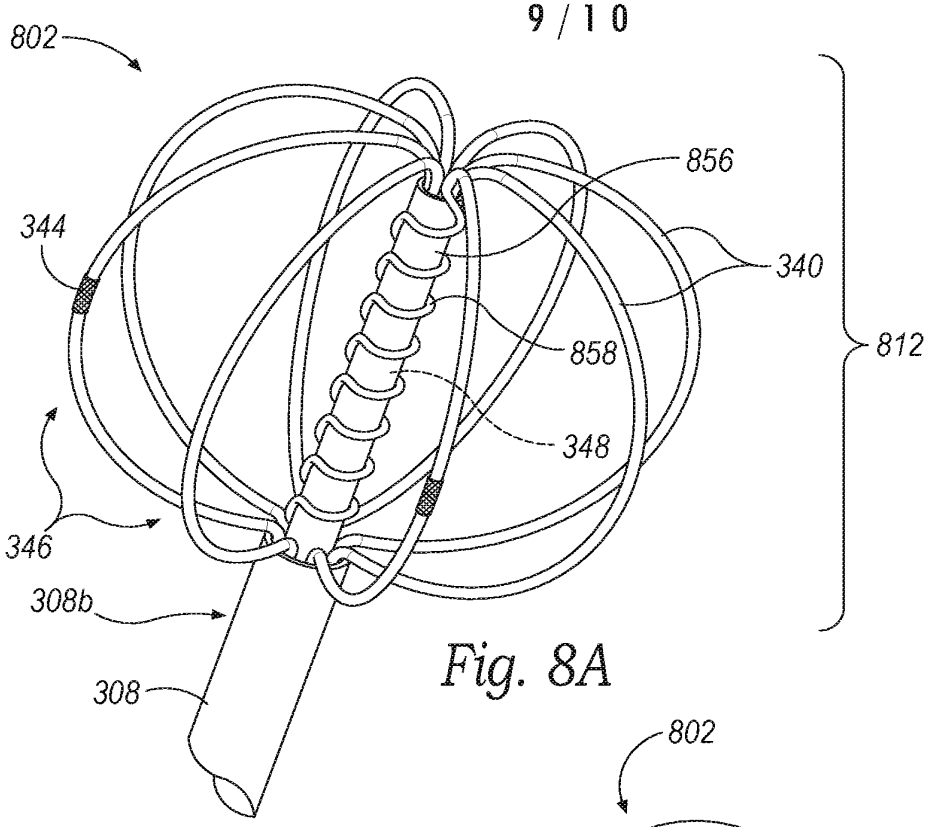

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Fig. 8A

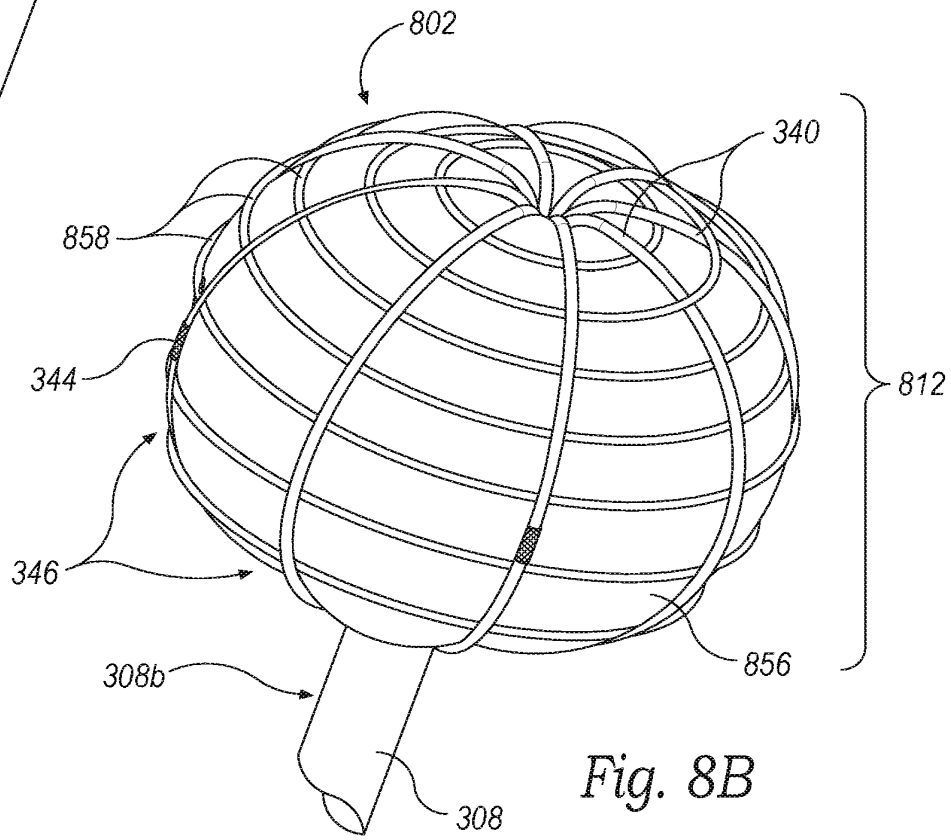

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Fig. 8B

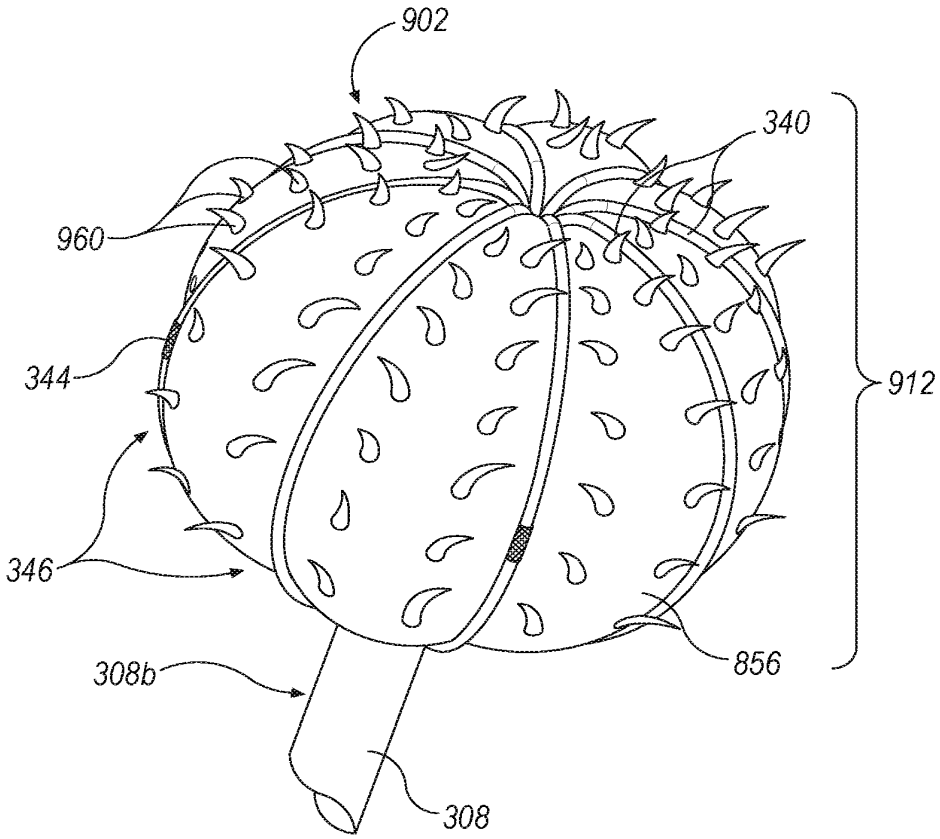


Fig. 9

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2017/001541

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61B5/00 A61B5/053
ADD. A61B18/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 2 929 852 A1 (HOLAIRA INC [US]) 14 October 2015 (2015-10-14) paragraphs [0094], [0118] - [0120], [0060], [0061]; figures 10,23 paragraphs [0094], [0095], [0093]; figure 22	1-23,43, 44
X	US 2015/066006 A1 (SRIVASTAVA NISHANT R [US]) 5 March 2015 (2015-03-05) paragraph [0031]; figures 1,5	1,43
X	WO 2016/134264 A1 (BOSTON SCIENT SCIMED INC [US]) 25 August 2016 (2016-08-25) paragraphs [0044], [0051]; figure 2	1,43

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 March 2018	03/04/2018

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Monogyiou, Efstratia

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Form PCT/ISA/210 (second sheet) (April 2005)

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IPR2025-01124

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2017/001541

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 2016/183337 A2 (NAT UNIV IRELAND GALWAY [IE]; QI ZHAN MICHELE [US]) 17 November 2016 (2016-11-17) cited in the application claims 26-41; figures 2,4 -----	1-23,43, 44

2

Form PCT/ISA/210 (continuation of second sheet) (April 2005)

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IPR2025-01124

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2017/001541

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 2929852 A1	14-10-2015	AU 2011237666 A1	08-11-2012
		CA 2795564 A1	04-10-2012
		CN 102905639 A	30-01-2013
		CN 104939920 A	30-09-2015
		EP 2555700 A2	13-02-2013
		EP 2929852 A1	14-10-2015
		JP 2013523346 A	17-06-2013
		US 2011301587 A1	08-12-2011
		WO 2011127216 A2	13-10-2011
US 2015066006 A1	05-03-2015	AU 2014312243 A1	17-03-2016
		EP 3038556 A1	06-07-2016
		US 2015066006 A1	05-03-2015
		US 2016287114 A1	06-10-2016
		WO 2015031648 A1	05-03-2015
WO 2016134264 A1	25-08-2016	CN 107223034 A	29-09-2017
		EP 3258832 A1	27-12-2017
		US 2016242667 A1	25-08-2016
		WO 2016134264 A1	25-08-2016
WO 2016183337 A2	17-11-2016	AU 2016262085 A1	04-01-2018
		CA 2984207 A1	17-11-2016
		EP 3294410 A2	21-03-2018
		US 2016331459 A1	17-11-2016
		WO 2016183337 A2	17-11-2016

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Aerin Medical Inc. v. Neurent Medical Ltd.
IPR2025-01124

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2017/001541

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 24-42
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[ ] No protest accompanied the payment of additional search fees.

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Aerin Medical Inc. v. Neurent Medical Ltd.
IPR2025-01124

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Claims Nos.: 24-42

Claims 24-42 relate to subject-matter considered by this Authority to be covered by the provisions of Art. 17(2)(a)(i) and Rule 39.1(iv) PCT, because said claims define a method of treatment by therapy comprising a step of delivering stimulation energy to a patient. Furthermore, according to Art. 34(4)(a)(i) and Rule 67.1(iv) PCT no examination will be carried out for said claims.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
1205338001WO00		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US2016/032132	12 May 2016 (12-05-2016)	12 May 2015 (12-05-2015)
Applicant		
NATIONAL UNIVERSITY OF IRELAND, GALWAY		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 8 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language,** the international search was carried out on the basis of:
      [X] the international application in the language in which it was filed
      [ ] a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
   b. [ ] This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).
   c. [ ] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. [X] **Certain claims were found unsearchable** (See Box No. II)

3. [X] **Unity of invention is lacking** (see Box No III)

4. With regard to the **title,**
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings,**
   a. the figure of the **drawings** to be published with the abstract is Figure No. 1
      [X] as suggested by the applicant
      [ ] as selected by this Authority, because the applicant failed to suggest a figure
      [ ] as selected by this Authority, because this figure better characterizes the invention
   b. [ ] none of the figures is to be published with the abstract

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Aerin Medical Inc. v. Neurent Medical Ltd.
IPR2025-01124

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2016/032132

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 45-93, 98-102
because they relate to subject matter not required to be searched by this Authority, namely:

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [X] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[X] No protest accompanied the payment of additional search fees.

Aerin Exhibit 1009, Page 1839 of 2072
Aerin Medical Inc. v. Neurent Medical Ltd.
IPR2025-01124

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2016/032132

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61N1/32 A61N1/18 A61B18/00 A61B18/02 A61B18/18
A61N1/36 A61N1/05 A61B18/04
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61N A61B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2007/031341 A1 (DIMAURO THOMAS M [US] ET AL) 8 February 2007 (2007-02-08) abstract; figures 1-12C paragraphs [0028] - [0163]	1-3,6-8, 103
X	US 2012/323214 A1 (SHANTHA TOTADA R [US]) 20 December 2012 (2012-12-20) abstract; figures 1-26 paragraphs [0059] - [0458]	1-9,103
X	WO 2015/013252 A1 (WEDGE THERAPEUTICS LLC [US]) 29 January 2015 (2015-01-29) abstract; figures 1-30 pages 3-44	1-9,103

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 November 2016	14/11/2016

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Lins, Stephanie

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Form PCT/ISA/210 (second sheet) (April 2005)

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Aerin Medical Inc. v. Neurent Medical Ltd.
IPR2025-01124

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2016/032132

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2012/078377 A1 (GONZALES DONALD A [US] ET AL) 29 March 2012 (2012-03-29) abstract; figures 1-31B paragraphs [0016] - [0298]	1-8,103
X	US 2014/114233 A1 (DEEM MARK E [US] ET AL) 24 April 2014 (2014-04-24) abstract; figures 1-32 paragraphs [0059] - [0141]	26
X	US 2005/288730 A1 (DEEM MARK [US] ET AL) 29 December 2005 (2005-12-29) abstract; figures 1-22 paragraphs [0077] - [0144]	10,12, 15,16, 18-29, 37,39,40
X	US 2007/129760 A1 (DEMARAIS DENISE [US] ET AL) 7 June 2007 (2007-06-07) abstract; figures 1-10 paragraphs [0021] - [0074]	13,14, 19, 23-26, 30-33, 36-40
X	US 2014/025069 A1 (WILLARD MARTIN R [US] ET AL) 23 January 2014 (2014-01-23) abstract; figures 1-9 paragraphs [0026] - [0098]	26,34,35
X	US 2010/204560 A1 (SALAHIEH AMR [US] ET AL) 12 August 2010 (2010-08-12) abstract; figures 1-40 paragraphs [0074] - [0222]	17
X	US 2015/066006 A1 (SRIVASTAVA NISHANT R [US]) 5 March 2015 (2015-03-05) the whole document	11,41-44
X	US 2015/018818 A1 (WILLARD MARTIN R [US] ET AL) 15 January 2015 (2015-01-15) abstract; figures 1-7 paragraphs [0019] - [0100]	94-97
X	US 2013/165916 A1 (MATHUR PRABODH [US] ET AL) 27 June 2013 (2013-06-27) abstract; figures 1-49 paragraphs [0286] - [0462]	94-97

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Form PCT/ISA/210 (continuation of second sheet) (April 2005)

Aerin Exhibit 1009, Page 1841 of 2072
Aerin Medical Inc. v. Neurent Medical Ltd.
IPR2025-01124

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2016/032132

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		WO 2007019463 A2	15-02-2007
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2016/032132

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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-9, 103

   Device for chemical neuromodulation in a nasal region.

   ---

2. claims: 10, 12-40

   Therapeutic assembly with RF electrodes and expandable structure

   ---

3. claims: 11, 41-44

   System for neural mapping and neuromodulation

   ---

4. claims: 94-97

   Device for therapeutic neuromodulation with flexible support.

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2016/032132	12.05.2016	12.05.2015

International Patent Classification (IPC) or both national classification and IPC
INV. A61N1/32 A61N1/18 A61B18/00 A61B18/02 A61B18/18 A61N1/36 A61N1/05 A61B18/04

Applicant
NATIONAL UNIVERSITY OF IRELAND, GALWAY

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465	see form PCT/ISA/210	Lins, Stephanie Telephone No. +49 89 2399-0

Form PCT/ISA/237 (Cover Sheet) (January 2015)

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing:

   a. ☐ forming part of the international application as filed:

      ☐ in the form of an Annex C/ST.25 text file.

      ☐ on paper or in the form of an image file.

   b. ☐ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. ☐ furnished subsequent to the international filing date for the purposes of international search only:

      ☐ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).

      ☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos. 45-93, 98-102

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international search *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☒ no international search report has been established for the whole application or for said claims Nos. 45-93, 98-102

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing in the form of an Annex C/ST.25 text file, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.
- ☐ furnish a sequence listing on paper or in the form of an image file complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13*ter*.1(a) or (b).

☒ See Supplemental Box for further details

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has, within the applicable time limit:

   ☒ paid additional fees

   ☐ paid additional fees under protest and, where applicable, the protest fee

   ☐ paid additional fees under protest but the applicable protest fee was not paid

   ☐ not paid additional fees

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-103

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	19, 23-25, 37, 39, 40
	No:	Claims	1-18, 20-22, 26-36, 38, 41-44, 94-97, 103
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-44, 94-97, 103
Industrial applicability (IA)	Yes:	Claims	1-44, 94-97, 103
	No:	Claims	

2. Citations and explanations

   see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

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Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 45 to 89, 90 to 93 and 98 to 102 relate to a subject-matter mentioned in Rule 39.1 (iv) PCT and in Rule 67.1 (iv) PCT, in particular to a method of treatment of the human body by therapy.

The subject-matter of claims 45 to 89, 90 to 93 and 98 to 102 defines a method of therapeutically modulating nerves in a nasal region of a human patient. The method comprises the step of applying energy, with a therapeutic assembly, to the target site to therapeutically modulate nerves to therapeutically modulate autonomic activity. Therefore the subject-matter of these claims defines a method of treatment of the human body by therapy.

Under terms of Art.17(2)(a)(i) an International Search Authority is not required to carry out a search of such claims.

Furthermore, under terms of Art.34(4)(a)(i) an International Preliminary Examining Authority is not required to carry out examination of such claims.

Re Item IV

Lack of unity of invention

The application does not meet the requirements of unity of invention as defined in Rules 13.1 and 13.2 PCT.

1 This Authority considers that there are 4 inventions covered by the claims. The separate groups of inventions are as follows:

I: Claims : 1-9, 103

II: Claims : 10, 12-40

III: Claims : 11, 41-44

IV: Claims : 94-97

2 The reasons for which the inventions are not so linked as to form a single general inventive concept, as required by Rule 13.1 and 13.2 PCT, are as follows:

The features common to all independent apparatus claims 1, 26, 41, 94 and 103 are:

a flexible shaft configured to locate the distal portion at a target site within the nasal region.

Such a device is known from document US2007031341 (fig.2C, par.[0062]).

Since the technical feature in common to all independent apparatus claims is known, there is no common contribution over the cited prior art. Therefore, claims 1, 26, 41, 94 and 103 can not define a common inventive concept as required by Rules 13.1 and 13.2 PCT, therefore the requirement of unity of the invention is not fulfilled.

3 The following technical features of the independent apparatus claims make a contribution over this prior art and can be considered as special technical features within the meaning of Rule 13.2 PCT:

Group I: No further contribution over the prior art.

Group II: Therapeutic assembly transformable between a low-profile delivery state and an expanded state, including electrodes to apply RF energy.

Group III: Plurality of sensing electrodes at the distal portion of the shaft

Group IV: Flexible support at the distal portion of the shaft.

These features are obviously not the same.

4 The problem solved by theses special technical features can therefore be construed as:

Group I: No further problem solved.

Group II: To facilitate delivery of the therapeutic assembly through narrow passageways.

Group III: Allow the mapping and detection of the nerve location.

Group IV: Allow the shaft to conform to irregularities of local anatomy at the target site.

This shows lack of corresponding effects as well.

5 Consequently neither the objective problem underlying the subject of the claimed inventions, nor their solutions defined by the special technical features allow for a relationship to be established between the said inventions, which involves a single general inventive concept.

The application, hence does not meet the requirement of unity of invention as defined in Rules 13.1. and 13.2 PCT.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1 US 2007/031341 A1 (DIMAURO THOMAS M [US] ET AL) 8 February 2007 (2007-02-08)

D2 US 2012/323214 A1 (SHANTHA TOTADA R [US]) 20 December 2012 (2012-12-20)

D3 WO 2015/013252 A1 (WEDGE THERAPEUTICS LLC [US]) 29 January 2015 (2015-01-29)

D4 US 2012/078377 A1 (GONZALES DONALD A [US] ET AL) 29 March 2012 (2012-03-29)

D5 US 2014/114233 A1 (DEEM MARK E [US] ET AL) 24 April 2014 (2014-04-24)

D6 US 2005/288730 A1 (DEEM MARK [US] ET AL) 29 December 2005 (2005-12-29)

D7 US 2007/129760 A1 (DEMARAIS DENISE [US] ET AL) 7 June 2007 (2007-06-07)

D8 US 2014/025069 A1 (WILLARD MARTIN R [US] ET AL) 23 January 2014 (2014-01-23)

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D9 US 2010/204560 A1 (SALAHIEH AMR [US] ET AL) 12 August 2010 (2010-08-12)

D10 US 2015/066006 A1 (SRIVASTAVA NISHANT R [US]) 5 March 2015 (2015-03-05)

D11 US 2015/018818 A1 (WILLARD MARTIN R [US] ET AL) 15 January 2015 (2015-01-15)

D12 US 2013/165916 A1 (MATHUR PRABODH [US] ET AL) 27 June 2013 (2013-06-27)

FIRST INVENTION

6 INDEPENDENT CLAIMS 1 AND 103

6.1 The definition of "*an energy delivery element configured to therapeutically modulate parasympathetic nerves that innervate mucosa"* of present claims 1 and 103 is considered to be unclear and therefore does not meet the requirements of Article 6 PCT. The subject-matter for which protection is sought is not clearly defined. The claims attempt to define the subject-matter in terms of the result to be achieved, which merely amounts to a statement of the underlying problem, without providing the technical features necessary for achieving this result (e.g. waveform, type of stimulation, etc.). In terms of technical features, the above lines merely define an energy delivery element as such.

6.2 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1 and 103 is not new in the sense of Article 33(2) PCT.

6.2.1 The document D1 discloses (the references in parentheses applying to this document):

A system (fig.2C, abstract) for therapeutic neuromodulation in a nasal region of a human patient, the system comprising:
a shaft (fig.2C, par.[0062]) having a proximal portion and a distal portion, wherein the shaft is configured to locate the distal portion intraluminally at a target site inferior to a sphenopalatine foramen of the human patient; and
a therapeutic assembly (fig.2C, par.[0062]) at the distal portion of the

shaft, wherein the therapeutic assembly comprises an energy delivery element configured to therapeutically modulate (par.[0162]) postganglionic parasympathetic nerves innervating nasal mucosa at microforamina of a palatine bone of the human patient.

Therefore the subject-matter of claim 1 is not new.

6.2.2 The document D1 discloses (the references in parentheses applying to this document):

A system (fig.2C, abstract) for therapeutic neuromodulation in a nasal region of a human patient for treatment of chronic sinusitis, the system comprising:
a shaft (fig.2C, par.[0062]) having a proximal portion and a distal portion, wherein the shaft is configured to locate the distal portion intraluminally at a target site, wherein the target site is at least proximate to an ostium of at least one of a frontal sinus, an ethmoidal sinus, a sphenoidal sinus, or a maxillary sinus of the human patient; and
a therapeutic assembly (fig.2C, par.[0062]) at the distal portion of the shaft, wherein the therapeutic assembly is comprises an energy delivery element configured to therapeutically modulate (par.[0162]) parasympathetic nerves that innervate mucosa of at least one of the frontal sinus, the ethmoidal sinus, the sphenoidal sinus, or the maxillary sinus.

Therefore the subject-matter of claim 103 is not new.

6.2.3 Furthermore, the subject-matter of claims 1 and 103 is also not new compared to each of the following documents:

D2: abstract, fig.9, par.[0177], par.[0178].

D3: abstract, fig.2, fig.28, par.[0111].

D4: abstract, fig.1A, fig.2A, par.[0275]-[0281].

7 DEPENDENT CLAIMS 2-9

Dependent claims 2 to 9 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of novelty Article 33(2) PCT and/or inventive step Article 33(3) PCT.

7.1 The additional features being disclosed as follows:

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Claim 2:	D4: par.[0088].
Claim 3:	D1: abstract, par.[0162].
Claims 4, 5:	D2: par.[0179], fig.9 (529).
Claim 6:	D2: fig.7, metal being considered an obvious choice of material, cf. D4 par. [0266]
Claims 7, 8:	D4: fig.11F, fig.14E, 14F.
Claim 9:	D2: Fig.7, par.[0089].

SECOND INVENTION

8 INDEPENDENT CLAIM 26

8.1 The definition of "*radiofrequency (RF) energy applied to the target site to therapeutically modulate parasympathetic nerves proximate to the target site*" of present claim 26 is considered to be unclear and therefore does not meet the requirements of Article 6 PCT. The subject-matter for which protection is sought is not clearly defined. The claims attempt to define the subject-matter in terms of the result to be achieved, which merely amounts to a statement of the underlying problem, without providing the technical features necessary for achieving this result (e.g. waveform, type of stimulation, etc.). In terms of technical features, the above lines merely define an energy delivery element as such.

8.2 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 26 is not new in the sense of Article 33(2) PCT.

The document D5 discloses (the references in parentheses applying to this document):

A system for therapeutic neuromodulation in a nasal region of a human patient (abstract, fig.25, fig.5A, par.[0085]), the system comprising:
a shaft having a proximal portion and a distal portion (fig.5), wherein the shaft is configured to locate the distal portion intraluminally at a target site (fig.32), wherein the target site is at least one of proximate to the sphenopalatine foramen of a human patient or inferior to the

sphenopalatine foramen (not a technical feature of the device, system of D5 is considered suitable for such application); and
a therapeutic assembly (fig.32 (113)) at the distal portion of the shaft and transformable between a low-profile delivery state and an expanded state, wherein the therapeutic assembly comprises a plurality of struts and a plurality of electrodes disposed on the struts, and wherein the plurality of struts form a basket (fig.32 (113), par.[0112]) that positions at least two of the electrodes at the target site inferior to a sphenopalatine foramen of the human patient when the therapeutic assembly is in the expanded state, and
wherein the electrodes are configured to apply radiofrequency (RF) energy (par.[0065]) to the target site to therapeutically modulate parasympathetic nerves proximate to the target site.

Therefore the subject-matter of claim 26 is not new.

Furthermore the subject-matter of claim 26 is also not new compared to each of the following documents:

D6: abstract, fig.8, fig.9, par.[0095]-[0101];

D7: abstract, fig.5A - fig.6B, par.[0053]-[0056];

D8: abstract, fig.9, par.[0084]-[0088].

The systems disclosed in D6, D7 and D8 are considered to be suitable to be introduced into the nasal region.

9 DEPENDENT CLAIMS 10,12-25 AND 27-40

Dependent claims 10,12-25 and 27-40 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of novelty Article 33(2) PCT and/or inventive step Article 33(3) PCT.

9.1 The additional features being disclosed as follows:

Claims 10, 12:	D6: fig.8, fig.9 par.[0088].
Claims 13, 14:	D7: fig.4B, fig.5B, par.[0025], par.[0050]-[0055].
Claim 15:	D6: fig.5, par.[0088].
Claim 16:	D6: fig.6, par.[0089].

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Claim 17:	D9: par.[0123].
Claim 18:	D6: par.[0109].
Claims 20-22:	D6: fig.22, par.[0120]-[0128], D7, fig.6A.
Claims 27-28:	D6: fig.8, fig.9 par.[0088].
Claim 29:	D6: par.[0142].
Claim 30:	D7: par.[0041].
Claims 31-33, 36:	D7: fig.4B, fig.5B, par.[0025], par.[0050]-[0055].
Claims 34, 35:	D8: fig.9, par.[0085], par.[0088].
Claim 38:	D7: fig.6B.

9.2 The feature of claims 19, 23-25, 37, 39 and 40 is well known in the art and therefore is merely one of several straightforward possibilities from which the skilled person would select, in accordance with circumstances, without the exercise of inventive skill, in order to solve the problem posed.

THIRD INVENTION

10 INDEPENDENT CLAIM 41

10.1 The definition of *"an energy delivery element configured to therapeutically modulate postganglionic parasympathetic nerves innervating a nasal mucosa at the target site"* of present claim 41 is considered to be unclear and therefore does not meet the requirements of Article 6 PCT. The subject-matter for which protection is sought is not clearly defined. The claims attempt to define the subject-matter in terms of the result to be achieved, which merely amounts to a statement of the underlying problem, without providing the technical features necessary for achieving this result (e.g. waveform, type of stimulation, etc.). In terms of technical features, the above lines merely define an energy delivery element as such.

10.2 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 41 is not new in the sense of Article 33(2) PCT.

The document D10 discloses (the references in parentheses applying to this document):

A system for neural mapping (fig.3A, claim 23) and therapeutic neuromodulation in a nasal region of a human patient (not a technical feature), the system comprising:
a shaft (claim 23) having a proximal portion and a distal portion, wherein the shaft is configured to locate the distal portion intraluminally at a target site (claim 23) proximate to a sphenopalatine foramen of the human patient;
a plurality of electrodes (claim 23) at the distal portion of the shaft, wherein the electrodes are configured to detect locations of the parasympathetic nerves at the target site; and
a therapeutic assembly at the distal portion (claim 23) of the shaft, wherein the therapeutic assembly is comprises an energy delivery element configured to therapeutically modulate postganglionic parasympathetic nerves innervating a nasal mucosa at the target site.

Therefore the subject-matter of claim 41 is not new.

11 DEPENDENT CLAIMS 11 AND 42-44

Dependent claims 11 and 42-44 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of novelty Article 33(2) PCT and/or inventive step Article 33(3) PCT.

11.1 The additional features being disclosed as follows:

Claim 11 : D10: claim 23, par.[0051].

Claims 42-44 : D10: par.[0051].

FOURTH INVENTION

12 INDEPENDENT CLAIM 94

12.1 The definition of *"wherein the electrodes are configured to therapeutically modulate parasympathetic nerves of mucosal and sub-mucosal structures in direct or in-direct contact with the electrodes"* of present claim 94 is considered to be unclear and therefore does not meet the requirements of

Article 6 PCT. The subject-matter for which protection is sought is not clearly defined. The claims attempt to define the subject-matter in terms of the result to be achieved, which merely amounts to a statement of the underlying problem, without providing the technical features necessary for achieving this result (e.g. waveform, type of stimulation, etc.). In terms of technical features, the above lines merely define an energy delivery element as such.

12.2 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 94 is not new in the sense of Article 33(2) PCT.

The document D11 discloses (the references in parentheses applying to this document):

> *A device for therapeutic neuromodulation (abstract) in a nasal region of a human patient, the system comprising:*
> *a delivery catheter having a distal portion, wherein the delivery catheter is configured to locate the distal portion at a target site (par.[0030]) within the nasal region;*
> *a flexible support (fig.2B, par.[0036]) at the distal portion of the delivery catheter; and*
> *a plurality of electrodes carried by the flexible (fig.2B, par.[0037]) support,*
> *wherein the flexible support is configured to conform to irregularities of local anatomy at the target site (par.[0033], par.[0035]) to provide topographical compliance and a linkage for electrical activation of at least a portion of the electrodes, and*
> *wherein the electrodes are configured to therapeutically modulate parasympathetic nerves (par.[0036]) of mucosal and sub-mucosal structures in direct or in-direct contact with the electrodes.*

Therefore the subject-matter of claim 94 is not new.

Furthermore, the subject-matter of claim 94 is also not new compared to

D12: abstract, fig.1A, 1B, par.[0134]-[0137].

13 DEPENDENT CLAIMS 95 TO 97

Dependent claims 95 to 97 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of

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the PCT in respect of novelty Article 33(2) PCT and/or inventive step Article 33(3) PCT.

13.1 The additional features being disclosed as follows:

Claim 95:	D11: par.[0035].
Claim 96 :	The target site is not a technical feature of the device. D12: par[0134] defines an outer diameter of 4mm, which is considered suitable for nasal application.
Claim 87:	D12: par.[0140].

Re Item VII

Certain defects in the international application

1 The features of the claims are not provided with reference signs placed in parentheses (Rule 6.2(b) PCT).

2 Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1 and D4 is not mentioned in the description, nor are these documents identified therein.

3 The independent claims are not in the two-part form in accordance with Rule 6.3(b) PCT.

PATENT COOPERATION TREATY

ENTERED IN CPI

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To:
Schoen, Adam M.
BROWN RUDNICK LLP
One Financial Center
Boston, MA 02111
ETATS-UNIS D'AMERIQUE

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference NEURE-001/09WO 352	Date of mailing *(day/month/year)* 12 May 2020 (12-05-2020)
International application No. PCT/IB2019/001298	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
Applicant NEURENT MEDICAL LIMITED	International filing date *(day/month/year)* 6 December 2019 (06-12-2019)

1. [X] The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

   When? The time limit for filing such amendments is normally two months from the date of transmittal of the International Search Report.

   How? Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 338.82.70

   For more detailed instructions, see *PCT Applicant's Guide*, International Phase, paragraphs 9.004 - 9.011.

2. [ ] The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. [ ] **With regard to any protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   [ ] the protest together with the decision thereon has been transmitted to the International Bureau together with any applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

   [ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   The applicant may **submit comments on an informal basis on the written opinion of the International Searching Authority** to the International Bureau. These comments will be made available to the public after international publication. The international Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established.

   Shortly after the expiration of **18 months from the priority date, the international application will be published** by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau before the completion of the technical preparations for international publication (Rules 90*bis*.1 and 90*bis*.3).

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for **entry into the national phase** before those designated Offices. In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months. For details about the applicable time limits, Office by Office, see www.wipo.int/pct/en/texts/time_limits.html and the *PCT Applicant's Guide*, National Chapters.

   Within **22 months from the priority date, the applicant may request that a supplementary international search be carried out** by a different International Searching Authority that offers this service (Rule 45*bis*.1). The procedure for requesting supplementary international search is described in the *PCT Applicant's Guide*, International Phase, paragraphs 8.006-8.032.

Name and mailing address of the International Searching Authority European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040 Fax: (+31-70) 340-3016	Authorized officer MARRA, Emanuela Tel: +49 (0)89 2399-7235

Form PCT/ISA/220 (July 2017)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
NEURE-001/09WO 352		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/IB2019/001298	6 December 2019 (06-12-2019)	11 December 2018 (11-12-2018)

Applicant

NEURENT MEDICAL LIMITED

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 5 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language**, the international search was carried out on the basis of:
      [X] the international application in the language in which it was filed
      [ ] a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
   b. [ ] This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).
   c. [ ] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. [X] **Certain claims were found unsearchable** (See Box No. II)

3. [ ] **Unity of invention is lacking** (see Box No III)

4. With regard to the **title**,
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings**,
   a. the figure of the **drawings** to be published with the abstract is Figure No. 2
      [ ] as suggested by the applicant
      [X] as selected by this Authority, because the applicant failed to suggest a figure
      [ ] as selected by this Authority, because this figure better characterizes the invention
   b. [ ] none of the figures is to be published with the abstract

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2019/001298

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 11-20
because they relate to subject matter not required to be searched by this Authority, namely:

The subject-matter of claims 11-20 refers to a surgical and therapeutic treatment.According to the PCT neither search (Rule 39.1(iv) PCT) nor examination (Rule 67.1(iv) PCT) is required for such subject-matter.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[ ] No protest accompanied the payment of additional search fees.

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IPR2025-01124

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2019/001298

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61B18/14
ADD. A61B17/00 A61B18/12 A61B18/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, COMPENDEX, INSPEC, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2016/331459 A1 (TOWNLEY DAVID [IE] ET AL) 17 November 2016 (2016-11-17) cited in the application paragraphs [0002], [0030], [0070], [0083] - [0085], [0102]; figures 5F, 10A	1-10
X	US 2018/133460 A1 (TOWNLEY DAVID [IE] ET AL) 17 May 2018 (2018-05-17) cited in the application paragraphs [0002], [0042] - [0045]; figure 3B	1-10
A	US 2018/125560 A1 (SAADAT VAHID [US] ET AL) 10 May 2018 (2018-05-10) the whole document	1-10

-/--

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 April 2020	12/05/2020

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Aronsson, Fredrik

Form PCT/ISA/210 (second sheet) (April 2005)

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INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2019/001298

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2018/103994 A1 (FOX JASON WILLIAM [US] ET AL) 19 April 2018 (2018-04-19) the whole document	1-10
A	US 2018/042471 A1 (CHANDLER STEPHEN W [US] ET AL) 15 February 2018 (2018-02-15) the whole document	1-10

Form PCT/ISA/210 (continuation of second sheet) (April 2005)

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Aerin Medical Inc. v. Neurent Medical Ltd.
IPR2025-01124

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2019/001298

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2016331459 A1	17-11-2016	AU 2016262085 A1	04-01-2018
		CA 2984207 A1	17-11-2016
		CN 107835705 A	23-03-2018
		EP 3294410 A2	21-03-2018
		HK 1252823 A1	06-06-2019
		JP 2018515314 A	14-06-2018
		US 2016331459 A1	17-11-2016
		US 2019231429 A1	01-08-2019
		US 2019239953 A1	08-08-2019
		US 2019239954 A1	08-08-2019
		US 2019239955 A1	08-08-2019
		US 2019239956 A1	08-08-2019
		US 2019239957 A1	08-08-2019
		US 2020100838 A1	02-04-2020
		US 2020107882 A1	09-04-2020
		WO 2016183337 A2	17-11-2016
US 2018133460 A1	17-05-2018	AU 2017357869 A1	06-06-2019
		CA 3041440 A1	17-05-2018
		CN 110191674 A	30-08-2019
		EP 3537954 A1	18-09-2019
		JP 2019535386 A	12-12-2019
		US 2018133460 A1	17-05-2018
		US 2020086112 A1	19-03-2020
		US 2020101283 A1	02-04-2020
		WO 2018087601 A1	17-05-2018
US 2018125560 A1	10-05-2018	CN 109600988 A	09-04-2019
		EP 3471638 A1	24-04-2019
		JP 2019526300 A	19-09-2019
		US 2018125560 A1	10-05-2018
		WO 2017218854 A1	21-12-2017
US 2018103994 A1	19-04-2018	NONE	
US 2018042471 A1	15-02-2018	US 2015230700 A1	20-08-2015
		US 2015258315 A1	17-09-2015
		US 2016135671 A1	19-05-2016
		US 2018042471 A1	15-02-2018

Information on Search Strategy - Pilot phase (see OJ 2015, A86)
The type of information contained in this sheet may change during the pilot for improving the usefulness of this new service.

Application Number
PCT/IB2019/001298

TITLE: SYSTEMS AND METHODS FOR THERAPEUTIC NASAL NEUROMODULATION

APPLICANT: NEURENT MEDICAL LIMITED

IPC CLASSIFICATION: A61B18/14, A61B17/00, A61B18/12, A61B18/00

EXAMINER: Aronsson, Fredrik

CONSULTED DATABASES: BIOSIS, COMPDX, EPODOC, INSPEC, KIME, MEDLINE, NPL, WPI

CLASSIFICATION SYMBOLS DEFINING EXTENT OF THE SEARCH:

IPC:

CPC: A61B2017/00867, A61B18/1485, A61B2018/1475, A61B2018/1467, A61B2018/1407, A61B2018/144, A61B18/1206, A61B2018/00982, A61B2018/00916, A61B2018/00642, A61B2018/00702, A61B2018/00791, A61B2018/00875, A61B2018/00577, A61B2018/00327, A61B2018/00434, A61B2018/00839, A61B2018/143, A61B2018/00678, A61B2018/00214, A61B2018/0016

FI/F-TERMS:

KEYWORDS OR OTHER ELEMENTS FEATURING THE INVENTION:
Device for modulating nerves in the nose for treatment of rhinosinusitis, the device having two expandable deployable segments carrying electrodes.

EPO FORM P864.42

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IB2019/001298	06.12.2019	11.12.2018

International Patent Classification (IPC) or both national classification and IPC
INV. A61B18/14 ADD. A61B17/00 A61B18/12 A61B18/00

Applicant
NEURENT MEDICAL LIMITED

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465	see form PCT/ISA/210	Aronsson, Fredrik Telephone No. +49 89 2399-0

Form PCT/ISA/237 (Cover Sheet) (January 2015)

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☑ the international application in the language in which it was filed.

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing:

   a. ☐ forming part of the international application as filed:

      ☐ in the form of an Annex C/ST.25 text file.

      ☐ on paper or in the form of an image file.

   b. ☐ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. ☐ furnished subsequent to the international filing date for the purposes of international search only:

      ☐ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).

      ☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos. 11-20

because:

☒ the said international application, or the said claims Nos. 11-20 relate to the following subject matter which does not require an international search *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☒ no international search report has been established for the whole application or for said claims Nos. 11-20

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing in the form of an Annex C/ST.25 text file, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.

☐ furnish a sequence listing on paper or in the form of an image file complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13*ter*.1(a) or (b).

☒ See Supplemental Box for further details

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Aerin Medical Inc. v. Neurent Medical Ltd.
IPR2025-01124

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-10
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-10
Industrial applicability (IA)	Yes:	Claims	1-10
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

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Aerin Medical Inc. v. Neurent Medical Ltd.
IPR2025-01124

1 Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The subject-matter of claims 11-20 refers to a surgical and therapeutic treatment.

According to the PCT neither search (Rule 39.1(iv) PCT) nor examination (Rule 67.1(iv) PCT) is required for such subject-matter.

2 Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

2.1 Reference is made to the following documents:

D1	US 2016/331459 A1 (TOWNLEY DAVID [IE] ET AL) 17 November 2016 (2016-11-17)cited in the application
D2	US 2018/133460 A1 (TOWNLEY DAVID [IE] ET AL) 17 May 2018 (2018-05-17)cited in the application
D3	US 2018/125560 A1 (SAADAT VAHID [US] ET AL) 10 May 2018 (2018-05-10)
D4	US 2018/103994 A1 (FOX JASON WILLIAM [US] ET AL) 19 April 2018 (2018-04-19)
D5	US 2018/042471 A1 (CHANDLER STEPHEN W [US] ET AL) 15 February 2018 (2018-02-15)

2.2 The present application does not meet the criteria of Article 33(2) PCT, because the subject-matter of claim 1 is not new.

D1 discloses:

A device for treating a condition within a nasal cavity of a patient [0002], the device comprising: a multi-segment end effector (fig. 10A) for delivering energy to one or more target sites within the nasal cavity of the patient, the multi-segment end effector comprising a proximal segment (1060) that is spaced apart from a distal segment (1048).

D1 also discloses:

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A device for treating a condition within a nasal cavity of a patient [0002], the device comprising: a multi-segment end effector (fig. 5F) for delivering energy to one or more target sites within the nasal cavity of the patient, the multi-segment end effector comprising a proximal segment (proximal part of struts 440) that is spaced apart from a distal segment (distal parts of struts 440).

2.3 Dependent claims 2-10 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of novelty and/or inventive step, see:

claims 2-6: Fig. 5F: proximal electrode pairs 444a/444b and distal electrode pairs 444a/444b; claim 7: [0070]; claims 8-10: [0030].

3 Re Item VII

Certain defects in the international application

3.1 The independent claim is not in the two-part form in accordance with Rule 6.3(b) PCT.

3.2 The features of the claims are not provided with reference signs placed in parentheses (Rule 6.2(b) PCT).

3.3 Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in D3-D5 is not mentioned in the description, nor are these documents identified therein.

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Aerin Medical Inc. v. Neurent Medical Ltd.
IPR2025-01124

Possible steps after receipt of the international search report (ISR) and written opinion of the International Searching Authority (WO/ISA)

General information

For all international applications, the competent International Searching Authority (ISA) will establish an international search report (**ISR**) accompanied by a written opinion of the International Searching Authority (**WO/ISA**). The **WO/ISA** may be responded to by

- filing informal comments with the International **Bureau of WIPO (IB)** (where no demand for international preliminary examination (**demand**) is filed)
- filing amendments under Art. 19 PCT (this can be done whether or not a **demand** is filed)
- filing amendments under Art. 34 PCT and/or formal observations in response to objections raised in the **WO/ISA** (where a **demand** *is* actually filed)

This document explains these possibilities.

Filing informal comments

After receipt of the **ISR and WO/ISA**, the applicant may file informal comments on the **WO/ISA, directly with the IB** (see International Search and Preliminary Examination Guidelines 2.15). These will be communicated to the designated/elected Offices, together with the International Preliminary Report on Patentability (**IPRP**) at 30 months from the priority date.

Amending claims under Art. 19 PCT

The applicant may file **amended claims** under Art. 19 PCT, **directly with the IB** by the later of the following dates:

- 2 months from the date of mailing of the **ISR** and the **WO/ISA**
- 16 months from the priority date

However, any such amendment received by the **IB** after the expiration of the applicable time limit shall be **considered to have been received on time** by the IB, if it reaches it before the technical preparations for international publication have been completed (the 15th day prior to the date of publication, see PCT Applicant's Guide, International Phase, 9.013).

For further information, please see Rule 46 PCT as well as form PCT/ISA/220.

Please also note that, when filing amended claims under Art. 19 PCT, such amendments shall be **accompanied by a letter** identifying the amendments made and also the basis for the amendments in the application as originally filed (Rule 46.5(b) PCT). Where a **demand** is filed, failure to comply with this requirement may result in the amendments being ignored in the International Preliminary Examination Report (**IPER**), see Rule 70.2(*c-bis*) PCT.

Filing a demand for international preliminary examination

In principle, the **WO/ISA** will be considered to be the written opinion of the International Preliminary Examining Authority (**IPEA**). Where the **WO/ISA** issued by the **EPO** as **ISA** gives a positive opinion on the international application and the invention to which it relates, filing a **demand** with the **EPO** as **IPEA** would normally be unnecessary, since a positive IPRP would anyway be established by the IB based on the WO/ISA (see also further below).

If the applicant wishes to file a **demand** (for example, to allow him to argue his case in international preliminary examination with regard to objections raised in a negative **WO/ISA** before the **IPEA** issues an **IPER**), this must be done before expiration of **3 months after the date of mailing of the ISR and WO/ISA** or **22 months after priority date**, whichever expires later (Rule 54*bis* PCT). Amendments under Art. 34 PCT can be filed with the IPEA, normally at the same time as filing the demand (Rule 66.1(b) PCT) or within the time limit set for reply to any written opinion issued during international preliminary examination by the **IPEA**.

If a **demand** is filed at the **EPO** as **IPEA** and no comments/amendments have been received by the time the **EPO** starts drawing up the **IPER** (Rule 66.4*bis* PCT), the **WO/ISA** will be transformed by the **IPEA** into an **IPER** (also called the **IPRP (Chapter II)** which would merely reflect the content of the **WO/ISA** (OJ 10/2011, 532). The **demand** can still be withdrawn (Art. 37 PCT).

Please also note that, when filing amendments under Art. 34 PCT, such amendments shall be accompanied by a letter which identifies the amendments made and also the basis for the amendments in the application as originally filed (Rule 66.8(a) PCT). Failure to comply with this requirement may result in the amendments being ignored in the **IPER (IPRP (Chapter II))**, see Rule 70.2(*c-bis*) PCT.

Filing a request for supplementary international search

The applicant may, with the **IB**, file a request for **supplementary international search** under Rule 45*bis*.1 PCT. The present **ISR** and **WO/ISA** may also be taken into account in the execution of that supplementary international search, provided that these are available to the Authority charged with this task before it starts the supplementary search (Rule 45*bis*.5 PCT).

This kind of request **cannot be filed specifying the ISA** who did the **international search**.

More information on this topic can be found in the **PCT Applicant's Guide**, Chapter 8 (http://www.wipo.int/pct/en/guide/ip08.html).

End of the international phase

Where no **demand** is filed, at the end of the international phase, the **IB** will transform the **WO/ISA** into the IPRP (PCT Chapter I) (Rule 44*bis* PCT), which will then be transmitted together with possible informal comments to the designated Offices. Where a demand is filed, the **WO/ISA** is not transformed into an **IPRP (Chapter I)** by the **IB**, but rather the **IPEA** will establish an **IPER**, (the IPER is the same as the IPRP (PCT Chapter II), see Rule 70.15 PCT).

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IPR2025-01124

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To:
Schoen, Adam M.
BROWN RUDNICK LLP
One Financial Center
Boston, MA 02111
ETATS-UNIS D'AMERIQUE

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference NEURE-007/01WO 35242/66	Date of mailing *(day/month/year)* 6 August 2021 (06-08-2021) **FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/IB2021/000234	International filing date *(day/month/year)* 8 April 2021 (08-04-2021)
Applicant NEURENT MEDICAL LIMITED	

1. [X] The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

   When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

   How? Directly to the International Bureau preferably through ePCT, or on paper to:
   The International Bureau of WIPO, 34 chemin des Colombettes, 1211 Geneva 20, Switzerland

   For more detailed instructions, see the *PCT Applicant's Guide*, International Phase, paragraphs 9.004 - 9.011.

2. [ ] The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. [ ] **With regard to any protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   [ ] the protest together with the decision thereon has been transmitted to the International Bureau together with any request to forward the texts of both the protest and the decision thereon to the designated Offices.

   [ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   The applicant may **submit comments on an informal basis on the written opinion of the International Searching Authority** to the International Bureau. These comments will be made available to the public after international publication. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established.

   Shortly after the expiration of **18 months from the priority date, the international application will be published** by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau before the completion of the technical preparations for international publication (Rules 90*bis*.1 and 90*bis*.3).

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for **entry into the national phase** before those designated Offices. In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months. For details about the applicable time limits, Office by Office, see www.wipo.int/pct/en/texts/time_limits.html and the *PCT Applicant's Guide*, National Chapters.

   Within **22 months from the priority date, the applicant may request that a supplementary international search be carried out** by a different International Searching Authority that offers this service (Rule 45*bis*.1). The procedure for requesting supplementary international search is described in the *PCT Applicant's Guide*, International Phase, paragraphs 8.006-8.032.

Name and mailing address of the International Searching Authority European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040 Fax: (+31-70) 340-3016	Authorized officer MARRA, Emanuela Tel: +49 (0)89 2399-7235

Form PCT/ISA/220 (revised January 2020)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
NEURE-007/01WO 35242/66		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/IB2021/000234	8 April 2021 (08-04-2021)	9 April 2020 (09-04-2020)

Applicant

NEURENT MEDICAL LIMITED

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language,** the international search was carried out on the basis of:
      [X] the international application in the language in which it was filed
      [ ] a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
   b. [ ] This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).
   c. [ ] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. [X] **Certain claims were found unsearchable** (See Box No. II)

3. [ ] **Unity of invention is lacking** (see Box No III)

4. With regard to the **title,**
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings,**
   a. the figure of the **drawings** to be published with the abstract is Figure No. 2
      [ ] as suggested by the applicant
      [X] as selected by this Authority, because the applicant failed to suggest a figure
      [ ] as selected by this Authority, because this figure better characterizes the invention
   b. [ ] none of the figures is to be published with the abstract

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IPR2025-01124

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2021/000234

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 11-20
because they relate to subject matter not required to be searched by this Authority, namely:

The subject-matter of claims 11-20 refers to a surgical and therapeutic treatment.According to the PCT neither search (Rule 39.1(iv) PCT) nor examination (Rule 67.1(iv) PCT) is required for such subject-matter.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[ ] No protest accompanied the payment of additional search fees.

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Aerin Medical Inc. v. Neurent Medical Ltd.
IPR2025-01124

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2021/000234

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61B18/02 A61B18/08 A61B18/14
ADD. A61B18/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, COMPENDEX, INSPEC, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	US 2016/331459 A1 (TOWNLEY DAVID [IE] ET AL) 17 November 2016 (2016-11-17) cited in the application paragraphs [0002], [0058], [0066], [0102]; figures 1-5,10	1-8 9,10
Y	US 2017/151014 A1 (PERFLER ENRICO [IT]) 1 June 2017 (2017-06-01) paragraphs [0101] - [0104]; figures 11,12	9,10
A	US 2018/125560 A1 (SAADAT VAHID [US] ET AL) 10 May 2018 (2018-05-10) cited in the application the whole document	1-10

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 July 2021	06/08/2021

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Aronsson, Fredrik

1

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2021/000234

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2016331459 A1	17-11-2016	AU 2016262085 A1	04-01-2018
		AU 2021200322 A1	18-03-2021
		CA 2984207 A1	17-11-2016
		CN 107835705 A	23-03-2018
		EP 3294410 A2	21-03-2018
		HK 1252823 A1	06-06-2019
		JP 6854015 B2	07-04-2021
		JP 2018515314 A	14-06-2018
		JP 2021087861 A	10-06-2021
		US 2016331459 A1	17-11-2016
		US 2019231429 A1	01-08-2019
		US 2019239953 A1	08-08-2019
		US 2019239954 A1	08-08-2019
		US 2019239955 A1	08-08-2019
		US 2019239956 A1	08-08-2019
		US 2019239957 A1	08-08-2019
		US 2020100838 A1	02-04-2020
		US 2020107882 A1	09-04-2020
		WO 2016183337 A2	17-11-2016
US 2017151014 A1	01-06-2017	AU 2015232999 A1	03-11-2016
		CA 2976749 A1	24-09-2015
		CN 106102628 A	09-11-2016
		EP 3125802 A1	08-02-2017
		ES 2730967 T3	13-11-2019
		GE P20197025 B	10-10-2019
		JP 6507226 B2	24-04-2019
		JP 2017509458 A	06-04-2017
		KR 20160145034 A	19-12-2016
		PL 3125802 T3	18-05-2020
		SG 11201706466S A	28-09-2017
		TR 201908664 T4	22-07-2019
		US 2017151014 A1	01-06-2017
		US 2021212760 A1	15-07-2021
		WO 2015140741 A1	24-09-2015
		ZA 201607094 B	30-08-2017
US 2018125560 A1	10-05-2018	CN 109600988 A	09-04-2019
		EP 3471638 A1	24-04-2019
		JP 2019526300 A	19-09-2019
		US 2018125560 A1	10-05-2018
		WO 2017218854 A1	21-12-2017

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Information on Search Strategy - Pilot phase (see OJ 2015, A86)
The type of information contained in this sheet may change during the pilot for improving the usefulness of this new service.

Application Number
PCT/IB2021/000234

TITLE: SYSTEMS AND METHODS FOR THERAPEUTIC NASAL TREATMENT

APPLICANT: NEURENT MEDICAL LIMITED

IPC CLASSIFICATION: A61B18/02, A61B18/08, A61B18/14, A61B18/00

EXAMINER: Aronsson, Fredrik

CONSULTED DATABASES: BIOSIS, COMPDX, EPODOC, INSPEC, KIME, MEDLINE, NPL, WPI, DOSYS

CLASSIFICATION SYMBOLS DEFINING EXTENT OF THE SEARCH:

IPC:

CPC: A61B18/02, A61B18/082, A61B18/1485, A61B18/1492, A61B2018/00267, A61B2018/00327, A61B2018/00404, A61B2018/00434, A61B2018/00577

FI/F-TERMS:

KEYWORDS OR OTHER ELEMENTS FEATURING THE INVENTION:
A device for treating a condition within a sino-nasal cavity of a patient, the device comprising an elongate body comprising one or more of a first set of electrodes provided along a length thereof; and a retractable and expandable end effector operably associated with the elongate body and comprising one or more of a second set of electrodes provided thereon.

EPO FORM P0442

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IB2021/000234	08.04.2021	09.04.2020

International Patent Classification (IPC) or both national classification and IPC
INV. A61B18/02 A61B18/08 A61B18/14 ADD. A61B18/00

Applicant
NEURENT MEDICAL LIMITED

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465	see form PCT/ISA/210	Aronsson, Fredrik Telephone No. +49 89 2399-0

Form PCT/ISA/237 (Cover Sheet) (January 2015)

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing:

   a. ☐ forming part of the international application as filed:

      ☐ in the form of an Annex C/ST.25 text file.

      ☐ on paper or in the form of an image file.

   b. ☐ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. ☐ furnished subsequent to the international filing date for the purposes of international search only:

      ☐ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).

      ☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

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IPR2025-01124

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos. 11-20

because:

☒ the said international application, or the said claims Nos. 11-20 relate to the following subject matter which does not require an international search *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☒ no international search report has been established for the whole application or for said claims Nos. 11-20

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing in the form of an Annex C/ST.25 text file, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.
- ☐ furnish a sequence listing on paper or in the form of an image file complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13*ter*.1(a) or (b).

☒ See Supplemental Box for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	9, 10
	No:	Claims	1-8
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-10
Industrial applicability (IA)	Yes:	Claims	1-10
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

1 **Re Item III**

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The subject-matter of claims 11-20 refers to a surgical and therapeutic treatment.

According to the PCT neither search (Rule 39.1(iv) PCT) nor examination (Rule 67.1(iv) PCT) is required for such subject-matter.

2 **Re Item V**

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

2.1 Reference is made to the following documents:

D1	US 2016/331459 A1 (TOWNLEY DAVID [IE] ET AL) 17 November 2016 (2016-11-17)cited in the application
D2	US 2017/151014 A1 (PERFLER ENRICO [IT]) 1 June 2017 (2017-06-01)
D3	US 2018/125560 A1 (SAADAT VAHID [US] ET AL) 10 May 2018 (2018-05-10)cited in the application

2.2 The present application does not meet the criteria of Article 33(2) PCT, because the subject-matter of claim 1 is not new.

D1 discloses:

A device for treating a condition within a sino-nasal cavity of a patient [0002], the device comprising:

an elongate body (408) comprising one or more of a first set of electrodes (1060) provided along a length thereof; and

a retractable and expandable end effector (442) operably associated with the elongate body (Fig. 4) and comprising one or more of a second set of electrodes (444) provided thereon.

2.3 Dependent claims 2-10 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of novelty and/or inventive step, see: claim 2: D1, Fig. 4 (shaft 408); claim 3: D1, Fig. 4 and 10 (outer sheath 408, hypotube or metallic member 448, one or more electrodes 1060); claim 4: D1, Fig. 4; claim 5: D1, Fig. 10A, 10B

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and [0102]; claim 6: D1, [0066]; claim 7: D1, Fig. 10B and [0058]; claim 8: D1, Fig. 4 (proximal parts of struts 440 and distal parts of struts 440); claim 9: D2, Fig. 11, 12; claim 10: D1, [0041].

3 **Re Item VII**

Certain defects in the international application

3.1 The independent claims are not in the two-part form in accordance with Rule 6.3(b) PCT.

3.2 The features of the claims are not provided with reference signs placed in parentheses (Rule 6.2(b) PCT).

3.3 Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in D2 is not mentioned in the description, nor are these documents identified therein.

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Possible steps after receipt of the international search report (ISR) and written opinion of the International Searching Authority (WO/ISA)

General information

For all international applications, the competent International Searching Authority **(ISA)** will establish an international search report **(ISR)** accompanied by a written opinion of the International Searching Authority **(WO/ISA)**. The **WO/ISA** may be responded to by

- filing informal comments with the **International Bureau of WIPO (IB)** (where no demand for international preliminary examination **(demand)** is filed)
- filing amendments under Art. 19 PCT (this can be done whether or not a **demand** is filed)
- filing amendments under Art. 34 PCT and/or formal observations in response to objections raised in the **WO/ISA** (where a **demand** *is* actually filed)

This document explains these possibilities.

Filing informal comments

After receipt of the **ISR and WO/ISA**, the applicant may file informal comments on the **WO/ISA, directly with the IB** (see International Search and Preliminary Examination Guidelines 2.15). These will be communicated to the designated/elected Offices, together with the International Preliminary Report on Patentability **(IPRP)** at 30 months from the priority date.

Amending claims under Art. 19 PCT

The applicant may file **amended claims** under Art. 19 PCT, **directly with the IB** by the later of the following dates:

- 2 months from the date of mailing of the **ISR** and the **WO/ISA**
- 16 months from the priority date

However, any such amendment received by the **IB** after the expiration of the applicable time limit shall be **considered to have been received on time** by the **IB**, if it reaches it **before** the technical preparations for international publication have been completed (the 15th day prior to the date of publication, see PCT Applicant's Guide, International Phase, 9.013).

For further information, please see Rule 46 PCT as well as form PCT/ISA/220.

Please also note that, when filing amended claims under Art. 19 PCT, such amendments shall be **accompanied by a letter** identifying the amendments made and also the basis for the amendments in the application as originally filed (Rule 46.5(b) PCT). Where a **demand** is filed, failure to comply with this requirement may result in the amendments being ignored in the International Preliminary Examination Report **(IPER)**, see Rule 70.2(c-*bis*) PCT.

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Filing a demand for international preliminary examination

In principle, the **WO/ISA** will be considered to be the written opinion of the International Preliminary Examining Authority (**IPEA**). Where the **WO/ISA** issued by the **EPO** as **ISA** gives a positive opinion on the international application and the invention to which it relates, filing a **demand** with the **EPO** as **IPEA** would normally be unnecessary, since a positive IPRP would anyway be established by the IB based on the WO/ISA (see also further below).

If the applicant wishes to file a **demand** (for example, to allow him to argue his case in international preliminary examination with regard to objections raised in a negative **WO/ISA** before the **IPEA** issues an **IPER**), this must be done before expiration of **3 months after the date of mailing of the ISR and WO/ISA** or **22 months after priority date**, whichever expires later (Rule 54*bis* PCT). Amendments under Art. 34 PCT can be filed with the IPEA, normally at the same time as filing the demand (Rule 66.1(b) PCT) or within the time limit set for reply to any written opinion issued during international preliminary examination by the **IPEA**.

If a **demand** is filed at the **EPO as IPEA** and no comments/amendments have been received by the time the **EPO** starts drawing up the **IPER** (Rule 66.4*bis* PCT), the **WO/ISA** will be transformed by the **IPEA** into an **IPER** (also called the **IPRP (Chapter II)** which would merely reflect the content of the **WO/ISA** (OJ 10/2011, 532). The **demand** can still be withdrawn (Art. 37 PCT).

Please also note that, when filing amendments under Art. 34 PCT, such amendments shall be accompanied by a letter which identifies the amendments made and also the basis for the amendments in the application as originally filed (Rule 66.8(a) PCT). Failure to comply with this requirement may result in the amendments being ignored in the **IPER (IPRP (Chapter II))**, see Rule 70.2(c-*bis*) PCT.

Filing a request for supplementary international search

The applicant may, with the **IB**, file a request for **supplementary international search** under Rule 45*bis*.1 PCT. The present **ISR** and **WO/ISA** may also be taken into account in the execution of that supplementary international search, provided that these are available to the Authority charged with this task before it starts the supplementary search (Rule 45*bis*.5 PCT).

This kind of request **cannot be filed specifying the ISA** who did the **international search**.

More information on this topic can be found in the **PCT Applicant's Guide**, Chapter 8 (http://www.wipo.int/pct/en/guide/ip08.html).

End of the international phase

Where no **demand** is filed, at the end of the international phase, the **IB** will transform the **WO/ISA** into the IPRP (PCT Chapter I) (Rule 44*bis* PCT), which will then be transmitted together with possible informal comments to the designated Offices. Where a demand is filed, the **WO/ISA** is not transformed into an **IPRP (Chapter I)** by the **IB**, but rather the **IPEA** will establish an **IPER**, (the IPER is the same as the IPRP (PCT Chapter II), see Rule 70.15 PCT).

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PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:
Schoen, Adam M.
BROWN RUDNICK LLP
One Financial Center
Boston, MA 02111
ETATS-UNIS D'AMERIQUE

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference NEURE-009/01WO 35242/70	Date of mailing *(day/month/year)* 25 August 2021 (25-08-2021) **FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/IB2021/000243	International filing date *(day/month/year)* 8 April 2021 (08-04-2021)
Applicant NEURENT MEDICAL LIMITED	

1. [X] The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

   When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

   How? Directly to the International Bureau preferably through ePCT, or on paper to:
   The International Bureau of WIPO, 34 chemin des Colombettes, 1211 Geneva 20, Switzerland

   For more detailed instructions, see the *PCT Applicant's Guide*, International Phase, paragraphs 9.004 - 9.011.

2. [ ] The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. [ ] **With regard to any protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   [ ] the protest together with the decision thereon has been transmitted to the International Bureau together with any request to forward the texts of both the protest and the decision thereon to the designated Offices.

   [ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   The applicant may **submit comments on an informal basis on the written opinion of the International Searching Authority** to the International Bureau. These comments will be made available to the public after international publication. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established.

   Shortly after the expiration of **18 months from the priority date, the international application will be published** by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau before the completion of the technical preparations for international publication (Rules 90*bis*.1 and 90*bis*.3).

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for **entry into the national phase** before those designated Offices. In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months. For details about the applicable time limits, Office by Office, see www.wipo.int/pct/en/texts/time_limits.html and the *PCT Applicant's Guide*, National Chapters.

   Within **22 months from the priority date, the applicant may request that a supplementary international search be carried out** by a different International Searching Authority that offers this service (Rule 45*bis*.1). The procedure for requesting supplementary international search is described in the *PCT Applicant's Guide*, International Phase, paragraphs 8.006-8.032.

Name and mailing address of the International Searching Authority European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040 Fax: (+31-70) 340-3016	Authorized officer OBLINGER, Sabine Tel: +49 (0)89 2399-7714

Form PCT/ISA/220 (revised January 2020)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
NEURE-009/01WO 35242/70		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/IB2021/000243	8 April 2021 (08-04-2021)	9 April 2020 (09-04-2020)
Applicant		
NEURENT MEDICAL LIMITED		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language**, the international search was carried out on the basis of:
      [X] the international application in the language in which it was filed
      [ ] a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
   b. [ ] This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).
   c. [ ] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. [X] **Certain claims were found unsearchable** (See Box No. II)

3. [ ] **Unity of invention is lacking** (see Box No III)

4. With regard to the **title,**
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings,**
   a. the figure of the **drawings** to be published with the abstract is Figure No. 9A
      [ ] as suggested by the applicant
      [X] as selected by this Authority, because the applicant failed to suggest a figure
      [ ] as selected by this Authority, because this figure better characterizes the invention
   b. [ ] none of the figures is to be published with the abstract

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2021/000243

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 1-22
because they relate to subject matter not required to be searched by this Authority, namely:

The subject-matter of claims 1-22 refers to a surgical and therapeutic treatment.According to the PCT neither search (Rule 39.1(iv) PCT) nor examination (Rule 67.1(iv) PCT) is required for such subject-matter.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[ ] No protest accompanied the payment of additional search fees.

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INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2021/000243

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61B18/12
ADD. A61B18/00 A61B18/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, COMPENDEX, INSPEC, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2018/133460 A1 (TOWNLEY DAVID [IE] ET AL) 17 May 2018 (2018-05-17) cited in the application paragraphs [0002] - [0003], [0031], [0053] - [0055], [0071], [0119]; figure 3A	23-44
X	WO 2016/183337 A2 (NAT UNIV IRELAND GALWAY [IE]; QI ZHAN MICHELE [US]) 17 November 2016 (2016-11-17)	23-30, 34,35, 37-44
A	paragraphs [0002], [0038] - [0044], [0093] - [0096], [0111]; figure 2	31-33,36

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 August 2021	25/08/2021

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Aronsson, Fredrik

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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2021/000243

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2018133460 A1	17-05-2018	AU 2017357869 A1	06-06-2019
		CA 3041440 A1	17-05-2018
		CN 110191674 A	30-08-2019
		EP 3537954 A1	18-09-2019
		JP 2019535386 A	12-12-2019
		US 2018133460 A1	17-05-2018
		US 2020086112 A1	19-03-2020
		US 2020101283 A1	02-04-2020
		US 2020171302 A1	04-06-2020
		WO 2018087601 A1	17-05-2018
WO 2016183337 A2	17-11-2016	AU 2016262085 A1	04-01-2018
		AU 2021200322 A1	18-03-2021
		CA 2984207 A1	17-11-2016
		CN 107835705 A	23-03-2018
		EP 3294410 A2	21-03-2018
		HK 1252823 A1	06-06-2019
		JP 6854015 B2	07-04-2021
		JP 2018515314 A	14-06-2018
		JP 2021087861 A	10-06-2021
		US 2016331459 A1	17-11-2016
		US 2019231429 A1	01-08-2019
		US 2019239953 A1	08-08-2019
		US 2019239954 A1	08-08-2019
		US 2019239955 A1	08-08-2019
		US 2019239956 A1	08-08-2019
		US 2019239957 A1	08-08-2019
		US 2020100838 A1	02-04-2020
		US 2020107882 A1	09-04-2020
		WO 2016183337 A2	17-11-2016

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Information on Search Strategy - Pilot phase (see OJ 2015, A86)
The type of information contained in this sheet may change during the pilot for improving the usefulness of this new service.

Application Number
PCT/IB2021/000243

TITLE: SYSTEMS AND METHODS FOR IDENTIFYING AND CHARACTERIZING TISSUE AND PROVIDING TARGETED TREATMENT THEREOF

APPLICANT: NEURENT MEDICAL LIMITED

IPC CLASSIFICATION: A61B18/12, A61B18/00, A61B18/14

EXAMINER: Aronsson, Fredrik

CONSULTED DATABASES: BIOSIS, COMPDX, EPODOC, INSPEC, KIME, MEDLINE, NPL, WPI

CLASSIFICATION SYMBOLS DEFINING EXTENT OF THE SEARCH:

IPC:

CPC: A61B18/1206, A61B2018/00839, A61B2018/00875, A61B2018/00904, A61B2018/00732, A61B2018/00577, A61B2018/00351, A61B2018/00327, A61B2018/00434, A61B2018/00267, A61B2018/0016, A61B18/1485, A61B18/1492, A61B2018/00791, A61B2018/00642, A61B2018/00648, A61B2018/00708, A61B2018/00672, A61B2018/00678, A61B2018/00886

FI/F-TERMS:

KEYWORDS OR OTHER ELEMENTS FEATURING THE INVENTION:
Receiving bioelectric data, identifying tissue types and relaxation patterns for each identified tissue type and determining an ablation pattern based on identified relaxation patterns

EPO FORM P0A42

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IB2021/000243	08.04.2021	09.04.2020

International Patent Classification (IPC) or both national classification and IPC
INV. A61B18/12 ADD. A61B18/00 A61B18/14

Applicant
NEURENT MEDICAL LIMITED

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465	see form PCT/ISA/210	Aronsson, Fredrik Telephone No. +49 89 2399-0

Form PCT/ISA/237 (Cover Sheet) (January 2015)

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing:

   a. ☐ forming part of the international application as filed:

      ☐ in the form of an Annex C/ST.25 text file.

      ☐ on paper or in the form of an image file.

   b. ☐ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. ☐ furnished subsequent to the international filing date for the purposes of international search only:

      ☐ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).

      ☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos. 1-22

because:

☒ the said international application, or the said claims Nos. 1-22 relate to the following subject matter which does not require an international search *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☒ no international search report has been established for the whole application or for said claims Nos. 1-22

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing in the form of an Annex C/ST.25 text file, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.
- ☐ furnish a sequence listing on paper or in the form of an image file complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13*ter*.1(a) or (b).

☒ See Supplemental Box for further details

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Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	30, 36
	No:	Claims	23-29, 31-35, 37-44
Inventive step (IS)	Yes:	Claims	
	No:	Claims	23-44
Industrial applicability (IA)	Yes:	Claims	23-44
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

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1 **Re Item III**

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The subject-matter of claims 1-22 refers to a surgical and therapeutic treatment.

According to the PCT neither search (Rule 39.1(iv) PCT) nor examination (Rule 67.1(iv) PCT) is required for such subject-matter.

2 **Re Item V**

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

2.1 Reference is made to the following documents:

D1 US 2018/133460 A1 (TOWNLEY DAVID [IE] ET AL) 17 May 2018 (2018-05-17)cited in the application

D2 WO 2016/183337 A2 (NAT UNIV IRELAND GALWAY [IE]; QI ZHAN MICHELE [US]) 17 November 2016 (2016-11-17)

2.2 D1 discloses:

A system (300) for treating a condition [0002], the system comprising:

a device (302) comprising an end effector (312) including a plurality of electrodes (344); and

a controller (318) operably associated with the device (fig. 3A) and configured to:

receive data from the device associated with bioelectric properties of one or more tissues at the target site [0053];

process the data to identify a type of each of the one or more tissues at the target site and further identify a relaxation pattern(s) for each of the one or more identified tissue types [0053]-[0054]; and

determine an ablation pattern to be delivered by one or more of the plurality of electrodes of the end effector based on identified relaxation patterns ([0055]: frequency attuned to target tissue),

wherein ablation energy associated with the ablation pattern is at a level sufficient to ablate a targeted tissue and minimize and/or prevent collateral damage to surrounding or adjacent non-targeted tissue at the target site [0071].

Thus, the subject-matter of claim 23 is not new (Article 33(2) PCT).

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Dependent claims 24-44 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of novelty and/or inventive step over D1, see:

claims 24-26: [0053]-[0054]; claims 27-33: [0055]; claims 34-35, 37: [0003]; claim 36: [0119]; claim 38-44: [0031].

2.3 D2 discloses:

A system (200) for treating a condition [0002], the system comprising:

a device (202) comprising an end effector (212) including a plurality of electrodes (214) [0043]; and

a controller (218) operably associated with the device (fig. 2) and configured to:

receive data from the device associated with bioelectric properties of one or more tissues at the target site [0044];

process the data to identify a type of each of the one or more tissues at the target site [0096] and further identify a relaxation pattern(s) for each of the one or more identified tissue types ([0093]: impedance mapping at different frequencies); and

determine an ablation pattern to be delivered by one or more of the plurality of electrodes of the end effector based on identified relaxation patterns ([0094]: electrode configuration),

wherein ablation energy associated with the ablation pattern is at a level sufficient to ablate a targeted tissue and minimize and/or prevent collateral damage to surrounding or adjacent non-targeted tissue at the target site [00111].

Thus, the subject-matter of claim 23 is not new (Article 33(2) PCT).

Dependent claims 24-30, 34-35 and 37-44 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of novelty and/or inventive step over D2, see:

claims 24-26, 29: [0094]; claims 27-28, 30: [0096]; claims 34-35, 37-38: [0002]; claims 39-44: [0038]-[0040].

3 **Re Item VII**

Certain defects in the international application

3.1 The independent claim is not in the two-part form in accordance with Rule 6.3(b) PCT.

3.2 The features of the claims are not provided with reference signs placed in parentheses (Rule 6.2(b) PCT).

3.3 Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in D2 is not mentioned in the description, nor is this document identified therein.

4 **Re Item VIII**

Certain observations on the international application

4.1 In claim 23 the last feature "wherein ablation energy associated with the ablation pattern is at a level sufficient to ablate a targeted tissue and minimize and/or prevent collateral damage to surrounding or adjacent non-targeted tissue at the target site" merely states the desired result rather than the technical features of the system that are actually responsible for the effect. This renders the subject-matter of claim 23 unclear (Article 6 PCT).

Possible steps after receipt of the international search report (ISR) and written opinion of the International Searching Authority (WO/ISA)

General information

For all international applications, the competent International Searching Authority **(ISA)** will establish an international search report **(ISR)** accompanied by a written opinion of the International Searching Authority **(WO/ISA)**. The **WO/ISA** may be responded to by

- filing informal comments with the **International Bureau of WIPO (IB)** (where no demand for international preliminary examination **(demand)** is filed)
- filing amendments under Art. 19 PCT (this can be done whether or not a **demand** is filed)
- filing amendments under Art. 34 PCT and/or formal observations in response to objections raised in the **WO/ISA** (where a **demand** *is* actually filed)

This document explains these possibilities.

Filing informal comments

After receipt of the **ISR and WO/ISA**, the applicant may file informal comments on the **WO/ISA, directly with the IB** (see International Search and Preliminary Examination Guidelines 2.15). These will be communicated to the designated/elected Offices, together with the International Preliminary Report on Patentability **(IPRP)** at 30 months from the priority date.

Amending claims under Art. 19 PCT

The applicant may file **amended claims** under Art. 19 PCT, **directly with the IB** by the later of the following dates:

- 2 months from the date of mailing of the **ISR** and the **WO/ISA**
- 16 months from the priority date

However, any such amendment received by the **IB** after the expiration of the applicable time limit shall be **considered to have been received on time** by the **IB**, if it reaches it **before** the technical preparations for international publication have been completed (the 15th day prior to the date of publication, see PCT Applicant's Guide, International Phase, 9.013).

For further information, please see Rule 46 PCT as well as form PCT/ISA/220.

Please also note that, when filing amended claims under Art. 19 PCT, such amendments shall be **accompanied by a letter** identifying the amendments made and also the basis for the amendments in the application as originally filed (Rule 46.5(b) PCT). Where a **demand** is filed, failure to comply with this requirement may result in the amendments being ignored in the International Preliminary Examination Report **(IPER)**, see Rule 70.2(c-*bis*) PCT.

BNSDOCID: <XS_____20070401GK_I_>

Filing a demand for international preliminary examination

In principle, the **WO/ISA** will be considered to be the written opinion of the International Preliminary Examining Authority (**IPEA**). Where the **WO/ISA** issued by the **EPO** as **ISA** gives a positive opinion on the international application and the invention to which it relates, filing a **demand** with the **EPO** as **IPEA** would normally be unnecessary, since a positive IPRP would anyway be established by the IB based on the WO/ISA (see also further below).

If the applicant wishes to file a **demand** (for example, to allow him to argue his case in international preliminary examination with regard to objections raised in a negative **WO/ISA** before the **IPEA** issues an **IPER**), this must be done before expiration of **3 months after the date of mailing of the ISR and WO/ISA** or **22 months after priority date,** whichever expires later (Rule 54*bis* PCT). Amendments under Art. 34 PCT can be filed with the IPEA, normally at the same time as filing the demand (Rule 66.1(b) PCT) or within the time limit set for reply to any written opinion issued during international preliminary examination by the **IPEA**.

If a **demand** is filed at the **EPO** as **IPEA** and no comments/amendments have been received by the time the **EPO** starts drawing up the **IPER** (Rule 66.4*bis* PCT), the **WO/ISA** will be transformed by the **IPEA** into an **IPER** (also called the **IPRP (Chapter II)** which would merely reflect the content of the **WO/ISA** (OJ 10/2011, 532). The **demand** can still be withdrawn (Art. 37 PCT).

Please also note that, when filing amendments under Art. 34 PCT, such amendments shall be accompanied by a letter which identifies the amendments made and also the basis for the amendments in the application as originally filed (Rule 66.8(a) PCT). Failure to comply with this requirement may result in the amendments being ignored in the **IPER (IPRP (Chapter II))**, see Rule 70.2(c-*bis*) PCT.

Filing a request for supplementary international search

The applicant may, with the **IB**, file a request for **supplementary international search** under Rule 45*bis*.1 PCT. The present **ISR** and **WO/ISA** may also be taken into account in the execution of that supplementary international search, provided that these are available to the Authority charged with this task before it starts the supplementary search (Rule 45*bis*.5 PCT).

This kind of request **cannot be filed specifying the ISA** who did the **international search**.

More information on this topic can be found in the **PCT Applicant's Guide**, Chapter 8 (http://www.wipo.int/pct/en/guide/ip08.html).

End of the international phase

Where no **demand** is filed, at the end of the international phase, the **IB** will transform the **WO/ISA** into the IPRP (PCT Chapter I) (Rule 44*bis* PCT), which will then be transmitted together with possible informal comments to the designated Offices. Where a demand is filed, the **WO/ISA** is not transformed into an **IPRP (Chapter I)** by the **IB**, but rather the **IPEA** will establish an **IPER**, (the IPER is the same as the IPRP (PCT Chapter II), see Rule 70.15 PCT).

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
1205338002WO00		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/IB2017/001541	13 November 2017 (13-11-2017)	11 November 2016 (11-11-2016)
Applicant		
NATIONAL UNIVERSITY OF IRELAND, GALWAY		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 6 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language,** the international search was carried out on the basis of:
      [X] the international application in the language in which it was filed
      [ ] a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
   b. [ ] This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).
   c. [ ] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. [X] **Certain claims were found unsearchable** (See Box No. II)

3. [ ] **Unity of invention is lacking** (see Box No III)

4. With regard to the **title,**
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings,**
   a. the figure of the **drawings** to be published with the abstract is Figure No. 3A
      [X] as suggested by the applicant
      [ ] as selected by this Authority, because the applicant failed to suggest a figure
      [ ] as selected by this Authority, because this figure better characterizes the invention
   b. [ ] none of the figures is to be published with the abstract

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2017/001541

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 24-42
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[ ] No protest accompanied the payment of additional search fees.

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INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2017/001541

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61B5/00 A61B5/053
ADD. A61B18/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 2 929 852 A1 (HOLAIRA INC [US]) 14 October 2015 (2015-10-14) paragraphs [0094], [0118] - [0120], [0060], [0061]; figures 10,23 paragraphs [0094], [0095], [0093]; figure 22	1-23,43, 44
X	US 2015/066006 A1 (SRIVASTAVA NISHANT R [US]) 5 March 2015 (2015-03-05) paragraph [0031]; figures 1,5	1,43
X	WO 2016/134264 A1 (BOSTON SCIENT SCIMED INC [US]) 25 August 2016 (2016-08-25) paragraphs [0044], [0051]; figure 2	1,43

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 March 2018	03/04/2018

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Monogyiou, Efstratia

2

Form PCT/ISA/210 (second sheet) (April 2005)

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INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2017/001541

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 2016/183337 A2 (NAT UNIV IRELAND GALWAY [IE]; QI ZHAN MICHELE [US]) 17 November 2016 (2016-11-17) cited in the application claims 26-41; figures 2,4 -----	1-23,43, 44

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2017/001541

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 2929852 A1	14-10-2015	AU 2011237666 A1	08-11-2012
		CA 2795564 A1	04-10-2012
		CN 102905639 A	30-01-2013
		CN 104939920 A	30-09-2015
		EP 2555700 A2	13-02-2013
		EP 2929852 A1	14-10-2015
		JP 2013523346 A	17-06-2013
		US 2011301587 A1	08-12-2011
		WO 2011127216 A2	13-10-2011
US 2015066006 A1	05-03-2015	AU 2014312243 A1	17-03-2016
		EP 3038556 A1	06-07-2016
		US 2015066006 A1	05-03-2015
		US 2016287114 A1	06-10-2016
		WO 2015031648 A1	05-03-2015
WO 2016134264 A1	25-08-2016	CN 107223034 A	29-09-2017
		EP 3258832 A1	27-12-2017
		US 2016242667 A1	25-08-2016
		WO 2016134264 A1	25-08-2016
WO 2016183337 A2	17-11-2016	AU 2016262085 A1	04-01-2018
		CA 2984207 A1	17-11-2016
		EP 3294410 A2	21-03-2018
		US 2016331459 A1	17-11-2016
		WO 2016183337 A2	17-11-2016

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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Claims Nos.: 24-42

Claims 24-42 relate to subject-matter considered by this Authority to be covered by the provisions of Art. 17(2)(a)(i) and Rule 39.1(iv) PCT, because said claims define a method of treatment by therapy comprising a step of delivering stimulation energy to a patient. Furthermore, according to Art. 34(4)(a)(i) and Rule 67.1(iv) PCT no examination will be carried out for said claims.

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IB2017/001541	13.11.2017	11.11.2016

International Patent Classification (IPC) or both national classification and IPC
INV. A61B5/00 A61B5/053 ADD. A61B18/00

Applicant
NATIONAL UNIVERSITY OF IRELAND, GALWAY

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465	see form PCT/ISA/210	Monogyiou, Efstratia Telephone No. +49 89 2399-0

Form PCT/ISA/237 (Cover Sheet) (January 2015)

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing:

   a. ☐ forming part of the international application as filed:

      ☐ in the form of an Annex C/ST.25 text file.

      ☐ on paper or in the form of an image file.

   b. ☐ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. ☐ furnished subsequent to the international filing date for the purposes of international search only:

      ☐ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).

      ☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos. 24-42

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international search *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☒ no international search report has been established for the whole application or for said claims Nos. 24-42

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing in the form of an Annex C/ST.25 text file, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.
- ☐ furnish a sequence listing on paper or in the form of an image file complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13*ter*.1(a) or (b).

☒ See Supplemental Box for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	11, 13-15
	No:	Claims	1-10, 12, 16-23, 43, 44
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-23, 43, 44
Industrial applicability (IA)	Yes:	Claims	1-23, 43, 44
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

see form 210

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 24-42 relate to subject-matter considered by this Authority to be covered by the provisions of Art. 17(2)(a)(i) and Rule 39.1(iv) PCT, because said claims define a method of treatment by therapy comprising a step of delivering stimulation energy to a patient. Furthermore, according to Art. 34(4)(a)(i) and Rule 67.1(iv) PCT no examination will be carried out for said claims.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1 Reference is made to the following documents:

D1 EP 2 929 852 A1 (HOLAIRA INC [US]) 14 October 2015 (2015-10-14)

D2 US 2015/066006 A1 (SRIVASTAVA NISHANT R [US]) 5 March 2015 (2015-03-05)

D3 WO 2016/134264 A1 (BOSTON SCIENT SCIMED INC [US]) 25 August 2016 (2016-08-25)

D4 WO 2016/183337 A2 (NAT UNIV IRELAND GALWAY [IE]; QI ZHAN MICHELE [US]) 17 November 2016 (2016-11-17)cited in the application

2 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-10, 12, 16-23, 43, 44 is not new in the sense of Article 33(2) PCT for the following reasons:

2.1 Document D1 discloses a system (see Fig. 10) for detecting anatomical structures and therapeutic neuromodulation in a nasal region of a human patient, the system comprising all the features of claim 1:

a shaft having a proximal portion and a distal portion, wherein the shaft is configured to locate the distal portion intraluminally at a target site within a nasal cavity inferior to a sphenopalatine foramen of the human patient (see Fig. 10(230) and par. [0094];

an evaluation/modulation assembly at the distal portion of the shaft (see Fig. 10(220)),

wherein the evaluation/modulation assembly comprises a plurality of electrodes configured to emit stimulating energy to tissue at the target site at frequencies for locating target neural structures and detect bioelectric properties in response to the stimulating energy (Fig. 23(540) and pars. [0118]-[0120]);

and a console including a controller having a computer-readable medium carrying instructions, which when executed by the controller, causes the console to map locations of the target neural structures and causes the evaluation/modulation assembly to apply therapeutic neuromodulation energy in a predetermined neuromodulation pattern based on the locations of the target neural structures (see Fig. 10(210) and pars. [0060], [0061]).

2.2 The applicant's attention is drawn to the fact that documents D2 and D3 disclose a system suitable for detecting anatomical structures and therapeutic neuromodulation in a nasal region of a human patient comprising all the features of claim 1 (see D2: Figs. 1, 5 and par. [0031] and D3: Fig. 2 and pars. [0044], [0051]) and therefore also deprive the subject-matter of claim 1 of novelty.

2.3 Claim 18 although written as an independent claim, comprises all the features of claim 1 and is therefore dependent on claim 1. The additional features of claim 18 are also disclosed in D1: see Fig. 10(212) and par. [0118].

2.4 Claim 43 although written as an independent claim, appears to relate effectively to the same subject-matter of claim 1. Therefore claim 43 is also not new in view of D1-D3 and the passages cited above.

2.5 Notwithstanding the below mentioned lack of clarity, the additional features of dependent claims 2-10, 12, 16-17, 19-23, 44 are also disclosed in the prior art:

claims 2-4, 21, 44: see D1, par. [0120];

claim 5: see D1, par. [0118];

claim 6: see D1, Fig. 10(244) and par. [0060];

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claims 7, 8, 19, 20: see D1, par. [0119];

claims 9, 22: see D1, pars. [0094], [0095];

claims 10, 23: see D1, Fig. 10(212);

claims 12, 16: see D1, Fig. 22(500);

claim 17: see D1, par. [0093].

3 Dependent claims 11, 13-15 do not appear to contain any additional features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of inventive step in the sense of Article 33(3) PCT. Said claims merely define slight constructional changes in the system of claim 1 which come within the scope of the customary practice followed by persons skilled in the art, especially as the advantages thus achieved can readily be foreseen. Consequently, the subject-matter of said claims lacks an inventive step.

Re Item VI

Certain documents cited

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
PCT/US2016/032132	17/11/2016	12/05/2016	12/05/2015

The validity of the priority has not been considered because this Authority does not have in its possession a copy of the earlier application whose priority has been claimed. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43bisi and 641) is the claimed priority date. However, care of the

applicant is drawn to the fact that in case the validity of the priority drops, the document indicted in the search report as a P - document (WO 2016/183337) becomes part of the prior art and deprives the novelty of the present set of claims.

Furthermore, the applicant's attention is drawn to the following: The present application claims the priority of the US application US-62/421,135 (11.11.2016). In case the applicant decides to enter the European phase, this priority claim will not hold for the following reason: According to Article 87(1) EPC, only the date of filing of the "first application" can be claimed as a priority. In this case, the subject-matter of the claims 1-23, 43,44 of the present application is already contained in the earlier application PCT/US2016/032132 filed on 12.05.2016, prior to the priority date claimed by the present application, later published as WO 2016/183337 (D4) and originating from the same applicant. Accordingly, the claimed priority of the present application will not be valid in respect of the subject-matter already contained in the earlier application PCT/US2016/032132 (see also Guidelines F-VI, 1.4).

Re Item VII

Certain defects in the international application

1 Claim 18 comprises all the features of claim 1 and is therefore not appropriately formulated as a claim dependent on the latter (Rule 6.4 PCT).

2 Contrary to the requirements of Rule 5.1 (a)(iii) PCT, the relevant background art disclosed in the documents D1-D3 is not mentioned in the description, nor are these documents identified therein.

3 The features of the claims are not provided with reference signs placed in parentheses (Rule 6.2(b) PCT).

4 The independent claim is not in the two-part form in accordance with Rule 6.3 (b) PCT.

5 The incorporation of documents by reference (see for example description, par. [0020]) is not allowable in some of the Designated States.

Re Item VIII

Certain observations on the international application

1 Although claims 1, 18 and 43 have been drafted as separate independent claims, they appear to relate effectively to the same subject-matter and to differ from each other only with regard to the definition of the subject-matter for which protection is sought and/or in respect of the terminology used for the features of that subject-matter. The aforementioned claims therefore lack conciseness and as such do not meet the requirements of Article 6 PCT.

2 Claims 2-4, 21, 44 do not meet the requirements of Article 6 PCT because the matter for which protection is sought is not clearly defined. The claims attempt to define the subject-matter in terms of the result to be achieved (initiate ionic agitation of specific tissue), which merely amounts to a statement of the underlying problem, without providing the technical features necessary for achieving this result (i.e. value of applied frequency).

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To:
Schoen, Adam M.
BROWN RUDNICK LLP
One Financial Center
Boston, MA 02111
ETATS-UNIS D'AMERIQUE

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference NEURE-003/01WO 3524	Date of mailing *(day/month/year)* 11 January 2021 (11-01-2021) **FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/IB2020/000544	International filing date *(day/month/year)* 29 June 2020 (29-06-2020)
Applicant NEURENT MEDICAL LIMITED	

1. [X] The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

   When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

   How? Directly to the International Bureau preferably through ePCT, or on paper to:
   The International Bureau of WIPO, 34 chemin des Colombettes, 1211 Geneva 20, Switzerland

   For more detailed instructions, see the *PCT Applicant's Guide*, International Phase, paragraphs 9.004 - 9.011.

2. [ ] The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. [ ] **With regard to any protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   [ ] the protest together with the decision thereon has been transmitted to the International Bureau together with any request to forward the texts of both the protest and the decision thereon to the designated Offices.

   [ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   The applicant may **submit comments on an informal basis on the written opinion of the International Searching Authority** to the International Bureau. These comments will be made available to the public after international publication. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established.

   Shortly after the expiration of **18 months from the priority date, the international application will be published** by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau before the completion of the technical preparations for international publication (Rules 90*bis*.1 and 90*bis*.3).

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for **entry into the national phase** before those designated Offices. In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months. For details about the applicable time limits, Office by Office, see www.wipo.int/pct/en/texts/time_limits.html and the *PCT Applicant's Guide*, National Chapters.

   Within **22 months from the priority date, the applicant may request that a supplementary international search be carried out** by a different International Searching Authority that offers this service (Rule 45*bis*.1). The procedure for requesting supplementary international search is described in the *PCT Applicant's Guide*, International Phase, paragraphs 8.006-8.032.

Name and mailing address of the International Searching Authority European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040 Fax: (+31-70) 340-3016	Authorized officer ACQUAVIVA, Laure Tel: +49 (0)89 2399-5656

Form PCT/ISA/220 (revised January 2020)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
NEURE-003/01WO 3524		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/IB2020/000544	29 June 2020 (29-06-2020)	28 June 2019 (28-06-2019)
Applicant		
NEURENT MEDICAL LIMITED		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 7 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language,** the international search was carried out on the basis of:
      [X] the international application in the language in which it was filed
      [ ] a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
   b. [ ] This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).
   c. [ ] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. [X] **Certain claims were found unsearchable** (See Box No. II)

3. [X] **Unity of invention is lacking** (see Box No III)

4. With regard to the **title,**
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings,**
   a. the figure of the **drawings** to be published with the abstract is Figure No. 2
      [ ] as suggested by the applicant
      [X] as selected by this Authority, because the applicant failed to suggest a figure
      [ ] as selected by this Authority, because this figure better characterizes the invention
   b. [ ] none of the figures is to be published with the abstract

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2020/000544

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 11-33, 57-72, 86-98
because they relate to subject matter not required to be searched by this Authority, namely:

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by surgery

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [X] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-10, 44-56

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[ ] No protest accompanied the payment of additional search fees.

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INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2020/000544

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61B5/053 A61B18/14
ADD. A61B18/00 A61N1/05 A61N1/36

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61B A61N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2018/133460 A1 (TOWNLEY DAVID [IE] ET AL) 17 May 2018 (2018-05-17) cited in the application the whole document	1-10, 44-56
Y	WO 2007/008954 A2 (ABLATION FRONTIERS [US]; WERNETH RANDELL L [US]) 18 January 2007 (2007-01-18) abstract paragraph [0002] - paragraph [0013] paragraph [0096] - paragraph [0099] claims 52-61	1-10, 44-56
A	US 2016/331459 A1 (TOWNLEY DAVID [IE] ET AL) 17 November 2016 (2016-11-17) cited in the application the whole document	1-10, 44-56

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 October 2020	11/01/2021

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Artikis, T

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Form PCT/ISA/210 (second sheet) (April 2005)

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INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2020/000544

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2015/048806 A2 (NIDUS MEDICAL LLC [US]) 2 April 2015 (2015-04-02) abstract paragraph [0149]; figures 20A-20E	1-10, 44-56
A	US 2005/283148 A1 (JANSSEN WILLIAM M [US] ET AL) 22 December 2005 (2005-12-22) the whole document	1-10, 44-56

1

Form PCT/ISA/210 (continuation of second sheet) (April 2005)

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2020/000544

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2018133460 A1	17-05-2018	AU 2017357869 A1	06-06-2019
		CA 3041440 A1	17-05-2018
		CN 110191674 A	30-08-2019
		EP 3537954 A1	18-09-2019
		JP 2019535386 A	12-12-2019
		US 2018133460 A1	17-05-2018
		US 2020086112 A1	19-03-2020
		US 2020101283 A1	02-04-2020
		US 2020171302 A1	04-06-2020
		WO 2018087601 A1	17-05-2018
WO 2007008954 A2	18-01-2007	AU 2006268238 A1	18-01-2007
		CA 2615267 A1	18-01-2007
		EP 1909679 A2	16-04-2008
		US 2007083195 A1	12-04-2007
		US 2009182325 A1	16-07-2009
		US 2015005767 A1	01-01-2015
		WO 2007008954 A2	18-01-2007
US 2016331459 A1	17-11-2016	AU 2016262085 A1	04-01-2018
		CA 2984207 A1	17-11-2016
		CN 107835705 A	23-03-2018
		EP 3294410 A2	21-03-2018
		HK 1252823 A1	06-06-2019
		JP 2018515314 A	14-06-2018
		US 2016331459 A1	17-11-2016
		US 2019231429 A1	01-08-2019
		US 2019239953 A1	08-08-2019
		US 2019239954 A1	08-08-2019
		US 2019239955 A1	08-08-2019
		US 2019239956 A1	08-08-2019
		US 2019239957 A1	08-08-2019
		US 2020100838 A1	02-04-2020
		US 2020107882 A1	09-04-2020
		WO 2016183337 A2	17-11-2016
WO 2015048806 A2	02-04-2015	US 2015164571 A1	18-06-2015
		US 2016354135 A1	08-12-2016
		US 2016354136 A1	08-12-2016
		US 2017360494 A1	21-12-2017
		US 2018263678 A1	20-09-2018
		US 2018317993 A1	08-11-2018
		US 2019083157 A1	21-03-2019
		US 2020054379 A1	20-02-2020
		WO 2015048806 A2	02-04-2015
US 2005283148 A1	22-12-2005	BR PI0512233 A	19-02-2008
		CA 2570911 A1	26-01-2006
		CN 1981256 A	13-06-2007
		CR 8817 A	18-03-2008
		EP 1769320 A2	04-04-2007
		JP 2008503255 A	07-02-2008
		KR 20070047762 A	07-05-2007
		US 2005283148 A1	22-12-2005
		US 2007060921 A1	15-03-2007
		US 2007167943 A1	19-07-2007
		US 2010114095 A1	06-05-2010
		US 2013046292 A1	21-02-2013

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2020/000544

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		US 2016066984 A1	10-03-2016
		WO 2006009705 A2	26-01-2006
		ZA 200610576 B	30-07-2008

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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-10, 44-56

Systems for treating a condition comprising: a device comprising an end effector including a plurality of electrodes; and a controller operably associated with the device and configured to: receive data from the device associated at least with presence and/or a depth/location of neural tissue at a position of each of the plurality of electrodes; and process the data to determine a level of energy to be delivered by each of the plurality of electrodes such that the energy delivered at each position by each of the plurality of electrodes is sufficient to ablate the neural tissue at each position and minimize and/or prevent damage to non-neural tissue including a blood vessel adjacent to the neural tissue at each position.

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2. claims: 34-43

A system for treating at least one of rhinitis, congestion, and rhinorrhea within a nasal cavity of a patient, the system comprising: a device comprising an end effector including a plurality of electrodes; a controller operably associated with the device and configured to: receive data from the device associated at least with presence and/or a depth/location of blood vessels associated with mucus producing and/or mucosal engorgement elements at a position of each of the plurality of electrodes within the nasal cavity; and process the data to determine a level of energy to be delivered by each of the plurality of electrodes such that the energy delivered at each position by each of the plurality of electrodes is sufficient to: cause thrombus formation within one or more blood vessels associated with the mucus producing and/or mucosal engorgement elements, resulting in local hypoxia of the mucus producing and/or mucosal engorgement elements, thereby decreasing production of mucus and/or mucosal engorgement.

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3. claims: 73-85

A system for diagnosing and/or treating a neurological condition of a patient, the system comprising: a device comprising an end effector including a plurality of electrodes; and a controller operably associated with the device and configured to: receive data from the device that is associated with neural tissue at a target site; process the data to determine a type of neural tissue at the target site; and determine energy output from the end effector based on the type of neural tissue at the target site.

Information on Search Strategy - Pilot phase (see OJ 2015, A86)
The type of information contained in this sheet may change during the pilot for improving the usefulness of this new service.

Application Number
PCT/IB2020/000544

TITLE: SYSTEMS AND METHODS FOR TARGETED THERAPEUTIC NASAL NEUROMODULATION

APPLICANT: NEURENT MEDICAL LIMITED

IPC CLASSIFICATION: A61B5/053, A61B18/14, A61B18/00, A61N1/05, A61N1/36

EXAMINER: Artikis, T

CONSULTED DATABASES: WPI, PRESEARCH, ANSERA, COMBI

CLASSIFICATION SYMBOLS DEFINING EXTENT OF THE SEARCH:

IPC:

CPC: A61B18/1492, A61B2018/00327, A61B2018/00434, A61N1/0546, A61N1/36014

FI/F-TERMS:

KEYWORDS OR OTHER ELEMENTS FEATURING THE INVENTION:
Systems for treating a condition comprising: a device comprising an end effector including a plurality of electrodes; and a controller operably associated with the device and configured to: receive data from the device associated at least with presence and/or a depth/location of neural tissue at a position of each of the plurality of electrodes; and process the data to determine a level of energy to be delivered by each of the plurality of electrodes such that the energy delivered at each position by each of the plurality of electrodes is sufficient to ablate the neural tissue at each position and minimize and/or prevent damage to non-neural tissue including a blood vessel adjacent to the neural tissue at each position.

EPO FORM P0462

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IB2020/000544	29.06.2020	28.06.2019

International Patent Classification (IPC) or both national classification and IPC
INV. A61B5/053 A61B18/14 ADD. A61B18/00 A61N1/05 A61N1/36

Applicant
NEURENT MEDICAL LIMITED

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465	see form PCT/ISA/210	Artikis, T Telephone No. +49 89 2399-0

Form PCT/ISA/237 (Cover Sheet) (January 2015)

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing:

   a. ☐ forming part of the international application as filed:

      ☐ in the form of an Annex C/ST.25 text file.

      ☐ on paper or in the form of an image file.

   b. ☐ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. ☐ furnished subsequent to the international filing date for the purposes of international search only:

      ☐ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).

      ☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos. 11-43, 57-98

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international search *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☒ no international search report has been established for the whole application or for said claims Nos. 11-43, 57-98

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing in the form of an Annex C/ST.25 text file, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.
- ☐ furnish a sequence listing on paper or in the form of an image file complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13*ter*.1(a) or (b).

☒ See Supplemental Box for further details

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Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has, within the applicable time limit:

   ☐ paid additional fees

   ☐ paid additional fees under protest and, where applicable, the protest fee

   ☐ paid additional fees under protest but the applicable protest fee was not paid

   ☒ not paid additional fees

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-10, 44-56

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-10, 44-56
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-10, 44-56
Industrial applicability (IA)	Yes:	Claims	1-10, 44-56
	No:	Claims	

2. Citations and explanations

   see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

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Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1 No examination will be carried out in respect of claims 11-43 and 57-98, because they have not been searched (see Art. 17(2)(a) or (3) PCT, Rule 66.1(e) PCT and the international search report).

Re Item IV

Lack of unity of invention

2 The present application lacks unity according to Rule 13.1 PCT, because the three inventions of claims I) 1-10 and 44-56, II) 34-43, and III) 73-85 are not linked by a single general inventive concept and no technical relationship in the sense of Rule 13.2 PCT exists between them.

Document US2018/133460 discloses (see fig. 3A and the corresponding description) the common subject-matter of independent claims 1 (or 44), 34 and 73, namely a system (300) comprising: a device comprising (302) an end effector (312) including a plurality of electrodes (344); and a controller (304, 318, 320) operably associated with the device (302) and configured (see par. 38) to receive data from the device (302), process the data and determine (see par. 46) energy output (activate the electrodes 344 or not) from the end effector (312) based on the processed data.

Furthermore, said independent claims do not share any corresponding special technical features in the sense of Rule 13.2 PCT, because the problems that they seek to solve are completely different, namely:

- how to select an energy delivery parameter for neural tissue ablation in order to minimise or prevent damage to a blood vessel adjacent to the neural tissue for claim 1 (or 44);
- how to select an energy delivery parameter in order to form thrombus within nasal blood vessels for claim 34; and
- how to determine energy output based on neural tissue type in order to diagnose and/or treat a neurological condition for claim 73.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

3 Reference is made to the following documents:

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D1 US 2018/133460 A1 (TOWNLEY DAVID [IE] ET AL) 17 May 2018 (2018-05-17) cited in the application

D2 WO 2007/008954 A2 (ABLATION FRONTIERS [US]; WERNETH RANDELL L [US]) 18 January 2007 (2007-01-18)

4 The present application does not meet the criteria of Article 33(3) PCT, because the subject-matter of independent claims 1 and 44 does not involve an inventive step.

4.1 D1 is regarded as being the prior art closest to the subject-matter of claim and discloses (see the passages of said document cited under item IV above) a system (300) for treating a condition within a nasal cavity of a patient, the system comprising:
a device (302) comprising an end effector (312) including a plurality of electrodes (344); and
a controller (304, 318, 320) operably associated with the device (302) and configured to:
receive data from the device (302) associated at least with presence and/or a depth/location of neural tissue at a position of each of the plurality of electrodes within the nasal cavity; and
process the data to determine (see par. 100) a parameter (frequency) of energy to be delivered by each of the plurality of electrodes such that the energy delivered at each position by each of the plurality of electrodes is sufficient to modulate/ablate the neural tissue at each position and minimize and/or prevent damage to an artery or arterial wall adjacent to the neural tissue at each position.
The subject-matter of claim 1 therefore differs from this known system in that the level of energy is determined and is therefore new (Art. 33(2) PCT).
The problem to be solved by the present invention may therefore be regarded as how to select an energy delivery parameter for neural tissue ablation in order to minimise or prevent said damage.
The solution proposed in claim 1 of the present application cannot be considered as involving an inventive step (Article 33(3) PCT), because D2 discloses (see claims 52-61) that the energy level is an alternative to the frequency for targeted tissue ablation. Therefore, it appears obvious to the skilled person to substitute energy level as disclosed in D2 for the frequency disclosed in D1, thereby arriving at the subject-matter of claim 1 without the exercise of an inventive step (Art. 33(3) PCT).

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4.2 The argumentation of the previous point can be applied in an analogous manner to the subject-matter of independent claim 44.

5 Dependent claims 2-10 and 45-56 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of inventive step (Art. 33(3) PCT), because said additional features are already disclosed in D1 or D2 as explained below:
Claims 2-9, 45-52, 54-55: see the aforementioned passages of D1;
Claims 10, 53, 56: see D2, par. 96-99.

Re Item VII

Certain defects in the international application

6 The independent claims are not in the two-part form in accordance with Rule 6.3(b) PCT, which in the present case would be appropriate, with those features known in combination from the prior art, namely D1, being placed in the preamble (Rule 6.3(b)(i) PCT) and the remaining features being included in the characterising part (Rule 6.3(b)(ii) PCT).

7 The features of the claims are not provided with reference signs placed in parentheses (Rule 6.2(b) PCT).

The following points should be considered when filing amendments:

A) Any information the applicant may wish to submit concerning the subject-matter of the invention, for example further details of its advantages or of the problem it solves, and for which there is no basis in the application as filed, should be confined to the letter of reply and not be incorporated into the application (Article 34(2)(b) PCT).

B) In order to facilitate the examination of the conformity of the amended application with the requirements of Article 34(2)(b) PCT, the applicant is requested to clearly identify the amendments carried out, no matter whether they concern amendments by addition, replacement or deletion, and to indicate the passages of the application as filed on which these amendments are based (see also Rule 66.8(a) PCT). If the applicant regards it as appropriate these indications could be submitted in handwritten form on a copy of the relevant parts of the application as filed.

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Possible steps after receipt of the international search report (ISR) and written opinion of the International Searching Authority (WO/ISA)

General information

For all international applications, the competent International Searching Authority **(ISA)** will establish an international search report **(ISR)** accompanied by a written opinion of the International Searching Authority **(WO/ISA)**. The **WO/ISA** may be responded to by

- filing informal comments with the **International Bureau of WIPO (IB)** (where no demand for international preliminary examination **(demand)** is filed)
- filing amendments under Art. 19 PCT (this can be done whether or not a **demand** is filed)
- filing amendments under Art. 34 PCT and/or formal observations in response to objections raised in the **WO/ISA** (where a **demand** *is* actually filed)

This document explains these possibilities.

Filing informal comments

After receipt of the **ISR and WO/ISA**, the applicant may file informal comments on the **WO/ISA, directly with the IB** (see International Search and Preliminary Examination Guidelines 2.15). These will be communicated to the designated/elected Offices, together with the International Preliminary Report on Patentability **(IPRP)** at 30 months from the priority date.

Amending claims under Art. 19 PCT

The applicant may file **amended claims** under Art. 19 PCT, **directly with the IB** by the later of the following dates:

- 2 months from the date of mailing of the **ISR** and the **WO/ISA**
- 16 months from the priority date

However, any such amendment received by the **IB** after the expiration of the applicable time limit shall be **considered to have been received on time** by the **IB**, if it reaches it **before** the technical preparations for international publication have been completed (the 15th day prior to the date of publication, see PCT Applicant's Guide, International Phase, 9.013).

For further information, please see Rule 46 PCT as well as form PCT/ISA/220.

Please also note that, when filing amended claims under Art. 19 PCT, such amendments shall be **accompanied by a letter** identifying the amendments made and also the basis for the amendments in the application as originally filed (Rule 46.5(b) PCT). Where a **demand** is filed, failure to comply with this requirement may result in the amendments being ignored in the International Preliminary Examination Report **(IPER)**, see Rule 70.2(*c-bis*) PCT.

BNSDOCID: <XS_____20070401GK_1_>

Filing a demand for international preliminary examination

In principle, the **WO/ISA** will be considered to be the written opinion of the International Preliminary Examining Authority (**IPEA**). Where the **WO/ISA** issued by the **EPO** as **ISA** gives a positive opinion on the international application and the invention to which it relates, filing a **demand** with the **EPO** as **IPEA** would normally be unnecessary, since a positive IPRP would anyway be established by the IB based on the WO/ISA (see also further below).

If the applicant wishes to file a **demand** (for example, to allow him to argue his case in international preliminary examination with regard to objections raised in a negative **WO/ISA** before the **IPEA** issues an **IPER**), this must be done before expiration of **3 months after the date of mailing of the ISR and WO/ISA** or **22 months after priority date**, whichever expires later (Rule 54*bis* PCT). Amendments under Art. 34 PCT can be filed with the IPEA, normally at the same time as filing the demand (Rule 66.1(b) PCT) or within the time limit set for reply to any written opinion issued during international preliminary examination by the **IPEA**.

If a **demand** is filed at the **EPO** as **IPEA** and no comments/amendments have been received by the time the **EPO** starts drawing up the **IPER** (Rule 66.4*bis* PCT), the **WO/ISA** will be transformed by the **IPEA** into an **IPER** (also called the **IPRP (Chapter II)** which would merely reflect the content of the **WO/ISA** (OJ 10/2011, 532). The **demand** can still be withdrawn (Art. 37 PCT).

Please also note that, when filing amendments under Art. 34 PCT, such amendments shall be accompanied by a letter which identifies the amendments made and also the basis for the amendments in the application as originally filed (Rule 66.8(a) PCT). Failure to comply with this requirement may result in the amendments being ignored in the **IPER (IPRP (Chapter II))**, see Rule 70.2(c-*bis*) PCT.

Filing a request for supplementary international search

The applicant may, with the IB, file a request for **supplementary international search** under Rule 45*bis*.1 PCT. The present **ISR** and **WO/ISA** may also be taken into account in the execution of that supplementary international search, provided that these are available to the Authority charged with this task before it starts the supplementary search (Rule 45*bis*.5 PCT).

This kind of request **cannot be filed specifying the ISA** who did the **international search**.

More information on this topic can be found in the **PCT Applicant's Guide**, Chapter 8 (http://www.wipo.int/pct/en/guide/ip08.html).

End of the international phase

Where no **demand** is filed, at the end of the international phase, the **IB** will transform the **WO/ISA** into the IPRP (PCT Chapter I) (Rule 44*bis* PCT), which will then be transmitted together with possible informal comments to the designated Offices. Where a demand is filed, the **WO/ISA** is not transformed into an **IPRP (Chapter I)** by the **IB**, but rather the **IPEA** will establish an **IPER**, (the IPER is the same as the IPRP (PCT Chapter II), see Rule 70.15 PCT).

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Electronic Acknowledgement Receipt

EFS ID:	44015406
Application Number:	17225560
International Application Number:	
Confirmation Number:	9752
Title of Invention:	SYSTEMS AND METHODS FOR IMPROVING SLEEP WITH THERAPEUTIC NASAL TREATMENT
First Named Inventor/Applicant Name:	David Townley
Customer Number:	21710
Filer:	Adam M Schoen/Kelley Warren
Filer Authorized By:	Adam M Schoen
Attorney Docket Number:	NEURE-008/01US 35242/69
Receipt Date:	13-OCT-2021
Filing Date:	08-APR-2021
Time Stamp:	16:37:08
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Information Disclosure Statement (IDS) Form (SB08)	35242_69US_-_Information_Disclosure_Statement_Fillable_PDF.pdf	1039203 8449e9743c4654ba5993609cf5dc1f91a3b9a95a	no	20

Warnings:

Information:					
2	Foreign Reference	35242_8US_-_EP2929852A1.pdf	4697192 979ca55c356a0c51e8dad7d779ea6fe7f42f59ab	no	87
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3	Foreign Reference	35242_56WO_-_WO2007008954A2.pdf	3858680 5eeee07e14e9a309629e0e75c6310e9dec960087	no	94
Warnings:					
Information:					
4	Foreign Reference	35242_26US_-_WO2015013252A1.pdf	6155651 aad62ac5efe35b4900ebdf1914c742354a6ce887	no	117
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Information:					
5	Foreign Reference	35242_56WO_-_WO2015048806A2.pdf	7516885 65b7c45fbc5f0f41043914e48cecd9ed5a90d29c	no	107
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Information:					
6	Foreign Reference	35242_8US_-_WO2016134264A1.pdf	1918954 6919b2d8c4d4442416d6454099941c2ef1ab3fe2	no	43
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7	Foreign Reference	35242_26US_-_WO2016183337A2.pdf	6124579 1cb660e91fba1c244594f743b6c866a0087792e8	no	119
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8	Foreign Reference	35242_8US_-_WO2018087601A1.pdf	4555825 16adde1c800839c11faae5c6481b4a3217ede136	no	89
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9	Non Patent Literature	35242_37US_-_Arora_-_1980.pdf	455802 632b493a739d19f25795a340afa825bda2bab571	no	3
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10	Non Patent Literature	35242_26US_-_IKEDA-2009.pdf	338688 8e45634592e0e231f87f1a647d122f65e729c92b	no	6
Warnings:					
Information:					
11	Non Patent Literature	35242_8US_-_International_Search_Report_and_Written_Opinion_for_PCTUS2016032132.pdf	871642 21022c407c07cc068dcd2fb9d9baf0d30fe51a2c	no	24
Warnings:					
Information:					
12	Non Patent Literature	35242_27US_-_ISR__WO_PCT_IB2019001298.pdf	1597128 81a8e3fc2060493479490c2523989ab5c73c20bd	no	15
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Information:					
13	Non Patent Literature	35242_29US_-_ISR__WO_PCTIB2021000234.pdf	858171 f61e1d2d6cc882c1af3a660a2d653a18f182f981	no	14
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14	Non Patent Literature	35242_71US_-_ISR_WO_PCTIB2021000243.pdf	918418 9b28a6a3efaa2adb1e492ee47f7e84c2960533ba	no	15
Warnings:					
Information:					
15	Non Patent Literature	35242_8US_-_International_Search_Report_and_Written_Opinion_for_PCTIB2017001541.pdf	509562 f819fc44ebf8e5ac598bc1cdd83ce1a8f95eccad	no	15
Warnings:					
Information:					

16	Non Patent Literature	35242_56WO_-_ISR__W_PCTIB2020000544.pdf	1203346 72c01898cc2c0948a09df531e0831a8128d6221a	no	19
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17	Non Patent Literature	35242_26US_-_KAYANA-2009.pdf	1454458 534e5df500f52e34c85709e6a1eb870147e61006	no	4
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Information:					
18	Non Patent Literature	35242_69US_-_KIKAWADA-2007.pdf	324512 e132e24400c53fbaffd323fc96a97866f87a7583	no	4
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Information:					
19	Non Patent Literature	35242_26US_-_KOBAYASHI-2012.pdf	288781 1dd3fe9a49b557a81ad1f7dd83138209651ee6c6	no	4
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22	Non Patent Literature	35242_29US_-_NFOA_US16701869.pdf	846420 562525943053fd10af4981291b988e4e3e5196f7	no	23
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23	Non Patent Literature	35242_67US_-_NFOA16701890.pdf	277193 a4705ffe764d71232c96a2cf15cd2b08d6c4d343	no	8
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24	Non Patent Literature	35242_8US_-_NFOA_US16703348.pdf	462644 67d8e09c78963a39eba2e5ca96fdc96b82875680	no	13
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26	Non Patent Literature	35242_37US_-_Ozenberger_-_Cryosurgery_in_chronic_rhinitis.pdf	553734 51714bbe4a045e3e5ca7aafda1867d089a3fd833	no	12
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27	Non Patent Literature	35242_37US_-_Ozenberger_-_Cryosurgery_for_the_treatment_of_chronic_rhinitis.pdf	546349 75cba8bab62ecbab2cd7920887394 86d5bbafab0	no	9
Warnings:					
Information:					
		Total Files Size (in bytes):	49303878		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
17/225,560	04/08/2021		910	NEURE-008/01US 35242/69	20	1

CONFIRMATION NO. 9752

21710
BROWN RUDNICK LLP
ONE FINANCIAL CENTER
BOSTON, MA 02111

FILING RECEIPT

OC000000124895413

Date Mailed: 04/15/2021

Receipt is acknowledged of this non-provisional utility patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF FIRST INVENTOR, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection.

Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please submit a written request for a corrected Filing Receipt, including a properly marked-up ADS showing the changes with strike-through for deletions and underlining for additions. If you received a "Notice to File Missing Parts" or other Notice requiring a response for this application, please submit any request for correction to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections provided that the request is grantable.

Inventor(s)

David Townley, County Clare, IRELAND;

Applicant(s)

Neurent Medical Limited, Oranmore, IRELAND;

Power of Attorney: None

Domestic Priority data as claimed by applicant

This appln claims benefit of 63/007,584 04/09/2020

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

If Required, Foreign Filing License Granted: 04/14/2021

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The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 17/225,560**

Projected Publication Date: 10/14/2021

Non-Publication Request: No

Early Publication Request: No
**** SMALL ENTITY ****
Title

SYSTEMS AND METHODS FOR IMPROVING SLEEP WITH THERAPEUTIC NASAL TREATMENT

Preliminary Class

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

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LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

SelectUSA

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The U.S. offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to promote and facilitate business investment. SelectUSA provides information assistance to the international investor community; serves as an ombudsman for existing and potential investors; advocates on behalf of U.S. cities, states, and regions competing for global investment; and counsels U.S. economic development organizations on investment attraction best practices. To learn more about why the United States is the best country in the world to develop technology, manufacture products, deliver services, and grow your business, visit http://www.SelectUSA.gov or call +1-202-482-6800.

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 17/225,560

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	80		N/A	
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	350		N/A	
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	400		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	20 minus 20 =	*	x 50 =	0.00	OR		
INDEPENDENT CLAIMS (37 CFR 1.16(h))	1 minus 3 =	*	x 240 =	0.00			
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			0.00			
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				0.00			
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	830		TOTAL	

APPLICATION AS AMENDED - PART II

AMENDMENT A

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
Application Size Fee (37 CFR 1.16(s))									
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

AMENDMENT B

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE($)	ADDITIONAL FEE($)		RATE($)	ADDITIONAL FEE($)
Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
Application Size Fee (37 CFR 1.16(s))									
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

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UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
17/225,560	04/08/2021	David Townley	NEURE-008/01US 35242/69

CONFIRMATION NO. 9752

21710
BROWN RUDNICK LLP
ONE FINANCIAL CENTER
BOSTON, MA 02111

INFORMAL NOTICE

OC000000124895414

Date Mailed: 04/15/2021

INFORMATIONAL NOTICE TO APPLICANT

Applicant is notified that the above-identified application contains the deficiencies noted below. No period for reply is set forth in this notice for correction of these deficiencies. However, if a deficiency relates to the inventor's oath or declaration, the applicant must file an oath or declaration in compliance with 37 CFR 1.63, or a substitute statement in compliance with 37 CFR 1.64, executed by or with respect to each actual inventor no later than the expiration of the time period set in the "Notice of Allowability" to avoid abandonment. See 37 CFR 1.53(f).

The item(s) indicated below are also required and should be submitted with any reply to this notice to avoid further processing delays.

- A properly executed inventor's oath or declaration has not been received for the following inventor(s):
  David Townley

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/elbanaybanay/

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	NEURE-008/01US 35242/69
	Application Number	
Title of Invention	SYSTEMS AND METHODS FOR IMPROVING SLEEP WITH THERAPEUTIC NASAL TREATMENT	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2:

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Inventor Information:

Inventor 1 — Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
Mr.	David		Townley	

Residence Information (Select One) US Residency ● Non US Residency Active US Military Service

City	County Clare	Country of Residence [i]	IE

Mailing Address of Inventor:

Address 1	Latoon North, Newmarket-on-Fergus
Address 2	
City	County Clare
State/Province	
Postal Code	
Country [i]	IE

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below.
For further information see 37 CFR 1.33(a).

☐ **An Address is being provided for the correspondence Information of this application.**

Customer Number	21710		
Email Address	ip@brownrudnick.com	Add Email	Remove Email

Application Information:

Title of the Invention	SYSTEMS AND METHODS FOR IMPROVING SLEEP WITH THERAPEUTIC NASAL TREATMENT		
Attorney Docket Number	NEURE-008/01US 35242/69	**Small Entity Status Claimed**	☒
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	23	**Suggested Figure for Publication (if any)**	

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Filing By Reference:

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

Please Select One:	● Customer Number	US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	21710		

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, 365(c), or 386(c) or indicate National Stage entry from a PCT application. Providing benefit claim information in the Application Data Sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.
When referring to the current application, please leave the "Application Number" field blank.

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
	Claims benefit of provisional	63/007584	2020-04-09

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button. Add

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	NEURE-008/01US 35242/69
	Application Number	
Title of Invention	SYSTEMS AND METHODS FOR IMPROVING SLEEP WITH THERAPEUTIC NASAL TREATMENT	

Foreign Priority Information:

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55. When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX)[i] the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(i)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

Remove

Application Number	Country[i]	Filing Date (YYYY-MM-DD)	Access Code[i] (if applicable)

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button. Add

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.
NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	NEURE-008/01US 35242/69
	Application Number	
Title of Invention	SYSTEMS AND METHODS FOR IMPROVING SLEEP WITH THERAPEUTIC NASAL TREATMENT	

Authorization or Opt-Out of Authorization to Permit Access:

When this Application Data Sheet is properly signed and filed with the application, applicant has provided written authority to permit a participating foreign intellectual property (IP) office access to the instant application-as-filed (see paragraph A in subsection 1 below) and the European Patent Office (EPO) access to any search results from the instant application (see paragraph B in subsection 1 below).

Should applicant choose not to provide an authorization identified in subsection 1 below, applicant **must opt-out** of the authorization by checking the corresponding box A or B or both in subsection 2 below.

NOTE: This section of the Application Data Sheet is **ONLY** reviewed and processed with the **INITIAL** filing of an application. After the initial filing of an application, an Application Data Sheet cannot be used to provide or rescind authorization for access by a foreign IP office(s). Instead, Form PTO/SB/39 or PTO/SB/69 must be used as appropriate.

1. Authorization to Permit Access by a Foreign Intellectual Property Office(s)

A. Priority Document Exchange (PDX) - Unless box A in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the State Intellectual Property Office of the People's Republic of China (SIPO), the World Intellectual Property Organization (WIPO), and any other foreign intellectual property office participating with the USPTO in a bilateral or multilateral priority document exchange agreement in which a foreign application claiming priority to the instant patent application is filed, access to: (1) the instant patent application-as-filed and its related bibliographic data, (2) any foreign or domestic application to which priority or benefit is claimed by the instant application and its related bibliographic data, and (3) the date of filing of this Authorization. See 37 CFR 1.14(h)(1).

B. Search Results from U.S. Application to EPO - Unless box B in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the EPO access to the bibliographic data and search results from the instant patent application when a European patent application claiming priority to the instant patent application is filed. See 37 CFR 1.14(h)(2).

The applicant is reminded that the EPO's Rule 141(1) EPC (European Patent Convention) requires applicants to submit a copy of search results from the instant application without delay in a European patent application that claims priority to the instant application.

2. Opt-Out of Authorizations to Permit Access by a Foreign Intellectual Property Office(s)

☐ A. Applicant **DOES NOT** authorize the USPTO to permit a participating foreign IP office access to the instant application-as-filed. If this box is checked, the USPTO will not be providing a participating foreign IP office with any documents and information identified in subsection 1A above.

☐ B. Applicant **DOES NOT** authorize the USPTO to transmit to the EPO any search results from the instant patent application. If this box is checked, the USPTO will not be providing the EPO with search results from the instant application.

NOTE: Once the application has published or is otherwise publicly available, the USPTO may provide access to the application in accordance with 37 CFR 1.14.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	NEURE-008/01US 35242/69
	Application Number	
Title of Invention	SYSTEMS AND METHODS FOR IMPROVING SLEEP WITH THERAPEUTIC NASAL TREATMENT	

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant 1 — Remove

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

Clear

● Assignee	Legal Representative under 35 U.S.C. 117	Joint Inventor
Person to whom the inventor is obligated to assign.	Person who shows sufficient proprietary interest	

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor:

If the Applicant is an Organization check here. ☒

Organization Name	Neurent Medical Limited		
Mailing Address Information For Applicant:			
Address 1	No. 1 Oran Point		
Address 2	Main Street		
City	Oranmore, Galway	**State/Province**	
Country	IE	Postal Code	
Phone Number		Fax Number	
Email Address			

Additional Applicant Data may be generated within this form by selecting the Add button. — Add

Assignee Information including Non-Applicant Assignee Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

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	Application Number	
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Assignee 1

Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication. An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.

Remove

If the Assignee or Non-Applicant Assignee is an Organization check here. ☐

Prefix	**Given Name**	Middle Name	**Family Name**	Suffix

Mailing Address Information For Assignee including Non-Applicant Assignee:

Address 1			
Address 2			
City		**State/Province**	
Country i		Postal Code	
Phone Number		Fax Number	
Email Address			

Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button. Add

Signature:

Remove

NOTE: This Application Data Sheet must be signed in accordance with 37 CFR 1.33(b). **However, if this Application Data Sheet is submitted with the INITIAL filing of the application and either box A or B is not checked in subsection 2 of the "Authorization or Opt-Out of Authorization to Permit Access" section, then this form must also be signed in accordance with 37 CFR 1.14(c).**

This Application Data Sheet **must** be signed by a patent practitioner if one or more of the applicants is a **juristic entity** (e.g., corporation or association). If the applicant is two or more joint inventors, this form must be signed by a patent practitioner, **all** joint inventors who are the applicant, or one or more joint inventor-applicants who have been given power of attorney (e.g., see USPTO Form PTO/AIA/81) on behalf of **all** joint inventor-applicants.

See 37 CFR 1.4(d) for the manner of making signatures and certifications.

Signature	/Adam M. Schoen/			Date (YYYY-MM-DD)	2021-04-08
First Name	Adam	Last Name	Schoen	Registration Number	58,576

Additional Signature may be generated within this form by selecting the Add button. Add

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	NEURE-008/01US 35242/69
	Application Number	
Title of Invention	SYSTEMS AND METHODS FOR IMPROVING SLEEP WITH THERAPEUTIC NASAL TREATMENT	

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1 The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3 A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent CooperationTreaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Aerin Exhibit 1009, Page 1958 of 2072
Aerin Medical Inc. v. Neurent Medical Ltd.
IPR2025-01124

SYSTEMS AND METHODS FOR IMPROVING SLEEP WITH THERAPEUTIC NASAL TREATMENT

Cross-reference to Related Applications

This application claims the benefit of, and priority to, U.S. Provisional Patent Application No. 63/007,584, filed April 9, 2020, the contents of which are incorporated by reference.

Field of the Invention

The invention generally relates to systems and methods for improving sleep by treating at least one of rhinitis, congestion, and/or rhinorrhea to thereby reduce or eliminate symptoms associated therewith, including, but not limited to, nasal congestion, coughing, sneezing, and nasal or throat irritation and itching.

Background

Many people suffer from breathing issues as a result of various health-related problems. For example, rhinitis is an inflammatory disease of the nose and is reported to affect up to 40% of the population. It is the fifth most common chronic disease in the United States. Allergic rhinitis accounts for up to 65% of all rhinitis patients. Allergic rhinitis is an immune response to an exposure to allergens, such as airborne plant pollens, pet dander or dust. As non-allergic rhinitis is not an immune response, its symptoms are not normally seasonal and are often more persistent.

The most common and impactful symptoms of rhinitis (both allergic and non-allergic) include a runny nose, coughing, sneezing, nasal and/or throat irritation and itching, and overall general congestion of the nasal passage. As a result, sleep problems are very common in individuals suffering from rhinitis, as such symptoms impact a person's ability to either fall asleep or remain asleep for adequate periods of time. In addition, sleep problems are linked with fatigue and daytime sleepiness, as well as decreased productivity at work or school, impaired learning and memory, depression, and a reduced quality of life.

For example, most individuals suffering from rhinitis are unable to breathe efficiently through their nose due to restricted nasal passages, and are prone to breathe through their mouth. Studies have established that nocturnal mouth breathing is a primary cause of loud snoring,

which is a precursor to sleep apnea, and sleep apnea is a precursor to heart attacks. Due to the lack of proper oxygenation, the ability to deliver fully oxygenated blood to the cells is also greatly reduced. In contrast, proper nose breathing delivers fully oxygenated blood to the body, reduces hypertension and stress, and promotes cardiovascular health. Thus, proper nose breathing is essential for one's wellbeing.

Conventional nose breathing aids may provide relief from restricted breathing, but such relief is temporary. For example, traditional aids include nasal sprays, and various types of nasal dilators, sinus cones, nasal strips, and springs to hold nasal passages open. The disadvantage of most nose mounted dilators, particularly those mounted within the nasal cavity, is that while most of them dilate the nasal passages, the product itself becomes a new obstruction, and is most noticeable during exhalation. Upon exhalation, the user will experience the deflection of hoi breath against the apparatus. Consequently, this apparatus can become bothersome, and will generally not be worn for extended periods of time, thereby forfeiting the benefits of enhanced nose breathing.

Similarly, while allergen avoidance and pharmacotherapy are relatively effective in the majority of mild cases of rhinitis, such medications need to be taken on a long-term basis, incurring costs and side effects and often have suboptimal efficacy. For example, pharmaceutical agents prescribed for rhinosinusitis have limited efficacy and undesirable side effects, such as sedation, irritation, impairment to taste, sore throat, dry nose, and other side effects.

There are two modern surgical options: the delivery of thermal energy to the inflamed soft tissue, resulting in scarring and temporary volumetric reduction of the tissue to improve nasal airflow; and microdebrider resection of the inflamed soft tissue, resulting in the removal of tissue to improve nasal airflow. Both options address congestion as opposed to rhinorrhea and have risks ranging from bleeding and scarring to the use of general anesthetic. Accordingly, current surgical options fail to adequately address the various conditions and the associated symptoms causing breathing issues.

Summary

The invention recognizes that a problem with current aids and surgical procedures is that such products and procedures are either temporary or are not accurate and cause significant

collateral damage in order to treat rhinitis and further fail to adequately treat the underlying symptoms and thus further fail to address sleeping problems.

The invention solves that problem by providing treatment devices having a combination of unique components, including an elongate body (which may be in the form of a shaft or sheath, or other elongate body), a retractable and expandable multi-segment end effector, and handle, that, as a whole, provide a high level of precise control and feedback to an operator during a procedure. In particular, the elongate body is configured to not only aid an operator in the positioning and delivery of the multi-segment end effector to a desired target site within the nasal cavity, but further includes an electrode array provided along a length thereof that is configured to deliver energy to specific target sites within the nasal passage and nasal cavity, in conjunction with neuromodulation provided by the multi-segment end effector. The multi-segment end effector is configured to complement anatomy at multiple different locations within the nasal cavity. The handle is configured with multiple ergonomic and functional features that improve device use and feedback, such as independent control of deployment of the end effector and energy delivery and a shape associated with the architecture of the end effector in the deployed configuration. The handle may also include one or more markings that provide a user with a spatial orientation of the end effector while the end effector is in a nasal cavity.

In that manner, the present invention provides devices that are capable of highly conforming to anatomical variations within a nasal passage and nasal cavity while providing unprecedented control and guidance to an operator so that an operator can perform an accurate, minimally invasive, and localized application of energy to one or more target sites within the nasal passage and nasal cavity to cause multi-point interruption of neural signal without causing collateral damage or disruption to other neural structures.

Unlike other surgical treatments for rhinitis, the devices of the invention are minimally invasive. Accordingly, a procedure can be performed in an office environment under local anesthetic. The multi-segment end-effector allows for targeting the autonomic supply to the nasal turbinates and will have a positive impact on both allergic and non-allergic rhinitis. Using this approach, it is expected that devices of the invention will be able to provide long-term symptom relief (e.g., years instead of months). Since the treatment is accurate with minimal collateral damage to the surrounding tissue, patients will begin to feel symptom relief immediately following the treatment. It is fully expected that patients will be removed from their

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pharmacotherapies following this therapy.

The systems and methods of the present invention include a handheld device comprising a retractable and expandable multi-segment end effector that, once delivered to the one more target sites within the nasal cavity, can expand to a specific shape and/or size corresponding to anatomical structures within the nasal cavity and associated with the target sites. In particular, the end effector includes at least a first flexible segment and a second flexible segment, each of which includes a specific geometry when in a deployed configuration to complement anatomy of respective locations within the nasal cavity. Once deployed, the first and second segments contact and conform to a shape of the respective locations, including conforming to and complementing shapes of one or more anatomical structures at the respective locations. In turn, the first and second segments become accurately positioned within the nasal cavity to subsequently deliver, via one or more electrodes, precise and focused application of RF thermal energy to the one or more target sites to thereby therapeutically modulate associated neural structures. More specifically, the first and second segments have shapes and sizes when in the expanded configuration that are specifically designed to place portions of the first and second segments, and thus one or more electrodes associated therewith, into contact with target sites within nasal cavity associated with postganglionic parasympathetic fibers that innervate the nasal mucosa.

The handheld device further includes an elongate body operably associated with the end effector and a handle operably associated with the elongate body. The elongate body may be in the form of a shaft or sheath (or other elongate body operably associated with or coupled to the end effector). The elongate body may include a pre-defined shape (i.e., bent or angled at a specific orientation) so as to assist the surgeon (or other medical professional) for placement of the end effector at the target sites. The elongate body further includes one or more electrodes provided on one or respective portions along a length thereof and can be used to deliver energy to tissue adjacent to, or in contact with, such portions of the elongate body. For example, in some embodiments, the elongate body may reside with a portion of the nasal cavity proximate to the inferior turbinate upon advancing and deploying the multi-segment end effector in the desired location (i.e., a target site associated with a sphenopalatine foramen within the nasal cavity of the patient). Accordingly, in addition to delivering energy from the electrodes of the multi-segment end effector, the surgeon may also activate and deliver energy from electrodes

associated with the elongate body to tissue associated with the inferior turbinate. Such energy may be delivered at a level sufficient to reduce engorgement of tissue associated with the inferior turbinate to thereby increase volumetric flow through a nasal passage of the patient and improve a patient's ability to breathe.

Accordingly, the treatment device of the present invention recognizes the desire or need to treat larger areas within the nasal cavity or passage that are located outside of a treatment zone associated with the end effector. For example, when performing surgical procedures using current rhinitis treatment devices, the surgeon must reposition an end effector when attempting to treat multiple areas within the nasal cavity, particularly those areas that are located outside of any given treatment zone. The need to reposition the end effector multiple times during a given procedure can lead to inaccuracy when delivering energy, resulting in unintended collateral damage, and further increases the time in which it takes to complete a given procedure. The treatment device of the present invention recognizes and addresses this problem by providing an elongate body including one or more electrodes thereon, in addition to a multi-segment end effector operably associated with the elongate body and including separate electrodes thereon. Accordingly, the elongate body serves to not only aid in positioning and delivering the end effector to a desired target site (to which the end effector may deliver energy), but the elongate body can also deliver energy to a target site that is separate and remote from the end effector. Such a design improves the efficiency with which a given procedure can be accomplished, particularly those procedures requiring treatment to multiple, separate areas within the nasal cavity or passage.

The handle includes an ergonomically-designed grip portion which provides ambidextrous use for both left and right handed use and conforms to hand anthropometrics to allow for at least one of an overhand grip style and an underhand grip style during use in a procedure. The handle further includes multiple user-operated mechanisms, including at least a first mechanism for deployment of the end effector from the retracted configuration to the expanded deployed configuration and a second mechanism for controlling of energy output by the end effector. The user inputs for the first and second mechanisms are positioned a sufficient distance to one another to allow for simultaneous one-handed operation of both user inputs during a procedure. Accordingly, the handle accommodates various styles of grip and provides a degree of comfort for the surgeon, thereby further improving execution of the procedure and

overall outcome. Furthermore, the handle and/or the elongate body may include markings (e.g., text, symbols, color-coding insignia, etc.) that provide a surgeon with a spatial orientation of the end effector while the end effector is in a nasal cavity. In particular, multiple markings may be provided on the handle and/or elongate body and provide a visual indication of the spatial orientation of one or more portions of the first segment and second segment of the end effector when in the deployed configurations. Thus, during initial placement of the end effector, when in a retracted configuration and enclosed within the elongate body, a surgeon can rely on the markings on the handle and/or elongate body as a visual indication of the spatial orientation of the end effector (e.g., linear, axial, and/or depth position) prior to deployment to thereby ensure that, once deployed, the end effector, including both the first and second segments, are positioned in the intended locations within the nasal cavity.

Accordingly, the handheld device of the present invention provides a surgeon with a user-friendly, non-invasive, and precise means for treating rhinorrhea and other symptoms of rhinosinusitis, notably nasal congestion, coughing, sneezing, and nasal and throat irritation, to thereby improve a patient's sleep (i.e., improve a patient's nasal breathability to increase chances of successfully falling asleep and remaining asleep for adequate periods of time). By improving one's sleep, the systems and methods of the present invention can further improve one's overall quality of life by reducing the subsequent issues commonly associated with poor sleep, such as fatigue and daytime sleepiness, as well as decreased productivity at work or school, impaired learning and memory, and depression.

The handheld device provides for the precise and focused application of energy to the intended target sites for therapeutic modulation of the intended structures, including, but not limited to, engorged sub-mucosal tissue as well as neural structures without causing collateral and unintended damage or disruption to other structures. In particular, by targeting only those specific structures associated with such conditions, notably tissue responsible for providing engorgement of certain structures (i.e., inferior and middle turbinates) and postganglionic parasympathetic nerves innervating nasal mucosa, thereby reducing engorgement of inferior turbinate tissue to thereby increase volumetric flow through a nasal passage of the patient as well as disrupting the parasympathetic nerve supply and interrupting parasympathetic tone. The device further allows for treatment of multiple areas within the nasal passage and/or nasal cavity that would normally require repositioning of an end effector due to their separated locations. In

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particular, inclusion of an elongate body with a dedicated set of electrodes, in addition to the multi-segment end effector with its own set of electrodes, allows for two separate target sites to receive treatment simultaneously, thereby reducing the need to reposition the end effector. Accordingly, such treatment is effective at treating rhinosinusitis conditions while greatly reducing the risk of causing lateral damage or disruption to other tissues, including other nerve fibers, thereby reducing the likelihood of unintended complications and side effects.

One aspect of the invention provides a method for improving a patient's sleep by treating at least one of rhinitis, congestion, and rhinorrhea within a sino-nasal cavity of the patient. The method includes delivering energy to one or more target sites within a sino-nasal cavity of the patient to disrupt multiple neural signals to, and/or result in local hypoxia of, mucus producing and/or mucosal engorgement elements, thereby reducing production of mucus and/or mucosal engorgement within a nose of the patient and reducing or eliminate one or more symptoms associated with at least one of rhinitis, congestion, and rhinorrhea to improve nasal breathability of the patient. The one or more symptoms associated with at least one of rhinitis, congestion, and rhinorrhea are selected from the group consisting of nasal congestion, coughing, sneezing, and nasal or throat irritation and itching.

In some embodiments, the step of delivering energy results in ablation of targeted tissue at one or more locations to thereby disrupt the multiple neural signals to the mucus producing and/or mucosal engorgement elements within the nose. For example, the targeted tissue may be associated with one or more target sites proximate or inferior to a sphenopalatine foramen. The energy may be delivered at a level sufficient to therapeutically modulate postganglionic parasympathetic nerves innervating nasal mucosa at foramina and or microforamina of a palatine bone of the patient. As a result, the energy delivered may cause multiple points of interruption of neural branches extending through foramina and microforamina of palatine bone.

In some embodiments, the step of delivering energy results in ablation of targeted tissue at one or more locations to thereby result in local hypoxia of the mucus producing and/or mucosal engorgement elements within the nose. For example, in some embodiments, the ablation of targeted tissue may cause thrombus formation within one or more blood vessels associated with mucus producing and/or mucosal engorgement elements within the nose. As such, the resulting local hypoxia of the mucus producing and/or mucosal engorgement elements

may result in decreased mucosal engorgement to thereby increase volumetric flow through a nasal passage of the patient.

In some embodiments, the ablation is thermal ablation. The thermal ablation may include cyro-ablation, for example. In other embodiments, the ablation may be caused by delivery of radiofrequency (RF) energy.

In some embodiments, the ablation may be caused by a treatment device comprising a handle, an elongate body extending therefrom, and a retractable and expandable end effector operably associated with the elongate body. Accordingly, during a procedure, the method may include advancing the end effector into the sino-nasal cavity under image guidance. The handle may generally control transformation of the end effector from a retracted state to an expanded state. The end effector may include a plurality of energy delivery elements provided thereon, such as electrodes, for example.

When in the expanded state, the end effector may generally position one or more of the plurality of energy delivery elements relative to the one or more target sites. In some embodiments, the end effector includes a proximal segment that is spaced apart from a separate distal segment. In some embodiments, the proximal segment may include a first set of flexible support elements arranged in a deployed configuration to fit around at least a portion of a middle turbinate at an anterior position relative to a lateral attachment and a posterior-inferior edge of the middle turbinate and position one or more energy delivery elements into contact with one or more respective tissue locations associated with the middle turbinate and the distal segment may include a second set of flexible support elements configured in a deployed configuration to position one or more energy delivery elements into contact with one or more respective tissue locations in a cavity at a posterior position relative to the lateral attachment and posterior-inferior edge of the middle turbinate.

In some embodiments, the elongate body may include a shaft to which the end effector is coupled. The shaft includes an outer sheath surrounding a hypotube or metallic member, wherein at least one of the outer sheath and hypotube and metallic member includes the one or more energy delivering elements provided thereon. Yet still, in other embodiments, the elongate body may include one or more of a plurality of support elements forming at least a portion of the end effector. The energy delivering elements of the elongate body may be configured to deliver energy at one or more target sites associated with an inferior or middle turbinate within the sino-

nasal cavity of the patient at a level sufficient to reduce engorgement of tissue associated therewith to thereby increase volumetric flow through a nasal passage of the patient.

Brief Description of the Drawings

FIGS. 1A and 1B are diagrammatic illustrations of a therapeutic neuromodulation system for treating a condition within a nasal cavity using a handheld device according to some embodiments of the present disclosure.

FIG. 2 is a diagrammatic illustration of the console coupled to the handheld neuromodulation device consistent with the present disclosure, further illustrating a multi-segment end effector of the handheld device for delivering energy, via proximal and distal segments, to tissue at the one or more target sites within the nasal cavity.

FIG. 3A is a cut-away side view illustrating the anatomy of a lateral nasal wall.

FIG. 3B is an enlarged side view of the nerves of the lateral nasal wall of FIG. 1A.

FIG. 3C is a front view of a left palatine bone illustrating geometry of microforamina in the left palatine bone.

FIG. 4 is a side view of one embodiment of a handheld device for providing therapeutic nasal neuromodulation consistent with the present disclosure.

FIG. 5A is an enlarged, perspective view of the multi-segment end effector illustrating the first (proximal) segment and second (distal) segment.

FIG. 5B is an exploded, perspective view of the multi-segment end effector.

FIG. 5C is an enlarged, top view of the multi-segment end effector.

FIG. 5D is an enlarged, side view of the multi-segment end effector.

FIG. 5E is an enlarged, front (proximal facing) view of the first (proximal) segment of the multi-segment end effector.

FIG. 5F is an enlarged, front (proximal facing) view of the second (distal) segment of the multi-segment end effector.

FIG. 6 is a perspective view, partly in section, of a portion of a support element illustrating an exposed conductive wire serving as an energy delivery element or electrode element.

FIG. 7 is a cross-sectional view of a portion of the shaft of the handheld device taken along lines 7-7 of FIG. 4.

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FIG. 7A is a side view of the shaft and multi-segment end effector extending from a distal end thereof, further illustrating a plurality of electrodes provided on separate respective portions of the shaft.

FIG. 7B is a sectional view of the shaft illustrating one embodiment in which a plurality of electrodes are embedded within the outer sheath of the shaft.

FIG. 7C is a sectional view of the shaft illustrating another embodiment in which a plurality of electrodes are provided on the hypotube and associated portions of the outer sheath are absent or removed to thereby expose the underlying electrodes on the hypotube.

FIG. 7D is a perspective view of a length of the shaft illustrating exposed portions of the outer sheath to reveal the underlying electrodes provided on the hypotube.

FIG. 7E is a sectional view of the shaft illustrating another embodiment in which a plurality of electrodes are provided on one or more support elements extending through the hypotube, portions of which form the end effector.

FIG. 7F is an enlarged, perspective view of the multi-segment end effector extending from the shaft and illustrating the plurality of electrodes provided on the support elements.

FIG. 7G is a cross-sectional view of the shaft illustrating exemplary portions of the shaft that are retractable and expandable.

FIG. 8 is a side view of the handle of the handheld device.

FIG. 9 is a side view of the handle illustrating internal components enclosed within.

FIG. 10 is a side view of the handle illustrating multiple markings on a portion of the handle for providing a user with a spatial orientation of the end effector while the end effector is in a nasal cavity.

FIG. 11 is a perspective view of the shaft illustrating multiple markings on a distal portion thereof for providing a user with a spatial orientation of the end effector while the end effector is in a nasal cavity.

FIG. 12 is a partial cut-away side views illustrating one approach for delivering a shaft and an associated end effector to respective target sites within a nasal region in accordance with embodiments of the present disclosure.

FIG. 13 is a flow diagram illustrating one embodiment of a method for treating a condition within a nasal cavity of a patient.

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FIG. 14 is a flow diagram illustrating another embodiment of a method for treating a condition within a nasal cavity of a patient.

FIG. 15 is a flow diagram illustrating another embodiment of a method for treating a condition within a nasal cavity of a patient.

FIG. 16 is a flow diagram illustrating another embodiment of a method for treating a condition within a sino-nasal cavity of a patient.

FIG. 17 is a flow diagram illustrating an embodiment of a method for improving a patient's sleep by treating at least one of rhinitis, congestion, and rhinorrhea within a sino-nasal cavity of the patient.

Detailed Description

There are various conditions related to the nasal cavity which may impact breathing and other functions of the nose. One of the more common conditions is rhinitis, which is defined as inflammation of the membranes lining the nose. The symptoms of rhinitis include nasal blockage, obstruction, congestion, nasal discharge (e.g., rhinorrhea and/or posterior nasal drip), facial pain, facial pressure, and/or reduction or complete loss of smell and/or taste. Sinusitis is another common condition, which involves an inflammation or swelling of the tissue lining the sinuses, and results in similar symptoms as rhinitis, and may further lead to infection if left untreated or if it persists for prolonged periods of time. Rhinitis and sinusitis are frequently associated with one another, as sinusitis is often preceded by rhinitis. Accordingly, the term rhinosinusitis is often used to describe both conditions.

As a result of such symptoms, many who suffer from rhinosinusitis also have sleeping difficulties (i.e., difficulty falling asleep and/or remaining asleep). Sleep is a vital component of a person's overall health and well-being. Studies have shown that sleep problems are linked with fatigue and daytime sleepiness, as well as decreased productivity at work or school, impaired learning and memory, depression, and a reduced quality of life.

Depending on the duration and type of systems, rhinosinusitis can fall within different subtypes, including allergic rhinitis, non-allergic rhinitis, chronic rhinitis, acute rhinitis, recurrent rhinitis, chronic sinusitis, acute sinusitis, recurrent sinusitis, and medical resistant rhinitis and/or sinusitis, in addition to combinations of one or more of the preceding conditions. It should be noted that an acute rhinosinusitis condition is one in which symptoms last for less than twelve

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weeks, whereas a chronic rhinosinusitis condition refers to symptoms lasting longer than twelve weeks.

A recurrent rhinosinusitis condition refers to four or more episodes of an acute rhinosinusitis condition within a twelve-month period, with resolution of symptoms between each episode. There are numerous environmental and biological causes of rhinosinusitis. Non-allergic rhinosinusitis, for example, can be caused by environmental irritants, medications, foods, hormonal changes, and/or nasal septum deviation. Triggers of allergic rhinitis can include exposure to seasonal allergens, perennial allergens that occur any time of year, and/or occupational allergens. Accordingly, rhinosinusitis affects millions of people and is a leading cause for patients to seek medical care.

The invention recognizes that a problem with current aids and surgical procedures is that such products and procedures are either temporary or are not accurate and cause significant collateral damage in order to treat rhinitis and further fail to adequately treat the underlying symptoms and thus further fail to address sleeping problems.

The invention solves that problem by providing treatment devices having a combination of unique components, including an elongate body (which may be in the form of a shaft or sheath, or other elongate body), a retractable and expandable multi-segment end effector, and handle, that, as a whole, provide a high level of precise control and feedback to an operator during a procedure. In particular, the elongate body is configured to not only aid an operator in the positioning and delivery of the multi-segment end effector to a desired target site within the nasal cavity, but further includes an electrode array provided along a length thereof that is configured to deliver energy to specific target sites within the nasal passage and nasal cavity, in conjunction with neuromodulation provided by the multi-segment end effector. The multi-segment end effector is configured to complement anatomy at multiple different locations within the nasal cavity. The handle is configured with multiple ergonomic and functional features that improve device use and feedback, such as independent control of deployment of the end effector and energy delivery and a shape associated with the architecture of the end effector in the deployed configuration. The handle may also include one or more markings that provide a user with a spatial orientation of the end effector while the end effector is in a nasal cavity.

In that manner, the present invention provides devices that are capable of highly conforming to anatomical variations within a nasal passage and nasal cavity while providing

unprecedented control and guidance to an operator so that an operator can perform an accurate, minimally invasive, and localized application of energy to one or more target sites within the nasal passage and nasal cavity to cause multi-point interruption of neural signal without causing collateral damage or disruption to other neural structures.

Unlike other surgical treatments for rhinitis, the devices of the invention are minimally invasive. Accordingly, a procedure can be performed in an office environment under local anesthetic. The multi-segment end-effector allows for targeting the autonomic supply to the nasal turbinates and will have a positive impact on both allergic and non-allergic rhinitis. Using this approach, it is expected that devices of the invention will be able to provide long-term symptom relief (e.g., years instead of months). Since the treatment is accurate with minimal collateral damage to the surrounding tissue, patients will begin to feel symptom relief immediately following the treatment. It is fully expected that patients will be removed from their pharmacotherapies following this therapy.

The treatment devices of the present invention provides a surgeon with a user-friendly, non-invasive, and precise means for treating rhinorrhea and other symptoms of rhinosinusitis, notably nasal congestion, coughing, sneezing, and nasal and throat irritation, to thereby improve a patient's sleep (i.e., improve a patient's nasal breathability to increase chances of successfully falling asleep and remaining asleep for adequate periods of time). By improving one's sleep, the systems and methods of the present invention can further improve one's overall quality of life by reducing the subsequent issues commonly associated with poor sleep, such as fatigue and daytime sleepiness, as well as decreased productivity at work or school, impaired learning and memory, and depression.

The treatment devices provide for the precise and focused application of energy to the intended target sites for therapeutic modulation of the intended structures, including, but not limited to, engorged sub-mucosal tissue as well as neural structures without causing collateral and unintended damage or disruption to other structures. In particular, by targeting only those specific structures associated with such conditions, notably tissue responsible for providing engorgement of certain structures (i.e., inferior and middle turbinates) and postganglionic parasympathetic nerves innervating nasal mucosa, thereby reducing engorgement of inferior turbinate tissue to thereby increase volumetric flow through a nasal passage of the patient as well as disrupting the parasympathetic nerve supply and interrupting parasympathetic tone. The

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device further allows for treatment of multiple areas within the nasal passage and/or nasal cavity that would normally require repositioning of an end effector due to their separated locations. In particular, inclusion of an elongate body with a dedicated set of electrodes, in addition to the multi-segment end effector with its own set of electrodes, allows for two separate target sites to receive treatment simultaneously, thereby reducing the need to reposition the end effector. Accordingly, such treatment is effective at treating rhinosinusitis conditions while greatly reducing the risk of causing lateral damage or disruption to other tissues, including other nerve fibers, thereby reducing the likelihood of unintended complications and side effects.

For example, the systems and methods of the present invention include a handheld device comprising a retractable and expandable multi-segment end effector that, once delivered to the one more target sites within the nasal cavity, can expand to a specific shape and/or size corresponding to anatomical structures within the nasal cavity and associated with the target sites. In particular, the end effector includes at least a first flexible segment and a second flexible segment, each of which includes a specific geometry when in a deployed configuration to complement anatomy of respective locations within the nasal cavity. Once deployed, the first and second segments contact and conform to a shape of the respective locations, including conforming to and complementing shapes of one or more anatomical structures at the respective locations. In turn, the first and second segments become accurately positioned within the nasal cavity to subsequently deliver, via one or more electrodes, precise and focused application of RF thermal energy to the one or more target sites to thereby therapeutically modulate associated neural structures. More specifically, the first and second segments have shapes and sizes when in the expanded configuration that are specifically designed to place portions of the first and second segments, and thus one or more electrodes associated therewith, into contact with target sites within nasal cavity associated with postganglionic parasympathetic fibers that innervate the nasal mucosa.

The handheld device further includes an elongate body operably associated with the end effector and a handle operably associated with the elongate body. The elongate body may be in the form of a shaft or sheath (or other elongate body operably associated with or coupled to the end effector). The elongate body may include a pre-defined shape (i.e., bent or angled at a specific orientation) so as to assist the surgeon (or other medical professional) for placement of the end effector at the target sites. The elongate body further includes one or more electrodes

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provided on one or respective portions along a length thereof and can be used to deliver energy to tissue adjacent to, or in contact with, such portions of the elongate body. For example, in some embodiments, the elongate body may reside with a portion of the nasal cavity proximate to the inferior turbinate upon advancing and deploying the multi-segment end effector in the desired location (i.e., a target site associated with a sphenopalatine foramen within the nasal cavity of the patient). Accordingly, in addition to delivering energy from the electrodes of the multi-segment end effector, the surgeon may also activate and deliver energy from electrodes associated with the elongate body to tissue associated with the inferior turbinate. Such energy may be delivered at a level sufficient to reduce engorgement of tissue associated with the inferior turbinate to thereby increase volumetric flow through a nasal passage of the patient and improve a patient's ability to breathe.

Accordingly, the treatment device of the present invention recognizes the desire or need to treat larger areas within the nasal cavity or passage that are located outside of a treatment zone associated with the end effector. For example, when performing surgical procedures using current rhinitis treatment devices, the surgeon must reposition an end effector when attempting to treat multiple areas within the nasal cavity, particularly those areas that are located outside of any given treatment zone. The need to reposition the end effector multiple times during a given procedure can lead to inaccuracy when delivering energy, resulting in unintended collateral damage, and further increases the time in which it takes to complete a given procedure. The treatment device of the present invention recognizes and addresses this problem by providing an elongate body including one or more electrodes thereon, in addition to a multi-segment end effector operably associated with the elongate body and including separate electrodes thereon. Accordingly, the elongate body serves to not only aid in positioning and delivering the end effector to a desired target site (to which the end effector may deliver energy), but the elongate body can also deliver energy to a target site that is separate and remote from the end effector. Such a design improves the efficiency with which a given procedure can be accomplished, particularly those procedures requiring treatment to multiple, separate areas within the nasal cavity or passage.

It should be noted that, although many of the embodiments are described with respect to devices, systems, and methods for therapeutically modulating tissue (neural and/or non-neural tissue) in the nasal region for the treatment of rhinitis, congestion, and/or rhinorrhea, other

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applications and other embodiments in addition to those described herein are within the scope of the present disclosure. For example, at least some embodiments of the present disclosure may be useful for the treatment of other indications, such as the treatment of chronic sinusitis and epistaxis. In particular, the embodiments described herein may be configured to treat allergic rhinitis, non-allergic rhinitis, chronic rhinitis, acute rhinitis, chronic sinusitis, acute sinusitis, chronic rhinosinusitis, acute rhinosinusitis, and/or medical resistant rhinitis.

It should further be noted that the devices described herein, most notably the elongate body (which may be in the form of a shaft, outer sheath, hypotube, or other elongate body that is operably associated with the end effector) may be included and incorporated in any of the treatment devices, systems, and methods illustrated and described in U.S. Publication Nos.: 2016/0331459; 2018/0133460; 2017/0231651; 2017/0252089; 2018/0177542; 2018/0177546; 2018/0185085; 2018/0228533; 2018/0317997; 2018/0344378; 2019/0076185; 2019/0175242; 2019/0201069; 2019/0231409; 2019/0282289; 2016/0354136; 2017/0231474; 2018/0078327; 2018/0103994; 2018/0125560; 2018/0153375; 2018/0317993; 2018/0344411; and 2019/0083157, as well as U.S. Patent Nos.: 8,936,594; 8,986,301; 9,072,597; 9,179,964; 9,179,967; 9,237,924; 9,415,194; 9,433,463; 9,452,010; 9,486,278; 9,526,571; 9,687,296; 9,788,886; 9,801,752; 9,888,957; 9,913,682; 9,943,361; 10,028,780; 10,265,115; 10,335,221; 10,376,300; 10,398,489; 10,456,185; 10,456,186; 10,485,603; 7,758,571; 9,687,288; 9,763,723; 9,763,743; 10,028,781; 10,159,538; 10,201,687; 10,307,200; and 10,448,985, the contents of each of which are incorporated by reference herein in their entireties.

FIGS. 1A and 1B are diagrammatic illustrations of a therapeutic neuromodulation system 100 for treating a condition within a nasal cavity using a handheld device 102 according to some embodiments of the present disclosure. The system 100 generally includes a neuromodulation device 102 and a neuromodulation console 104 to which the device 102 is to be connected. FIG. 2 is a diagrammatic illustration of the console 104 coupled to the handheld neuromodulation device 102. As illustrated, the neuromodulation device 102 is a handheld device, which includes a retractable and expandable multi-segment end effector 114, a shaft 116 operably associated with the end effector 114 and a handle 118 operably associated with the shaft 116. The end effector 114 is configured to be advanced into the nasal cavity of a patient 12 and positioned at a location associated with one or more target sites to undergo therapeutic neuromodulation treatment. It should be noted that the terms "end effector" and "therapeutic assembly" may be

used interchangeably throughout this disclosure.

For example, a surgeon or other medical professional performing a procedure can utilize the handle 118 to manipulate and advance the shaft 116 within the nasal cavity, wherein the shaft 116 is configured to locate at least a distal portion thereof intraluminally at a treatment or target site within a nasal region. The one or more target sites may generally be associated with postganglionic parasympathetic fibers that innervate the nasal mucosa. The target site may be a region, volume, or area in which the target nerves are located and may differ in size and shape depending upon the anatomy of the patient. Once positioned, the end effector 114 may be deployed and subsequently deliver energy to the one or more target sites to thereby therapeutically modulating nerves of interest, particularly nerves associated with a rhinosinusitis condition so as to treat such condition. For example, the end effector 114 may include at least one energy delivery element, such as an electrode, configured to therapeutically modulate the postganglionic parasympathetic nerves. For example, one or more electrodes may be provided by one or more portions of the end-effector 114, wherein the electrodes may be configured to apply electromagnetic neuromodulation energy (e.g., radiofrequency (RF) energy) to target sites. In other embodiments, the end effector 114 may include other energy delivery elements configured to provide therapeutic neuromodulation using various other modalities, such as cryotherapeutic cooling, ultrasound energy (e.g., high intensity focused ultrasound ("HIFU") energy), microwave energy (e.g., via a microwave antenna), direct heating, high and/or low power laser energy, mechanical vibration, and/or optical power.

In some embodiments, the end effector 114 may include one or more sensors (not shown), such as one or more temperature sensors (e.g., thermocouples, thermistors, etc.), impedance sensors, and/or other sensors. The sensors and/or the electrodes may be connected to one or more wires extending through the shaft 116 and configured to transmit signals to and from the sensors and/or convey energy to the electrodes.

As shown, the device 102 is operatively coupled to the console 104 via a wired connection, such as cable 120. It should be noted, however, that the device 102 and console 104 may be operatively coupled to one another via a wireless connection. The console 104 is configured to provide various functions for the neuromodulation device 102, which may include, but is not limited to, controlling, monitoring, supplying, and/or otherwise supporting operation of the neuromodulation device 102. For example, when the neuromodulation device 102 is

configured for electrode-based, heat-element-based, and/or transducer-based treatment, the console 104 may include an energy generator 106 configured to generate RF energy (e.g., monopolar, bipolar, or multi-polar RF energy), pulsed electrical energy, microwave energy, optical energy, ultrasound energy (e.g., intraluminally-delivered ultrasound and/or HIFU), direct heat energy, radiation (e.g., infrared, visible, and/or gamma radiation), and/or another suitable type of energy.

In some embodiments, the console 104 may include a controller 107 communicatively coupled to the neuromodulation device 102. However, in the embodiments described herein, the controller 107 may generally be carried by and provided within the handle 118 of the neuromodulation device 102. The controller 107 is configured to initiate, terminate, and/or adjust operation of one or more electrodes provided by the end effector 114 directly and/or via the console 104. For example, the controller 107 can be configured to execute an automated control algorithm and/or to receive control instructions from an operator (e.g., surgeon or other medical professional or clinician). For example, the controller 107 and/or other components of the console 104 (e.g., processors, memory, etc.) can include a computer-readable medium carrying instructions, which when executed by the controller 107, causes the device 102 to perform certain functions (e.g., apply energy in a specific manner, detect impedance, detect temperature, detect nerve locations or anatomical structures, etc.). A memory includes one or more of various hardware devices for volatile and non-volatile storage, and can include both read-only and writable memory. For example, a memory can comprise random access memory (RAM), CPU registers, read-only memory (ROM), and writable non-volatile memory, such as flash memory, hard drives, floppy disks, CDs, DVDs, magnetic storage devices, tape drives, device buffers, and so forth. A memory is not a propagating signal divorced from underlying hardware; a memory is thus non-transitory.

The console 104 may further be configured to provide feedback to an operator before, during, and/or after a treatment procedure via evaluation/feedback algorithms 110. For example, the evaluation/feedback algorithms 110 can be configured to provide information associated with the temperature of the tissue at the treatment site, the location of nerves at the treatment site, and/or the effect of the therapeutic neuromodulation on the nerves at the treatment site. In certain embodiments, the evaluation/feedback algorithm 110 can include features to confirm efficacy of the treatment and/or enhance the desired performance of the system 100. For

example, the evaluation/feedback algorithm 110, in conjunction with the controller 107, can be configured to monitor temperature at the treatment site during therapy and automatically shut off the energy delivery when the temperature reaches a predetermined maximum (e.g., when applying RF energy) or predetermined minimum (e.g., when applying cryotherapy). In other embodiments, the evaluation/feedback algorithm 110, in conjunction with the controller 107, can be configured to automatically terminate treatment after a predetermined maximum time, a predetermined maximum impedance rise of the targeted tissue (i.e., in comparison to a baseline impedance measurement), a predetermined maximum impedance of the targeted tissue), and/or other threshold values for biomarkers associated with autonomic function. This and other information associated with the operation of the system 100 can be communicated to the operator via a graphical user interface (GUI) 112 provided via a display on the console 104 and/or a separate display (not shown) communicatively coupled to the console 104, such as a tablet or monitor. The GUI 112 may generally provide operational instructions for the procedure, such as directing the operator to select which nasal cavity to treat, indicating when the device 102 is primed and ready to perform treatment, and further providing status of therapy during the procedure, including indicating when the treatment is complete.

For example, in some embodiments, the end effector 114and/or other portions of the system 100 can be configured to detect various parameters of the heterogeneous tissue at the target site to determine the anatomy at the target site (e.g., tissue types, tissue locations, vasculature, bone structures, foramen, sinuses, etc.), locate nerves and/or other structures, and allow for neural mapping. For example, the end effector 114 may be configured to detect impedance, dielectric properties, temperature, and/or other properties that indicate the presence of neural fibers in the target region. As shown in FIG. 1, the console 104 may further include a monitoring system 108 configured to receive detected electrical and/or thermal measurements of tissue at the target site taken by the end effector 114, specifically sensed by appropriate sensors (e.g., temperature sensors and/or impedance sensors), and process this information to identify the presence of nerves, the location of nerves, and/or neural activity at the target site. The nerve monitoring system 108 can be operably coupled to the electrodes and/or other features of the end effector 102 via signal wires (e.g., copper wires) that extend through the cable 120 and through the length of the shaft 116. In other embodiments, the end effector 114 can be communicatively coupled to the nerve monitoring system 108 using other suitable communication means.

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The nerve monitoring system 108 can determine neural locations and activity before therapeutic neuromodulation to determine precise treatment regions corresponding to the positions of the desired nerves, during treatment to determine the effect of the therapeutic neuromodulation, and/or after treatment to evaluate whether the therapeutic neuromodulation treated the target nerves to a desired degree. This information can be used to make various determinations related to the nerves proximate to the target site, such as whether the target site is suitable for neuromodulation. In addition, the nerve monitoring system 108 can also compare the detected neural locations and/or activity before and after therapeutic neuromodulation, and compare the change in neural activity to a predetermined threshold to assess whether the application of therapeutic neuromodulation was effective across the treatment site. For example, the nerve monitoring system 108 can further determine electroneurogram (ENG) signals based on recordings of electrical activity of neurons taken by the end effector 114 before and after therapeutic neuromodulation. Statistically meaningful (e.g., measurable or noticeable) decreases in the ENG signal(s) taken after neuromodulation can serve as an indicator that the nerves were sufficiently ablated. Additional features and functions of the nerve monitoring system 108, as well as other functions of the various components of the console 104, including the evaluation/feedback algorithms 110 for providing real-time feedback capabilities for ensuring optimal therapy for a given treatment is administered, are described in at least U.S. Publication No. 2016/0331459 and U.S. Publication No. 2018/0133460, the contents of each of which are incorporated by reference herein in their entireties.

As will be described in greater detail herein, the neuromodulation device 102 provides access to target sites deep within the nasal region, such as at the immediate entrance of parasympathetic fibers into the nasal cavity to therapeutically modulate autonomic activity within the nasal cavity. In certain embodiments, for example, the neuromodulation device 102 can position the end effector 114 into contact with target sites within nasal cavity associated with postganglionic parasympathetic fibers that innervate the nasal mucosa.

FIG. 3A is a cut-away side view illustrating the anatomy of a lateral nasal wall and FIG. 3B is an enlarged side view of the nerves of the lateral nasal wall of FIG. 1A. The sphenopalatine foramen (SPF) is an opening or conduit defined by the palatine bone and the sphenoid bone through which the sphenopalatine vessels and the posterior superior nasal nerves travel into the nasal cavity. More specifically, the orbital and sphenoidal processes of the

perpendicular plate of the palatine bone define the sphenopalatine notch, which is converted into the SPF by the articulation with the surface of the body of the sphenoid bone.

The location of the SPF is highly variable within the posterior region of the lateral nasal cavity, which makes it difficult to visually locate the SPF. Typically, the SPF is located in the middle meatus (MM). However, anatomical variations also result in the SPF being located in the superior meatus (SM) or at the transition of the superior and middle meatuses. In certain individuals, for example, the inferior border of the SPF has been measured at about 19 mm above the horizontal plate of the palatine bone (i.e., the nasal sill), which is about 13 mm above the horizontal lamina of the inferior turbinate (IT) and the average distance from the nasal sill to the SPF is about 64.4 mm, resulting in an angle of approach from the nasal sill to the SPA of about 11.4°. However, studies to measure the precise location of the SPF are of limited practical application due to the wide variation of its location.

The anatomical variations of the SPF are expected to correspond to alterations of the autonomic and vascular pathways traversing into the nasal cavity. In general, it is thought that the posterior nasal nerves (also referred to as lateral posterior superior nasal nerves) branch from the pterygopalatine ganglion (PPG), which is also referred to as the sphenopalatine ganglion, through the SPF to enter the lateral nasal wall of the nasal cavity, and the sphenopalatine artery passes from the pterygopalatine fossa through the SPF on the lateral nasal wall. The sphenopalatine artery branches into two main portions: the posterior lateral nasal branch and the posterior septal branch. The main branch of the posterior lateral nasal artery travels inferiorly into the inferior turbinate IT (e.g., between about 1.0 mm and 1.5 mm from the posterior tip of the inferior turbinate IT), while another branch enters the middle turbinate MT and branches anteriorly and posteriorly.

Beyond the SPF, studies have shown that over 30% of human patients have one or more accessory foramen that also carries arteries and nerves into the nasal cavity. The accessory foramen are typically smaller than the SPF and positioned inferior to the SPF. For example, there can be one, two, three or more branches of the posterior nasal artery and posterior nasal nerves that extend through corresponding accessory foramen. The variability in location, size, and quantity associated with the accessory foramen and the associated branching arteries and nerves that travel through the accessory foramen gives rise to a great deal of uncertainty regarding the positions of the vasculature and nerves of the sphenopalatine region. Furthermore,

the natural anatomy extending from the SPF often includes deep inferior and/or superior grooves that carry neural and arterial pathways, which make it difficult to locate arterial and neural branches. For example the grooves can extend more than 5 mm long, more than 2 mm wide, and more than 1 mm deep, thereby creating a path significant enough to carry both arteries and nerves. The variations caused by the grooves and the accessory foramen in the sphenopalatine region make locating and accessing the arteries and nerves (positioned posterior to the arteries) extremely difficult for surgeons.

Recent microanatomic dissection of the pterygopalatine fossa (PPF) have further evidenced the highly variable anatomy of the region surrounding the SPF, showing that a multiplicity of efferent rami that project from the pterygopalatine ganglion (PPG) to innervate the orbit and nasal mucosa via numerous groups of small nerve fascicles, rather than an individual postganglionic autonomic nerves (e.g., the posterior nasal nerve). Studies have shown that at least 87% of humans have microforamina and micro rami in the palatine bone.

FIG. 3C, for example, is a front view of a left palatine bone illustrating geometry of microforamina and micro rami in a left palatine bone. In FIG. 3C, the solid regions represent nerves traversing directly through the palatine bone, and the open circles represent nerves that were associated with distinct microforamina. As such, FIG. 3C illustrates that a medial portion of the palatine bone can include at least 25 accessory posterolateral nerves.

The respiratory portion of the nasal cavity mucosa is composed of a type of ciliated pseudostratified columnar epithelium with a basement membrane. Nasal secretions (e.g., mucus) are secreted by goblet cells, submucosal glands, and transudate from plasma. Nasal seromucous glands and blood vessels are highly regulated by parasympathetic innervation deriving from the vidian and other nerves. Parasympathetic (cholinergic) stimulation through acetylcholine and vasoactive intestinal peptide generally results in mucus production. Accordingly, the parasympathetic innervation of the mucosa is primarily responsible submucosal gland activation/hyper activation, venous engorgement (e.g., congestion), and increased blood flow to the blood vessels lining the nose. Accordingly, severing or modulating the parasympathetic pathways that innervate the mucosa are expected to reduce or eliminate the hyper activation of the submucosal glands and engorgement of vessels that cause symptoms associated with rhinosinusitis and other indications.

As previously described herein, postganglionic parasympathetic fibers that innervate the nasal mucosa (i.e., posterior superior nasal nerves) were thought to travel exclusively through the SPF as a sphenopalatine neurovascular bundle. The posterior nasal nerves are branches of the maxillary nerve that innervate the nasal cavity via a number of smaller medial and lateral branches extending through the mucosa of the superior and middle turbinates ST, MT (i.e., nasal conchae) and to the nasal septum. The nasopalatine nerve is generally the largest of the medial posterior superior nasal nerves, and it passes anteroinferiorly in a groove on the vomer to the floor of the nasal cavity. From here, the nasopalatine nerve passes through the incisive fossa of the hard palate and communicates with the greater palatine nerve to supply the mucosa of the hard palate. The posterior superior nasal nerves pass through the pterygopalatine ganglion PPG without synapsing and onto the maxillary nerve via its ganglionic branches.

Based on the understanding that the posterior nasal nerves exclusively traverse the SPF to innervate the nasal mucosa, surgeries have been performed to selectively sever the posterior nasal nerve as it exits the SPF. However, as discussed above, the sinonasal parasympathetic pathway actually comprises individual rami project from the pterygopalatine ganglion (PPG) to innervate the nasal mucosa via multiple small nerve fascicles (i.e., accessory posterolateral nerves), not a single branch extending through the SPF. These rami are transmitted through multiple fissures, accessory foramina, and microforamina throughout the palatine bone and may demonstrate anastomotic loops with both the SPF and other accessory nerves. Thus, if only the parasympathetic nerves traversing the SPF were severed, almost all patients (e.g., 90% of patients or more) would retain intact accessory secretomotor fibers to the posterolateral mucosa, which would result in the persistence of symptoms the neurectomy was meant to alieve.

Accordingly, embodiments of the present disclosure are configured to therapeutically modulate nerves at precise and focused treatment sites corresponding to the sites of rami extending through fissures, accessory foramina, and microforamina throughout the palatine bone (e.g., target region T shown in FIG. 3B). In certain embodiments, the targeted nerves are postganglionic parasympathetic nerves that go on to innervate the nasal mucosa. This selective neural treatment is also expected to decrease the rate of postoperative nasal crusting and dryness because it allows a clinician to titrate the degree of anterior denervation through judicious sparing of the rami orbitonasal. Furthermore, embodiments of the present disclosure are also expected to maintain at least some sympathetic tone by preserving a portion of the sympathetic

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contributions from the deep petrosal nerve and internal maxillary periarterial plexus, leading to improved outcomes with respect to nasal obstruction. In addition, embodiments of the present disclosure are configured to target a multitude of parasympathetic neural entry locations (e.g., accessory foramen, fissures, and microforamina) to the nasal region to provide for a complete resection of all anastomotic loops, thereby reducing the rate of long-term re-innervation.

FIG. 4 is a side view of one embodiment of a handheld device 102 for providing therapeutic nasal neuromodulation consistent with the present disclosure. As illustrated, the device 102 includes a multi-segment end effector 114 transformable between a retracted configuration and an expanded deployed configuration, a shaft 116 operably associated with the end effector 114, and a handle 118 operably associated with the shaft 116. The multi-segment end effector 114 includes at least a first segment 122 and a second segment 124 spaced apart from one another. The first segment 122 is generally positioned closer to a distal end of the shaft 116, and is thus sometimes referred to herein as the proximal segment 122, while the second segment 124 is generally positioned further from the distal end of the shaft 116 and is thus sometimes referred to herein as the distal segment 124. Each of the first and second segments 122 and 124 is transformable between a retracted configuration, which includes a low-profile delivery state to facilitate intraluminal delivery of the end effector 114 to a treatment site within the nasal region, and a deployed configuration, which includes an expanded state, as shown in FIG. 4 and further illustrated in FIGS. 5A-5F. The handle 118 includes at least a first mechanism 126 for deployment of the multi-segment end effector 114, notably the first and second segments 122, 124, from the retracted configuration to the deployed configuration and a second mechanism 128, separate from the first mechanism 124, for control of energy output by either of the first and second segments 122, 124 of the end effector 114, specifically electrodes or other energy elements provided by first and/or second segments 122, 124. The handheld device 102 may further include an auxiliary line 121, which may provide a fluid connection between a fluid source, for example, and the shaft 116 such that fluid may be provided to a target site via the distal end of the shaft 116. In some embodiments, the auxiliary line 121 may provide a connection between a vacuum source and the shaft 116, such that the device 102 may include suction capabilities (via the distal end of the shaft 116).

FIGS. 5A, 5B, 5C, 5D, 5E, and 5F are enlarged views of the multi-segment end effector 114, illustrating various views of the first and second segments 122, 124 in greater detail. FIG.

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5A is an enlarged, perspective view of the multi-segment end effector 114. FIG. 5B is an exploded, perspective view of the multi-segment end effector 114. FIGS. 5C and 5D are enlarged, top and side views, respectively, of the multi-segment end effector 114. FIG. 5E is an enlarged, front (proximal facing) view of the first segment 122 of the multi-segment end effector 114. FIG. 5F is an enlarged, front (proximal facing) view of the second segment 124 of the multi-segment end effector 114.

As illustrated, the first segment 122 includes at least a first set of flexible support elements, generally in the form of wires, arranged in a first configuration, and the second segment 124 includes a second set of flexible support elements, also in the form of wires, arranged in a second configuration. The first and second sets of flexible support elements include composite wires having conductive and elastic properties. For example, in some embodiments, the composite wires include a shape memory material, such as nitinol. The flexible support elements may further include a highly lubricious coating, which may allow for desirable electrical insulation properties as well as desirable low friction surface finish. Each of the first and second segments 122, 124 is transformable between a retracted configuration and an expanded deployed configuration such that the first and second sets of flexible support elements are configured to position one or more electrodes provided on the respective segments (see electrodes 136 in FIGS. 5E and 5F) into contact with one or more target sites when in the deployed configuration.

As shown, when in the expanded deployed configuration, the first set of support elements of the first segment 122 includes at least a first pair of struts 130a, 130b, each comprising a loop (or leaflet) shape and extending in an upward direction and a second pair of struts 132a, 132b, each comprising a loop (or leaflet) shape and extending in a downward direction, generally in an opposite direction relative to at least the first pair of struts 130a, 130b. It should be noted that the terms upward and downward are used to describe the orientation of the first and second segments 122, 124 relative to one another. More specifically, the first pair of struts 130a, 130b generally extend in an outward inclination in a first direction relative to a longitudinal axis of the multi-segment end effector 114 and are spaced apart from one another. Similarly, the second pair of struts 132a, 132b extend in an outward inclination in a second direction substantially opposite the first direction relative to the longitudinal axis of the multi-segment end effector and spaced apart from one another.

The second set of support elements of the second segment 124, when in the expanded deployed configuration, includes a second set of struts 134(1), 134(2), 134(n) (approximately six struts), each comprising a loop shape extending outward to form an open-ended circumferential shape. As shown, the open-ended circumferential shape generally resembles a blooming flower, wherein each looped strut 134 may generally resemble a flower petal. It should be noted that the second set of struts 134 may include any number of individual struts and is not limited to six, as illustrated. For example, in some embodiments, the second segment 124 may include two, three, four, five, six, seven, eight, nine, ten, or more struts 134.

The first and second segments 122, 124, specifically struts 130, 132, and 134 include one or more energy delivery elements, such as a plurality of electrodes 136. It should be noted that any individual strut may include any number of electrodes 136 and is not limited to one electrode, as shown. In the expanded state, the struts 130, 132, and 134 can position any number of electrodes 136 against tissue at a target site within the nasal region (e.g., proximate to the palatine bone inferior to the SPF). The electrodes 136 can apply bipolar or multi-polar radiofrequency (RF) energy to the target site to therapeutically modulate postganglionic parasympathetic nerves that innervate the nasal mucosa proximate to the target site. In various embodiments, the electrodes 136 can be configured to apply pulsed RF energy with a desired duty cycle (e.g., 1 second on/0.5 seconds off) to regulate the temperature increase in the target tissue.

The first and second segments 122, 124 and the associated struts 130, 132, and 134 can have sufficient rigidity to support the electrodes 136 and position or press the electrodes 136 against tissue at the target site. In addition, each of the expanded first and second segments 122, 124 can press against surrounding anatomical structures proximate to the target site (e.g., the turbinates, the palatine bone, etc.) and the individual struts 130, 132, 134 can at least partially conform to the shape of the adjacent anatomical structures to anchor the end effector 114 In addition, the expansion and conformability of the struts 130, 132, 134 can facilitate placing the electrodes 136 in contact with the surrounding tissue at the target site. The electrodes 136 can be made from platinum, iridium, gold, silver, stainless steel, platinum-iridium, cobalt chromium, iridium oxide, polyethylenedioxythiophene (PEDOT), titanium, titanium nitride, carbon, carbon nanotubes, platinum grey, Drawn Filled Tubing (DFT) with a silver core, and/or other suitable materials for delivery RF energy to target tissue. In some embodiments, such as illustrated in

FIG. 6, a strut may include an outer jacket surrounding a conductive wire, wherein portions of the outer jacket are selectively absent along a length of the strut, thereby exposing the underlying conductive wire so as to act as an energy delivering element (i.e., an electrode) and/or sensing element, as described in greater detail herein.

In certain embodiments, each electrode 136 can be operated independently of the other electrodes 136. For example, each electrode can be individually activated and the polarity and amplitude of each electrode can be selected by an operator or a control algorithm (e.g., executed by the controller 107 previously described herein. The selective independent control of the electrodes 136 allows the end effector 114 to deliver RF energy to highly customized regions. For example, a select portion of the electrodes 136 can be activated to target neural fibers in a specific region while the other electrodes 136 remain inactive. In certain embodiments, for example, electrodes 136 may be activated across the portion of the second segment 124 that is adjacent to tissue at the target site, and the electrodes 136 that are not proximate to the target tissue can remain inactive to avoid applying energy to non-target tissue. Such configurations facilitate selective therapeutic modulation of nerves on the lateral nasal wall within one nostril without applying energy to structures in other portions of the nasal cavity.

The electrodes 136 are electrically coupled to an RF generator (e.g., the generator 106 of FIG. 1) via wires (not shown) that extend from the electrodes 136, through the shaft 116, and to the RF generator. When each of the electrodes 136 is independently controlled, each electrode 136 couples to a corresponding wire that extends through the shaft 116. In other embodiments, multiple electrodes 136 can be controlled together and, therefore, multiple electrodes 136 can be electrically coupled to the same wire extending through the shaft 116. As previously described, the RF generator and/or components operably coupled (e.g., a control module) thereto can include custom algorithms to control the activation of the electrodes 136. For example, the RF generator can deliver RF power at about 460-480 kHz (+ or - 5 kHz) to the electrodes 136, and do so while activating the electrodes 136 in a predetermined pattern selected based on the position of the end effector 114 relative to the treatment site and/or the identified locations of the target nerves. The RF generator is able to provide bipolar low power (10 watts with maximum setting of 50 watts) RF energy delivery, and further provide multiplexing capabilities (across a maximum of 30 channels).

Once deployed, the first and second segments 122, 124 contact and conform to a shape of

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the respective locations, including conforming to and complementing shapes of one or more anatomical structures at the respective locations. In turn, the first and second segments 122, 124 become accurately positioned within the nasal cavity to subsequently deliver, via one or more electrodes 136, precise and focused application of RF thermal energy to the one or more target sites to thereby therapeutically modulate associated neural structures. More specifically, the first and second segments 122, 124 have shapes and sizes when in the expanded configuration that are specifically designed to place portions of the first and second segments 122, 124, and thus one or more electrodes associated therewith 136, into contact with target sites within nasal cavity associated with postganglionic parasympathetic fibers that innervate the nasal mucosa.

For example, the first set of flexible support elements of the first segment 122 conforms to and complements a shape of a first anatomical structure at the first location when the first segment 122 is in the deployed configuration and the second set of flexible support elements of the second segment 124 conforms to and complements a shape of a second anatomical structure at the second location when the second segment is in the deployed configuration. The first and second anatomical structures may include, but are not limited to, inferior turbinate, middle turbinate, superior turbinate, inferior meatus, middle meatus, superior meatus, pterygopalatine region, pterygopalatine fossa, sphenopalatine foramen, accessory sphenopalatine foramen(ae), and sphenopalatine micro-foramen(ae).

In some embodiments, the first segment 122 of the multi-segment end effector 114 is configured in a deployed configuration to fit around at least a portion of a middle turbinate at an anterior position relative to the middle turbinate and the second segment 124 of the multi-segment end effector is configured in a deployed configuration to contact a plurality of tissue locations in a cavity at a posterior position relative to the middle turbinate.

For example, the first set of flexible support elements of the first segment (i.e., struts 130 and 132) conforms to and complements a shape of a lateral attachment and posterior-inferior edge of the middle turbinate when the first segment 122 is in the deployed configuration and the second set of flexible support elements (i.e., struts 134) of the second segment 124 contact a plurality of tissue locations in a cavity at a posterior position relative to the lateral attachment and posterior-inferior edge of middle turbinate when the second segment 124 is in the deployed configuration. Accordingly, when in the deployed configuration, the first and second segments 122, 124 are configured to position one or more associated electrodes 136 at one or more target

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sites relative to either of the middle turbinate and the plurality of tissue locations in the cavity behind the middle turbinate. In turn, electrodes 136 are configured to deliver RF energy at a level sufficient to therapeutically modulate postganglionic parasympathetic nerves innervating nasal mucosa at an innervation pathway within the nasal cavity of the patient.

As illustrated in FIG. 5E, the first segment 122 comprises a bilateral geometry. In particular, the first segment 122 includes two identical sides, including a first side formed of struts 130a, 132a and a second side formed of struts 130b, 132b. This bilateral geometry allows at least one of the two sides to conform to and accommodate an anatomical structure within the nasal cavity when the first segment 122 is in an expanded state. For example, when in the expanded state, the plurality of struts 130a, 132a contact multiple locations along multiple portions of the anatomical structure and electrodes provided by the struts are configured to emit energy at a level sufficient to create multiple micro-lesions in tissue of the anatomical structure that interrupt neural signals to mucus producing and/or mucosal engorgement elements. In particular, struts 130a, 132a conform to and complement a shape of a lateral attachment and posterior-inferior edge of the middle turbinate when the first segment 122 is in the deployed configuration, thereby allowing for both sides of the anatomical structure to receive energy from the electrodes. By having this independence between first and second side (i.e., right and left side) configurations, the first segment 122 is a true bilateral device. By providing a bilateral geometry, the multi-segment end effector 114 does not require a repeat use configuration to treat the other side of the anatomical structure, as both sides of the structure are accounted at the same time due to the bilateral geometry. The resultant micro-lesion pattern can be repeatable and is predictable in both macro element (depth, volume, shape parameter, surface area) and can be controlled to establish low to high effects of each, as well as micro elements (the thresholding of effects within the range of the macro envelope can be controlled), as well be described in greater detail herein. The systems of the present invention are further able to establish gradients within allowing for control over neural effects without having widespread effect to other cellular bodies, as will be described in greater detail herein.

FIG. 7 is a cross-sectional view of a portion of the shaft 116 of the handheld device taken along lines 7-7 of FIG. 4. As illustrated, the shaft 116 may be constructed from multiple components so as to have the ability to constrain the end effector 114 in the retracted configuration (i.e., the low-profile delivery state) when the end effector 114 is retracted within

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the shaft 116, and to further provide an atraumatic, low profile and durable means to deliver the end effector 114 to the target site. The shaft 116 includes coaxial tubes which travel from the handle 118 to a distal end of the shaft 116. The shaft 116 assembly is low profile to ensure trans-nasal delivery of therapy. The shaft 116 includes an outer sheath 138, surrounding a hypotube 140, which is further assembled over electrode wires 129 which surround an inner lumen 142. The outer sheath 138 serves as the interface between the anatomy and the device 102. The outer sheath 138 may generally include a low friction PTFE liner to minimize friction between the outer sheath 138 and the hypotube 140 during deployment and retraction. In particular, the outer sheath 138 may generally include an encapsulated braid along a length of the shaft 116 to provide flexibility while retaining kink resistance and further retaining column and/or tensile strength. For example, the outer sheath 138 may include a soft Pebax material, which is atraumatic and enables smooth delivery through the nasal passage. The outer sheath 138 may further include orientation/landmark markings on an exterior surface thereof, generally at the distal end, wherein the markings may provide a visual indication to an operator of the architecture and/or spatial orientation of first and/or second segments 122, 124 of the end effector 114 to assist in positioning and deployment of the end effector 114.

The hypotube 140 is assembled over the electrode wires starting within the handle 118 and travelling to the proximal end of the end effector 114. The hypotube 140 generally acts to protect the wires during delivery and is malleable to enable flexibility without kinking to thereby improve trackability. The hypotube 140 provides stiffness and enables torqueability of the device 102 to ensure accurate placement of the end effector 114. The hypotube 140 also provides a low friction exterior surface which enables low forces when the outer sheath 138 moves relative to the hypotube 140 during deployment and retraction or constraint. The shaft 116 may be pre-shaped in such a manner so as to complement the nasal cavity. For example, the hypotube 140 may be annealed to create a bent shaft 116 with a pre-set curve. The hypotube 140 may include a stainless-steel tubing, for example, which interfaces with a liner in the outer sheath 138 for low friction movement.

The inner lumen 142 may generally provide a channel for fluid extraction during a treatment procedure. For example, the inner lumen 142 extends from the distal end of the shaft 116 through the hypotube 140 and to atmosphere via a fluid line (line 121 of FIG. 4). The inner

lumen 142 materials are chosen to resist forces of external components acting thereon during a procedure.

FIG. 7A is a side view of one embodiment of an elongate body and a multi-segment end effector extending from a distal end thereof, further illustrating a plurality of electrodes provided on separate respective portions of the elongate body. In the illustrated example, the elongate body may generally be in the form of the shaft 116, including one or more specific components of the shaft 116, as previously described herein. For example, the elongate body in the present example may include the outer sheath 138, such that one or more electrodes 137 are provided and positioned on separate respective portions of the outer sheath 138. FIG. 7B is a sectional view of the shaft 116 illustrating one embodiment in which a plurality of electrodes are embedded within the outer sheath 138. As further illustrated in FIG. 7B, the electrodes 137 may be provided along an entirety of the circumference of the outer sheath 138 (i.e., along substantially all sides of the outer sheath 138).

FIG. 7C is a sectional view of the shaft 116 illustrating another embodiment in which a plurality of electrodes 137 are provided on the hypotube 140 and associated portions of the outer sheath 138 are absent or removed to thereby expose the underlying electrodes 137 on the hypotube 140. FIG. 7D is a perspective view of a length of the shaft 116 illustrating exposed portions of the outer sheath 138 to reveal the underlying electrodes 137 provided on the hypotube 140. More specifically, portions of the outer sheath 138 may be selectively absent along a length thereof, thereby exposing any underlying electrodes 137 provided on the enclosed portion of the hypotube 140. Accordingly, in such an embodiment, the elongate body is in the form of the hypotube 140.

FIG. 7E is a sectional view of the shaft 116 illustrating another embodiment in which a plurality of electrodes 137 are provided on one or more support elements 129 extending through the hypotube 140, portions of which form the end effector 114. FIG. 7F is an enlarged, perspective view of the multi-segment end effector 114 extending from the shaft 116, specifically the hypotube 140 and illustrating the plurality of electrodes 137 provided on the support elements 129. For example, during deployment of the end effector 114 from the retracted to expanded configurations, proximal portions of the support elements 129 that form the proximal and distal segments 122 and 124 may be further exposed to thereby further expose

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the electrodes 137 provided thereon. Accordingly, in such an embodiment, the elongate body is in the form of the assembly of support elements 129.

In some embodiments, respective portions of the elongate body may be transformable between a retracted configuration and an expanded configuration. For example, FIG. 7G is a cross-sectional view of the shaft 116, specifically the outer sheath 138, illustrating exemplary portions of the sheath 138 that may be retractable and expandable. When in the expanded configuration, each separate respective portion of the outer sheath 138 may be configured to position a separate associated one of the electrodes 137 into contact with a target tissue.

Similar to electrodes 136, the electrodes 137 may be configured to apply electromagnetic neuromodulation energy (e.g., radiofrequency (RF) energy) to target sites. In other embodiments, the electrodes 137 may be configured to provide therapeutic neuromodulation using various other modalities, such as cryotherapeutic cooling, ultrasound energy (e.g., high intensity focused ultrasound ("HIFU") energy), microwave energy (e.g., via a microwave antenna), direct heating, high and/or low power laser energy, mechanical vibration, and/or optical power. Yet still, in other embodiments, the electrodes can apply bipolar or multi-polar radiofrequency (RF) energy to a target site to therapeutically modulate tissue at the target site, which may include ablation of the tissue. For example, in various embodiments, the electrodes 136 can be configured to apply pulsed RF energy with a desired duty cycle (e.g., 1 second on/0.5 seconds off) to regulate the temperature increase in the target tissue.

In certain embodiments, each electrode 137 can be operated independently of the other electrodes 137. For example, each electrode can be individually activated and the polarity and amplitude of each electrode can be selected by an operator or a control algorithm (e.g., executed by the controller 107 previously described herein. The selective independent control of the electrodes 137 allows respective portions of the shaft to deliver RF energy to highly customized regions. For example, a select portion of the electrodes 137 can be activated to target tissue in a specific portion of the inferior turbinate while the other electrodes 137 remain inactive.

The electrodes 137 are electrically coupled to an RF generator (e.g., the generator 106 of FIG. 1) via wires (not shown) that extend from the electrodes 137, through the shaft 116, and to the RF generator. When each of the electrodes 137 is independently controlled, each electrode 137 couples to a corresponding wire that extends through the shaft 116. In other embodiments, multiple electrodes 137 can be controlled together and, therefore, multiple electrodes 137 can be

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electrically coupled to the same wire extending through the shaft 116. As previously described, the RF generator and/or components operably coupled (e.g., a control module) thereto can include custom algorithms to control the activation of the electrodes 137. For example, the RF generator can deliver RF power at about 460-480 kHz (+ or - 5 kHz) to the electrodes 137, and do so while activating the electrodes 137 in a predetermined pattern selected based on the position of the shaft 116 relative to the treatment site and/or the identified locations of the target tissue. The RF generator is able to provide bipolar low power (10 watts with maximum setting of 50 watts) RF energy delivery, and further provide multiplexing capabilities (across a maximum of 30 channels).

The electrodes 137 may be used to deliver energy to tissue adjacent to, or in contact with, such the respective portions of the shaft 116. For example, in some embodiments, the shaft 116 may generally reside with a portion of the nasal cavity proximate to the inferior turbinate upon advancing and deploying the multi-segment end effector 114 in the desired location (i.e., a target site associated with a sphenopalatine foramen within the nasal cavity of the patient). Accordingly, in addition to delivering energy from the electrodes 136 of the multi-segment end effector 114, the surgeon may also activate and deliver energy from electrodes 137 associated with a given component of the shaft 116 (i.e., outer sheath 138, hypotube 140, or assembly of support elements 129) to tissue associated with the inferior turbinate. Such energy may be delivered at a level sufficient to reduce engorgement of tissue associated with the inferior turbinate to thereby increase volumetric flow through the nasal passage of the patient and improve a patient's ability to breathe. For example, the energy may be delivered at a level sufficient to disrupt multiple neural signals to, or result in local hypoxia of, mucus producing and/or mucosal engorgement elements associated with the inferior turbinate. For example, delivery of energy may result in ablation of targeted tissue of the inferior turbinate. The ablation may be thermal ablation. The ablation may be caused by delivery of radiofrequency (RF) energy, for example.

Accordingly, in a given procedure, the surgeon may utilize the multi-segment end effector 114 to deliver energy (via electrodes 136) at a level sufficient to therapeutically modulate postganglionic parasympathetic nerves innervating nasal mucosa at microforamina of a palatine bone of the patient and further utilize a component of the shaft 116 or other elongate body operably associated with the end effector 114 (i.e., outer sheath 138, hypotube 140, or

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assembly of support elements 129) to deliver energy (via electrodes 137) at a level sufficient to reduce engorgement of tissue associated with the inferior turbinate to thereby increase volumetric flow through the nasal passage of the patient. Such a combination of energy delivery to two specific targeted sites improves the manner in which at least one of rhinitis, congestion, and rhinorrhea are treated, thereby increasing the potential for reducing or completely eliminating symptoms associated therewith, including, but not limited to, coughing, sneezing, nasal or throat irritation and itching, and difficulty sleeping.

FIG. 8 is a side view of the handle 118. FIG. 9 is a side view of the handle 118 illustrating internal components enclosed within. The handle 118 generally includes an ergonomically-designed grip portion which provides ambidextrous use for both left and right handed use and conforms to hand anthropometrics to allow for at least one of an overhand grip style and an underhand grip style during use in a procedure. For example, the handle 118 may include specific contours, including recesses 144, 146, and 148 which are designed to naturally receive one or more of an operator's fingers in either of an overhand grip or underhand grip style and provide a comfortable feel for the operator. For example, in an underhand grip, recess 144 may naturally receive an operator's index finger, recess 146 may naturally receive an operator's middle finger, and recess 148 may naturally receive an operator's ring and little (pinkie or pinky) fingers which wrap around the proximal protrusion 150 and the operator's thumb naturally rests on a top portion of the handle 118 in a location adjacent to the first mechanism 126. In an overhand grip, the operator's index finger may naturally rest on the top portion of the handle 118, adjacent to the first mechanism 126, while recess 144 may naturally receive the operator's middle finger, recess 146 may naturally receive a portion of the operator's middle and/or ring fingers, and recess 148 may naturally receive and rest within the space (sometimes referred to as the purlicue) between the operator's thumb and index finger.

As previously described, the handle includes multiple user-operated mechanisms, including at least a first mechanism 126 for deployment of the end effector 114 from the retracted configuration to the expanded deployed configuration and a second mechanism 128 for controlling of energy output by the end effector, notably energy delivery from one or more electrodes 136. As shown, the user inputs for the first and second mechanisms 126, 128 are positioned a sufficient distance to one another to allow for simultaneous one-handed operation of both user inputs during a procedure. For example, user input for the first mechanism 126 is

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positioned on a top portion of the handle 118 adjacent the grip portion and user input for the second mechanism 128 is positioned on side portions of the handle 118 adjacent the grip portion. As such, in an underhand grip style, the operator's thumb rests on the top portion of the handle adjacent to the first mechanism 126 and at least their middle finger is positioned adjacent to the second mechanism 128, each of the first and second mechanisms 126, 128 accessible and able to be actuated. In an overhand grip system, the operator's index finger rests on the top portion of the handle adjacent to the first mechanism 126 and at least their thumb is positioned adjacent to the second mechanism 128, each of the first and second mechanisms 126, 128 accessible and able to be actuated. Accordingly, the handle accommodates various styles of grip and provides a degree of comfort for the surgeon, thereby further improving execution of the procedure and overall outcome.

Referring to FIG. 9, the various components provided within the handle 118 are illustrated. As shown, the first mechanism 126 may generally include a rack and pinion assembly providing movement of the end effector 114 between the retracted and deployed configurations in response to input from a user-operated controller. The rack and pinion assembly generally includes a set of gears 152 for receiving input from the user-operated controller and converting the input to linear motion of a rack member 154 operably associated with at least one of the shaft 116 and the end effector 114. The rack and pinion assembly comprises a gearing ratio sufficient to balance a stroke length and retraction and deployment forces, thereby improving control over the deployment of the end effector. As shown, the rack member 154 may be coupled to a portion of the shaft 116, for example, such that movement of the rack member 154 in a direction towards a proximal end of the handle 118 results in corresponding movement of the shaft 116 while the end effector 114 remains stationary, thereby exposing the end effector 114 and allowing the end effector 114 to transition from the constrained, retracted configuration to the expanded, deployed configuration. Similarly, upon movement of the rack member 154 in a direction towards a distal end of the handle 118 results in corresponding movement of the shaft 116 while the end effector 114 remains stationary, thereby enclosing the end effector 114 within the shaft 116. It should be noted that, in other embodiments, the rack member 154 may be directly coupled to a portion of the end effector 114 such that movement of the rack member 154 results in corresponding movement of the end

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effector 114 while the shaft 116 remains stationary, thereby transitioning the end effector 114 between the retracted and deployed configurations.

The user-operated controller associated with the first mechanism 126 may include a slider mechanism operably associated with the rack and pinion rail assembly. Movement of the slider mechanism in a rearward direction towards a proximal end of the handle results in transitioning of the end effector 114 to the deployed configuration and movement of the slider mechanism in a forward direction towards a distal end of the handle results in transitioning of the end effector to the retracted configuration. In other embodiment, the user-operated controller associated with the first mechanism 126 may include a scroll wheel mechanism operably associated with the rack and pinion rail assembly. Rotation of the wheel in a rearward direction towards a proximal end of the handle results in transitioning of the end effector to the deployed configuration and rotation of the wheel in a forward direction towards a distal end of the handle results in transitioning of the end effector to the retracted configuration.

The user-operated controller associated with the first mechanism 126 may generally provide a high degree of precision and control over the deployment (and retraction) of the first and second segments 122, 124. For example, in some instances, the operator may wish to only deploy the second segment 124 during the procedure, while the first segment 122 remains in the retracted configuration. The user-operated controller allows for an operator to provide a sufficient degree of input (i.e., slide the slider mechanism or scroll the scroll wheel to a specific position) which results in only the second segment 124 transitioning from the retracted configuration to the deployed configuration (while the first segment 122 remains enclosed within the shaft 116 and in the retracted configuration). For example, in some embodiments, the end effector 114 may further include a detent feature, such as a catch or similar element, positioned between the first and second segments 122, 124 and configured to provide a surgeon with feedback, such as haptic or tactile feedback, during deployment of the end effector segments, alerting the surgeon when at least the second segment 124 is fully deployed. In particular, as the surgeon slides the slider mechanism or scrolls the scroll wheel during deployment of the second segment 124, the detect feature (provided between the first and second segments 122, 124) may then reach a portion of the shaft 116 and cause an increase in resistance on the slider mechanism or scroll wheel, thereby indicating to the surgeon that the second segment 124 has been deployed and the first segment 122 remains in the retracted configuration. Accordingly, the surgeon can

position and orient the second segment 124 as they desire without concern over the first segment 122 as it remains in the retracted configuration. In turn, one the second segment 124 is positioned at the desired target site, the surgeon may then deploy the first segment 122 to perform the procedure. Yet still, in some instances, only the second segment 124 may be used to perform a procedure (i.e., deliver energy to one or more target sites in contact with the second segment 124) and, as such, the first segment 122 may never be deployed.

The second mechanism 128 may generally include a user-operated controller configured to be actuated between at least an active position and an inactive position to thereby control delivery of energy from the end effector 114, notable delivery of energy from the electrodes 136. The user-operated controller may be multi-modal in that the user-operated controller may be actuated between multiple positions providing different functions/modes. For example, upon a single user input (i.e., single press of button associated within controller), the second mechanism may provide a baseline apposition / sensing check function prior to modulation. Upon pressing and holding the controller button for a pre-defined period of time, the energy output from the end effector may be activated. Further, upon double-tapping the controller button, energy output is deactivated.

Furthermore, the handle and/or the shaft may include markings that provide a surgeon with a spatial orientation of the end effector while the end effector is in a nasal cavity. FIG. 10 is a side view of the handle 118 illustrating multiple markings on a distal end of the handle 118 and FIG. 11 is a perspective view of a portion of the shaft 116 illustrating multiple markings on a distal end thereof. In particular, multiple markings may be provided on the handle and/or shaft and provide a visual indication of the spatial orientation of one or more portions of the first segment and second segment of the end effector when in the deployed configurations. The markings may include, for example, text, symbols, color-coding insignia, or the like. Thus, during initial placement of the end effector, when in a retracted configuration and enclosed within the shaft, a surgeon can rely on the markings on the handle and/or shaft as a visual indication of the spatial orientation of the end effector (e.g., linear, axial, and/or depth position) prior to deployment to thereby ensure that, once deployed, the end effector, including both the first and second segments, are positioned in the intended locations within the nasal cavity.

For example, the handle and/or shaft may include markings associated with each of the first pair of struts 130a, 130b and each of the second pair of struts 132a, 132b, so as to provide an

operator with a visual indication as to the resulting spatial orientation and architecture of at least the first segment 122 when initially navigating the nasal cavity and delivering the distal end of the shaft 116 to a target site, prior to deployment of the end effector 114. In other words, the markings provide an operator with an indication of the orientation of at least the first segment 122 of the end effector 114 prior to deploying the end effector 114, thereby ensuring accurate positioning at the desired location.

FIG. 12 is a partial cut-away side view illustrating one approach for delivering an end effector 114 a target site within a nasal region in accordance with embodiments of the present disclosure. As shown, the distal portion of the shaft 116 extends into the nasal passage (NP), through the inferior meatus (IM) between the inferior turbinate (IT) and the nasal sill (NS), and around the posterior portion of the inferior turbinate (IT) where the end effector 114 is deployed at a treatment site. The treatment site can be located proximate to the access point or points of postganglionic parasympathetic nerves (e.g., branches of the posterior nasal nerve and/or other parasympathetic neural fibers that innervate the nasal mucosa) into the nasal cavity. In other embodiments, the target site can be elsewhere within the nasal cavity depending on the location of the target nerves.

In various embodiments, the distal portion of the shaft 116 may be guided into position at the target site via a guidewire (not shown) using an over-the-wire (OTW) or a rapid exchange (RX) technique. For example, the end effector 114 can include a channel for engaging the guidewire. Intraluminal delivery of the end effector 114 can include inserting the guide wire into an orifice in communication with the nasal cavity (e.g., the nasal passage or mouth), and moving the shaft 116 and/or the end effector 114 along the guide wire until the end effector 114 reaches a target site (e.g., inferior to the SPF).

Yet still, in further embodiments, the neuromodulation device 102 can be configured for delivery via a guide catheter or introducer sheath (not shown) with or without using a guide wire. The introducer sheath can first be inserted intraluminally to the target site in the nasal region, and the distal portion of the shaft 116 can then be inserted through the introducer sheath. At the target site, the end effector 114 can be deployed through a distal end opening of the introducer sheath or a side port of the introducer sheath. In certain embodiments, the introducer sheath can include a straight portion and a pre-shaped portion with a fixed curve (e.g., a 5 mm curve, a 4 mm curve, a 3 mm curve, etc.) that can be deployed intraluminally to access the target site. In

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this embodiment, the introducer sheath may have a side port proximal to or along the pre-shaped curved portion through which the end effector 114 can be deployed. In other embodiments, the introducer sheath may be made from a rigid material, such as a metal material coated with an insulative or dielectric material. In this embodiment, the introducer sheath may be substantially straight and used to deliver the end effector 114 to the target site via a substantially straight pathway, such as through the middle meatus (MM) (FIG. 3A).

Image guidance may be used to aid the surgeon's positioning and manipulation of the distal portion of the shaft 116, as well as the deployment and manipulation of the end effector 114, specifically the first and second segments 122 thereof. For example, an endoscope 100 and/or other visualization device can be positioned to visualize the target site, the positioning of the end effector 114 at the target site, and/or the end effector 114 during therapeutic neuromodulation. The endoscope 100 may be delivered proximate to the target site by extending through the nasal passage NP and through the middle meatus MM between the inferior and middle turbinates IT and MT. From the visualization location within the middle meatus MM, the endoscope 100 can be used to visualize the treatment site, surrounding regions of the nasal anatomy, and the end effector 114.

In some embodiments, the distal portion of the shaft 116 may be delivered via a working channel extending through an endoscope, and therefore the endoscope can provide direct in-line visualization of the target site and the end effector 114. In other embodiments, an endoscope is incorporated with the end effector 114 and/or the distal portion of the shaft 116 to provide in-line visualization of the end effector 114 and/or the surrounding nasal anatomy. In other embodiments, image guidance can be provided with various other guidance modalities, such as image filtering in the infrared (IR) spectrum to visualize the vasculature and/or other anatomical structures, computed tomography (CT), fluoroscopy, ultrasound, optical coherence tomography (OCT), and/or combinations thereof. Yet still, in some embodiments, image guidance components may be integrated with the neuromodulation device 102 to provide image guidance during positioning of the end effector 114.

Once positioned at the target site, the therapeutic modulation may be applied via the one or more electrodes 136 and/or other features of the end effector 114 to precise, localized regions of tissue to induce one or more desired therapeutic neuromodulating effects to disrupt parasympathetic motor sensory function. The end effector 114 can selectively target

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postganglionic parasympathetic fibers that innervate the nasal mucosa at a target or treatment site proximate to or at their entrance into the nasal region. For example, the end effector 114 can be positioned to apply therapeutic neuromodulation at least proximate to the SPF (FIG. 3A) to therapeutically modulate nerves entering the nasal region via the SPF. The end effector 114 can also be positioned to inferior to the SPF to apply therapeutic neuromodulation energy across accessory foramen and microforamina (e.g., in the palatine bone) through which smaller medial and lateral branches of the posterior superior lateral nasal nerve enter the nasal region. The purposeful application of the energy at the target site may achieve therapeutic neuromodulation along all or at least a portion of posterior nasal neural fibers entering the nasal region. The therapeutic neuromodulating effects are generally a function of, at least in part, power, time, and contact between the energy delivery elements and the adjacent tissue. For example, in certain embodiments therapeutic neuromodulation of autonomic neural fibers are produced by applying RF energy at a power of about 2-20 W (e.g., 5 W, 7 W, 10 W, etc.) for a time period of about 1-20 sections (e.g., 5-10 seconds, 8-10 seconds, 10-12 seconds, etc.).

The therapeutic neuromodulating effects may include partial or complete denervation via thermal ablation and/or non-ablative thermal alteration or damage (e.g., via sustained heating and/or resistive heating). Desired thermal heating effects may include raising the temperature of target neural fibers above a desired threshold to achieve non-ablative thermal alteration, or above a higher temperature to achieve ablative thermal alteration. For example, the target temperature may be above body temperature (e.g., approximately 37° C.) but less than about 90° C. (e.g., 70-75° C.) for non-ablative thermal alteration, or the target temperature may be about 100° C. or higher (e.g., 110° C., 120° C., etc.) for the ablative thermal alteration. Desired non-thermal neuromodulation effects may include altering the electrical signals transmitted in a nerve.

Sufficiently modulating at least a portion of the parasympathetic nerves is expected to slow or potentially block conduction of autonomic neural signals to the nasal mucosa to produce a prolonged or permanent reduction in nasal parasympathetic activity. This is expected to reduce or eliminate activation or hyperactivation of the submucosal glands and venous engorgement and, thereby, reduce or eliminate the symptoms of rhinosinusitis. Further, because the device 102 applies therapeutic neuromodulation to the multitude of branches of the posterior nasal nerves rather than a single large branch of the posterior nasal nerve branch entering the nasal cavity at the SPF, the device 102 provides a more complete disruption of the parasympathetic

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neural pathway that affects the nasal mucosa and results in rhinosinusitis. Accordingly, the device 102 is expected to have enhanced therapeutic effects for the treatment of rhinosinusitis and reduced re-innervation of the treated mucosa.

In other embodiments, the device 102 can be configured to therapeutically modulate nerves and/or other structures to treat different indications. For example, the device 102 can be used to therapeutically modulate nerves that innervate the para-nasal sinuses to treat chronic sinusitis. In further embodiments, the system 100 and the device 102 disclosed herein can be configured therapeutically modulate the vasculature within the nasal anatomy to treat other indications, such as epistaxis (i.e., excessive bleeding from the nose). For example, the system 100 and the device 102 devices described herein can be used to apply therapeutically effective energy to arteries (e.g., the sphenopalatine artery and its branches) as they enter the nasal cavity (e.g., via the SPF, accessory foramen, etc.) to partially or completely coagulate or ligate the arteries. In other embodiments, the system 100 and the device 102 can be configured to partially or completely coagulate or ligate veins and/or other vessels. For such embodiments in which the end effector 114 ligates or coagulates the vasculature, the system 100 and device 102 would be modified to deliver energy at significantly higher power (e.g., about 100 W) and/or longer times (e.g., 1 minute or longer) than would be required for therapeutic neuromodulation.

As further illustrated in FIG. 12, the shaft 116 may reside with a portion of the nasal cavity proximate to the IT upon advancing and deploying the multi-segment end effector 114 in the desired location (i.e., a target site associated with a sphenopalatine foramen within the nasal cavity of the patient). Accordingly, in addition to delivering energy from the electrodes 136 of the multi-segment end effector 114, the surgeon may also activate and deliver energy from electrodes 137 associated with the shaft 116 ((i.e., outer sheath 138, hypotube 140, or assembly of support elements 129) to tissue associated with the IT. Such energy may be delivered at a level sufficient to reduce engorgement of tissue associated with the IT to thereby increase volumetric flow through a nasal passage of the patient and improve a patient's ability to breathe.

FIG. 13 is a flow diagram illustrating one embodiment of a method 400 for treating a condition within a nasal cavity of a patient. The method 400 includes advancing a multi-segment end effector within the nasal cavity of the patient (operation 410) wherein the multi-segment end effector includes a first segment spaced apart from a second segment. The multi-segment end effector is retractable and expandable such that, once delivered to the one more target sites

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within the nasal cavity, the first and second segments can expand to a specific shape and/or size corresponding to anatomical structures within the nasal cavity and associated with the target sites. The method 400 further includes deploying the first and second segments at respective first and second locations within the nasal cavity (operation 420). In particular, each of the first and second flexible segments includes a specific geometry when in a deployed configuration to complement anatomy of respective locations within the nasal cavity. Accordingly, once deployed, the first and second segments contact and conform to a shape of the respective locations, including conforming to and complementing shapes of one or more anatomical structures at the respective locations. The method 400 further includes delivering energy, via the first and second segments, to tissue at one or more target sites with respect to the first and second locations (operation 430). In particular, the first and second segments become accurately positioned within the nasal cavity to subsequently deliver, via one or more electrodes, precise and focused application of RF thermal energy to the one or more target sites to thereby therapeutically modulate associated neural structures. The first and second segments have shapes and sizes when in the expanded configuration that are specifically designed to place portions of the first and second segments, and thus one or more electrodes associated therewith, into contact with target sites within nasal cavity associated with postganglionic parasympathetic fibers that innervate the nasal mucosa.

FIG. 14 is a flow diagram illustrating another embodiment of a method 500 for treating a condition within a nasal cavity of a patient. The method 500 includes providing a treatment device comprising an end effector transformable between a retracted configuration and an expanded deployed configuration, a shaft operably associated with the end effector, and a handle operably associated with the shaft (operation 510). The method 500 further includes advancing the end effector to one or more target sites within the nasal cavity of the patient (operation 520). The shaft may include a pre-defined shape (i.e., bent or angled at a specific orientation) so as to assist the operation for placement of the end effector at the target sites. The handle includes an ergonomically-designed grip portion which provides ambidextrous use for both left and right handed use and conforms to hand anthropometrics to allow for at least one of an overhand grip style and an underhand grip style during use in a procedure.

The handle and/or the shaft may include markings (e.g., text, symbols, color-coding insignia, etc.) that provide a surgeon with a spatial orientation of the end effector while the end

effector is in a nasal cavity. In particular, multiple markings may be provided on the handle and/or shaft and provide a visual indication of the spatial orientation of one or more portions of the first segment and second segment of the end effector when in the deployed configurations. Thus, during initial placement of the end effector, when in a retracted configuration and enclosed within the shaft, a surgeon can rely on the markings on the handle and/or shaft as a visual indication of the spatial orientation of the end effector (e.g., linear, axial, and/or depth position) prior to deployment to thereby ensure that, once deployed, the end effector, including both the first and second segments, are positioned in the intended locations within the nasal cavity.

The method 500 further includes deploying the end effector at the one or more target sites (operation 530) and delivering energy from the end effector to tissue at the one or more target sites (operation 540). The handle includes multiple user-operated mechanisms, including at least a first mechanism for deployment of the end effector from the retracted configuration to the expanded deployed configuration and a second mechanism for controlling of energy output by the end effector. The user inputs for the first and second mechanisms are positioned a sufficient distance to one another to allow for simultaneous one-handed operation of both user inputs during a procedure. Accordingly, the handle accommodates various styles of grip and provides a degree of comfort for the surgeon, thereby further improving execution of the procedure and overall outcome.

FIG. 15 is a flow diagram illustrating another embodiment of a method 600 for treating a condition within a nasal cavity of a patient. The method 600 includes providing a treatment device comprising a multi-segment end effector, including a proximal segment that is spaced apart from a distal segment, and a visual marker (operation 610). As previously described herein, the visual marker may be provided by a shaft, for example, operably associated with the multi-segment end effector. The visual marker may be in the form of text, symbols, color-coding insignia, or the like, that generally provides a user (i.e., a surgeon or other medical professional) with a visual indication of a spatial orientation of one or more portions of the proximal segment while the multi-segment end effector is in a nasal cavity.

The method 600 further includes advancing, under image guidance, the proximal segment and the distal segment through a nasal cavity of a patient and past a middle turbinate (operation 620) and deploying the distal segment from a retracted configuration to an expanded configuration (operation 630). The image guidance may be in the form of an endoscope and/or

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other visualization device that can be positioned to so as to provide visualization to the user of one or more locations within the nasal cavity and to further provide visualization of the multi-segment end effector and other portions of the treatment device (i.e., at least a distal portion of the shaft with a visual marker) during advancement into the nasal cavity to assist the user in placement of the multi-segment end effector.

Upon deploying the distal segment to an expanded configuration, the method 600 further includes aligning, under the image guidance and with reference to the visual marker, the proximal segment with respect to the middle turbinate (operation 640). The visual marker may be provided on the shaft, for example, and provide a visual indication of the spatial orientation of one or more portions of the proximal segment when in the deployed configuration. For example, the deployed proximal segment may include a geometry to complement a shape of the middle turbinate. More specifically, the proximal segment may include a set of flexible support elements that conform to and complement a shape of the middle turbinate when the proximal segment is in the deployed expanded configuration. The visual marker, provided by the shaft, provides a visual indication of the spatial orientation of one or more portions of the proximal segment, including, for example, a spatial orientation of the set of flexible support elements when in a deployed expanded configuration. Accordingly, aligning the proximal segment with respect to the middle turbinate includes the user positioning, under the image guidance, the shaft and associated visual marker relative to the middle turbinate.

Thus, during initial placement of at least the proximal segment when it is in a retracted configuration, a surgeon can rely on the markings on the shaft as a visual indication of the spatial orientation (e.g., linear, axial, and/or depth position) of one or more portions of the proximal segment prior to its deployment, thereby ensuring that, once deployed, the proximal segment is positioned in the intended location within the nasal cavity.

The method 600 further includes deploying the proximal segment around the middle turbinate and advancing the deployed proximal segment toward the middle turbinate to establish contact and secure the proximal segment to the middle turbinate (operation 650). Again, the set of flexible support elements of the proximal segment are able to conform to and complement a shape of the middle turbinate when the proximal segment is in the deployed expanded configuration, thereby ensuring that the deployed proximal segment is secured to the middle turbinate.

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It should be noted that the treatment device further includes a handle operably associated with the multi-segment end effector and the shaft. The handle generally includes a controller mechanism for providing independent, controlled deployment of each of the proximal and distal segments from a retracted configuration to an expanded configuration within the nasal cavity. In particular, in some embodiments, the controller mechanism includes a rack and pinion assembly providing movement of the at least one of the proximal and distal segments between the retracted configuration and expanded configuration in response to user input from an associated user-operated controller. The rack and pinion assembly may include, for example, a set of gears for receiving user input from the user-operated controller and converting the user input to linear motion of a rack member operably associated with the multi-segment end effector.

The controller mechanism may further include a detent feature positioned relative to the proximal and distal segments and configured to provide active feedback to a user indicative of deployment of at least one of the proximal and distal segments. The active feedback may be in the form haptic feedback provided by the controller mechanism. For example, the haptic feedback may include an increase or decrease in resistance associated with user input with the controller mechanism for corresponding movement of the at least one of the proximal and distal segments between retracted and expanded configurations, and/or configurations therebetween (i.e., a plurality of configurations between a fully retracted configuration and a fully expanded configuration). For example, upon deploying the distal segment, the controller mechanism, as a result of interaction with the detent, may provide haptic feedback, in the form of a vibration or other motion (e.g., click(s) or change in resistance), to the user via the user-operated controller. The haptic feedback may indicate to the user that the distal segment is fully deployed and any further input with the user-operated controller will result in deployment of the proximal segment. The controller mechanism may further provide specific haptic feedback during deployment of a given segment, such as deployment of the proximal segment. For example, the haptic feedback may be in the form of an increase or decrease in resistance upon the user-operated controller, for example, which corresponds to the degree to which the proximal segment is deployed.

In some embodiments, the controller mechanism may further include a friction-based feature configured to provide stable movement of at least one of the proximal and distal segments between the retracted and expanded configurations and further provide active feedback to a user indicative of deployment of at least one of the proximal and distal segments. The

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friction-based feature may include, for example, a lock mechanism configured to provide constant friction between one or more portions of the rack and pinion assembly sufficient to maintain a position of at least one of the proximal and distal segments during deployment thereof.

For example, the constant friction may be sufficient to hold either of the proximal or distal segments in a certain position as the segment transitions between retracted and expanded configurations regardless of whether the user maintains contact with the user-operated controller. In other words, a user does not need to maintain contact with the user-operated controller in order to ensure that the proximal or distal segment holds a certain position during deployment thereof. Rather, a user can simply interact with the user-operated controller to transition one of the proximal and distal segments to a desired configuration and the constant friction provided by the locking mechanism is sufficient to maintain the configuration of proximal or distal segment in the event that the user goes hands free (i.e., removes any contact with the user-operated controller). The constant friction is of a level sufficient to prevent undesired movement of the proximal or distal segments (i.e., unintended collapsing or expanding), while still allowing for a user to overcome such friction to move the proximal or distal segment to a desired configuration upon user input with the user-operated controller.

In some embodiments, the user-operated controller includes a slider mechanism operably associated with the rack and pinion rail assembly, wherein movement of the slider mechanism in a first direction results in transitioning of at least one of the proximal and distal segments to an expanded configuration and movement of the slider mechanism in a second opposite direction results in transitioning of at least one of the proximal and distal segments to the retracted configuration. In other embodiments, the user-operated controller includes a scroll wheel mechanism operably associated with the rack and pinion rail assembly, wherein rotation of the wheel in a first direction results in transitioning of at least one of the proximal and distal segments to an expanded configuration and rotation of the wheel in a second opposite direction results in transitioning of at least one of the proximal and distal segments to the retracted configuration. As such, during deployment of the proximal segment, the slider mechanism or scroll wheel may provide increased resistance to a user as the user transitions the proximal segment from a fully retracted configuration to a fully deployed configuration.

Accordingly, during deployment of either of the distal and proximal segments, the controller mechanism provides active feedback to the user, wherein such active feedback can be indicative of which segment is being actively controlled and/or the extent of deployment of either of the distal or proximal segments, thereby improving user control over the deployment of either of the distal and proximal segments.

Upon securing the proximal segment to the middle turbinate, the method 600 further includes delivering energy, via the proximal segment, to the middle turbinate to treat a condition (operation 660). The condition may include, but is not limited to, allergic rhinitis, non-allergic rhinitis, chronic rhinitis, acute rhinitis, chronic sinusitis, acute sinusitis, chronic rhinosinusitis, acute rhinosinusitis, and medical resistant rhinitis, and a combination thereof. In some embodiments, delivering energy from the proximal segment includes delivering radiofrequency (RF) energy, via one or more electrodes provided by the proximal segment, to tissue of the middle turbinate at one or more target sites, wherein the one or more target sites are associated with parasympathetic nerve supply. In some embodiments, RF energy is delivered, via the one or more electrodes provided by the proximal segment, at a level sufficient to therapeutically modulate postganglionic parasympathetic nerves innervating nasal mucosa at an innervation pathway within the nasal cavity of the patient.

FIG. 16 is a flow diagram illustrating another embodiment of a method 700 for treating a condition within a nasal cavity of a patient. The method 700 includes providing a treatment device comprising an elongate body including one or more of a first set of electrodes provided along a length thereof and a retractable and expandable end effector operably associated with the elongate body and including one or more of a second set of electrodes provided thereon (operation 710).

The method 700 further includes advancing the shaft and end effector through a nasal passage and into a nasal cavity of a patient (operation 720) at which point a length of the elongate body is positioned at a first target site and the end effector is positioned at a second target site separate from the first target site (operation 730). For example, in some embodiments, the procedure may involve extending the elongate body into the nasal passage (NP), through the inferior meatus (IM) between the inferior turbinate (IT) and the nasal sill (NS). In other embodiments, the procedure may involve extending the elongate body into the nasal passage (NP), through the middle meatus (MM) between the inferior turbinate (IT) and the middle

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turbinate (MT). In each instance, a proximal segment (of the end effector) is arranged in a deployed configuration to fit around at least a portion of a middle turbinate at an anterior position relative to a lateral attachment and a posterior-inferior edge of the middle turbinate and a separate distal segment (of the end effector) is configured in a deployed configuration to contact a plurality of tissue locations in a cavity at a posterior position relative to the lateral attachment and posterior-inferior edge of the middle turbinate. Additionally, the elongate body resides in a location adjacent to the inferior turbinate (IT).

The method 700 further includes delivering energy from the first and second sets of electrodes (associated with elongate body and end effector, respectively) to tissue at the first and second target sites, respectively (operation 740). In particular, a given procedure, the surgeon may utilize the multi-segment end effector to deliver energy (via electrodes) at a level sufficient to therapeutically modulate postganglionic parasympathetic nerves innervating nasal mucosa at microforamina of a palatine bone of the patient and further utilize the elongate body to deliver energy (via electrodes) at a level sufficient to reduce engorgement of tissue associated with the inferior turbinate to thereby increase volumetric flow through the nasal passage of the patient. Such a combination of energy delivery to two specific targeted sites improves the manner in which at least one of rhinitis, congestion, and rhinorrhea are treated, thereby increasing the potential for reducing or completely eliminating symptoms associated therewith, including, but not limited to, coughing, sneezing, nasal or throat irritation and itching, and difficulty sleeping.

Accordingly, the treatment device of the present invention recognizes the desire or need to treat larger areas within the nasal cavity or passage that are located outside of a treatment zone associated with the end effector. For example, when performing surgical procedures using current rhinitis treatment devices, the surgeon must reposition an end effector when attempting to treat multiple areas within the nasal cavity, particularly those areas that are located outside of any given treatment zone. The need to reposition the end effector multiple times during a given procedure can lead to inaccuracy when delivering energy, resulting in unintended collateral damage, and further increases the time in which it takes to complete a given procedure. The treatment device of the present invention recognizes and addresses this problem by providing an elongate body including one or more electrodes thereon, in addition to a multi-segment end effector operably associated with the elongate body and including separate electrodes thereon. Accordingly, the elongate body serves to not only aid in positioning and delivering the end

effector to a desired target site (to which the end effector may deliver energy), but the elongate body can also deliver energy to a target site that is separate and remote from the end effector. Such a design improves the efficiency with which a given procedure can be accomplished, particularly those procedures requiring treatment to multiple, separate areas within the nasal cavity or passage.

FIG. 17 is a flow diagram illustrating an embodiment of a method 800 for improving a patient's sleep by treating at least one of rhinitis, congestion, and rhinorrhea within a sino-nasal cavity of the patient. As previously described, the most common and impactful symptoms of rhinosinusitis include a runny nose, coughing, sneezing, nasal and/or throat irritation and itching, and overall general congestion of the nasal passage. As a result, sleep problems are very common in individuals suffering from rhinitis, as such symptoms impact a person's ability to either fall asleep or remain asleep for adequate periods of time. In addition, sleep problems are linked with fatigue and daytime sleepiness, as well as decreased productivity at work or school, impaired learning and memory, depression, and a reduced quality of life.

The method 800 includes delivering energy to one or more target sites within a sino-nasal cavity of the patient to disrupt multiple neural signals to, and/or result in local hypoxia of, mucus producing and/or mucosal engorgement elements, thereby reducing production of mucus and/or mucosal engorgement within a nose of the patient and reducing or eliminate one or more symptoms associated with at least one of rhinitis, congestion, and rhinorrhea to improve nasal breathability of the patient (operation 810). The one or more symptoms associated with at least one of rhinitis, congestion, and rhinorrhea are selected from the group consisting of nasal congestion, coughing, sneezing, and nasal or throat irritation and itching.

In some embodiments, the step of delivering energy results in ablation of targeted tissue at one or more locations to thereby disrupt the multiple neural signals to the mucus producing and/or mucosal engorgement elements within the nose. For example, the targeted tissue may be associated with one or more target sites proximate or inferior to a sphenopalatine foramen. The energy may be delivered at a level sufficient to therapeutically modulate postganglionic parasympathetic nerves innervating nasal mucosa at foramina and or microforamina of a palatine bone of the patient. As a result, the energy delivered may cause multiple points of interruption of neural branches extending through foramina and microforamina of palatine bone.

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Additionally, or alternatively, the step of delivering energy may result in ablation of targeted tissue at one or more locations to thereby result in local hypoxia of the mucus producing and/or mucosal engorgement elements within the nose. For example, in some embodiments, the ablation of targeted tissue may cause thrombus formation within one or more blood vessels associated with mucus producing and/or mucosal engorgement elements within the nose. As such, the resulting local hypoxia of the mucus producing and/or mucosal engorgement elements may result in decreased mucosal engorgement to thereby increase volumetric flow through a nasal passage of the patient.

It should be noted that the ablation may include thermal ablation, which may be in the form of cyro-ablation, for example. In other embodiments, the ablation may be caused by delivery of radiofrequency (RF) energy.

In some embodiments, the ablation may be caused by a treatment device comprising a handle, an elongate body extending therefrom, and a retractable and expandable end effector operably associated with the elongate body. Accordingly, during a procedure, the method may include advancing the end effector into the sino-nasal cavity and positioning the end effector at a target site(s). The handle may generally control transformation of the end effector from a retracted state to an expanded state. The end effector may include a plurality of energy delivery elements provided thereon, such as electrodes, for example.

When in the expanded state, the end effector may generally position one or more of the plurality of energy delivery elements relative to the one or more target sites. In some embodiments, the end effector includes a proximal segment that is spaced apart from a separate distal segment. In some embodiments, the proximal segment may include a first set of flexible support elements arranged in a deployed configuration to fit around at least a portion of a middle turbinate at an anterior position relative to a lateral attachment and a posterior-inferior edge of the middle turbinate and position one or more energy delivery elements into contact with one or more respective tissue locations associated with the middle turbinate and the distal segment may include a second set of flexible support elements configured in a deployed configuration to position one or more energy delivery elements into contact with one or more respective tissue locations in a cavity at a posterior position relative to the lateral attachment and posterior-inferior edge of the middle turbinate.

In some embodiments, the elongate body may include a shaft to which the end effector is coupled. The shaft includes an outer sheath surrounding a hypotube or metallic member, wherein at least one of the outer sheath and hypotube and metallic member includes the one or more energy delivering elements provided thereon. Yet still, in other embodiments, the elongate body may include one or more of a plurality of support elements forming at least a portion of the end effector. The energy delivering elements of the elongate body may be configured to deliver energy at one or more target sites associated with an inferior or middle turbinate within the sino-nasal cavity of the patient at a level sufficient to reduce engorgement of tissue associated therewith to thereby increase volumetric flow through a nasal passage of the patient.

Neuromodulation Monitoring, Feedback, and Mapping Capabilities

As previously described, the system 100 includes a console 104 to which the device 102 is to be connected. The console 104 is configured to provide various functions for the neuromodulation device 102, which may include, but is not limited to, controlling, monitoring, supplying, and/or otherwise supporting operation of the neuromodulation device 102. The console 104 can further be configured to generate a selected form and/or magnitude of energy for delivery to tissue or nerves at the target site via the end effector 114, and therefore the console 104 may have different configurations depending on the treatment modality of the device 102. For example, when device 102 is configured for electrode-based, heat-element-based, and/or transducer-based treatment, the console 104 includes an energy generator 106 configured to generate RF energy (e.g., monopolar, bipolar, or multi-polar RF energy), pulsed electrical energy, microwave energy, optical energy, ultrasound energy (e.g., intraluminally-delivered ultrasound and/or HIFU), direct heat energy, radiation (e.g., infrared, visible, and/or gamma radiation), and/or another suitable type of energy. When the device 102 is configured for cryotherapeutic treatment, the console 104 can include a refrigerant reservoir (not shown), and can be configured to supply the device 102 with refrigerant. Similarly, when the device 102 is configured for chemical-based treatment (e.g., drug infusion), the console 104 can include a chemical reservoir (not shown) and can be configured to supply the device 102 with one or more chemicals.

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In some embodiments, the console 104 may include a controller 107 communicatively coupled to the neuromodulation device 102. However, in the embodiments described herein, the controller 107 may generally be carried by and provided within the handle 118 of the neuromodulation device 102. The controller 107 is configured to initiate, terminate, and/or adjust operation of one or more electrodes provided by the end effector 114 directly and/or via the console 104. For example, the controller 107 can be configured to execute an automated control algorithm and/or to receive control instructions from an operator (e.g., surgeon or other medical professional or clinician). For example, the controller 107 and/or other components of the console 104 (e.g., processors, memory, etc.) can include a computer-readable medium carrying instructions, which when executed by the controller 107, causes the device 102 to perform certain functions (e.g., apply energy in a specific manner, detect impedance, detect temperature, detect nerve locations or anatomical structures, perform nerve mapping, etc.). A memory includes one or more of various hardware devices for volatile and non-volatile storage, and can include both read-only and writable memory. For example, a memory can comprise random access memory (RAM), CPU registers, read-only memory (ROM), and writable non-volatile memory, such as flash memory, hard drives, floppy disks, CDs, DVDs, magnetic storage devices, tape drives, device buffers, and so forth. A memory is not a propagating signal divorced from underlying hardware; a memory is thus non-transitory.

The console 104 may further be configured to provide feedback to an operator before, during, and/or after a treatment procedure via mapping/evaluation/feedback algorithms 110. For example, the mapping/evaluation/feedback algorithms 110 can be configured to provide information associated with the location of nerves at the treatment site, the location of other anatomical structures (e.g., vessels) at the treatment site, the temperature at the treatment site during monitoring and modulation, and/or the effect of the therapeutic neuromodulation on the nerves at the treatment site. In certain embodiments, the mapping/evaluation/feedback algorithm 110 can include features to confirm efficacy of the treatment and/or enhance the desired performance of the system 100. For example, the mapping/evaluation/feedback algorithm 110, in conjunction with the controller 107 and the end effector 114, can be configured to monitor neural activity and/or temperature at the treatment site during therapy and automatically shut off the energy delivery when the neural activity and/or temperature reaches a predetermined threshold (e.g., a threshold reduction in neural activity, a threshold maximum temperature when

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applying RF energy, or a threshold minimum temperature when applying cryotherapy). In other embodiments, the mapping/evaluation/feedback algorithm 110, in conjunction with the controller 107, can be configured to automatically terminate treatment after a predetermined maximum time, a predetermined maximum impedance or resistance rise of the targeted tissue (i.e., in comparison to a baseline impedance measurement), a predetermined maximum impedance of the targeted tissue), and/or other threshold values for biomarkers associated with autonomic function. This and other information associated with the operation of the system 100 can be communicated to the operator via a display 112 (e.g., a monitor, touchscreen, user interface, etc.) on the console 104 and/or a separate display (not shown) communicatively coupled to the console 104.

In various embodiments, the end effector 114 and/or other portions of the system 100 can be configured to detect various bioelectric-parameters of the tissue at the target site, and this information can be used by the mapping/evaluation/feedback algorithms 110 to determine the anatomy at the target site (e.g., tissue types, tissue locations, vasculature, bone structures, foramen, sinuses, etc.), locate neural structures, differentiate between different types of neural structures, map the anatomical and/or neural structure at the target site, and/or identify neuromodulation patterns of the end effector 114 with respect to the patient's anatomy. For example, the end effector 114 can be used to detect resistance, complex electrical impedance, dielectric properties, temperature, and/or other properties that indicate the presence of neural fibers and/or other anatomical structures in the target region. In certain embodiments, the end effector 114, together with the mapping/evaluation/feedback algorithms 110, can be used to determine resistance (rather than impedance) of the tissue (i.e., the load) to more accurately identify the characteristics of the tissue. The mapping/evaluation/feedback algorithms 110 can determine resistance of the tissue by detecting the actual power and current of the load (e.g., via the electrodes 136).

In some embodiments, the system 100 provides resistance measurements with a high degree of accuracy and a very high degree of precision, such as precision measurements to the hundredths of an Ohm (e.g., 0.01Ω) for the range of 1-50Ω. The high degree of resistance detection accuracy provided by the system 100 allows for the detection sub-microscale structures, including the firing of neural structures, differences between neural structures and other anatomical structures (e.g., blood vessels), and event different types of neural structures.

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This information can be analyzed by the mapping/evaluation/feedback algorithms and/or the controller 107 and communicated to the operator via a high resolution spatial grid (e.g., on the display 112) and/or other type of display to identify neural structures and other anatomy at the treatment site and/or indicate predicted neuromodulation regions based on the ablation pattern with respect to the mapped anatomy.

As previously described, in certain embodiments, each electrode 136 can be operated independently of the other electrodes 136. For example, each electrode can be individually activated and the polarity and amplitude of each electrode can be selected by an operator or a control algorithm executed by the controller 107. The selective independent control of the electrodes 136 allows the end effector 114 to detect information and deliver RF energy to highly customized regions. For example, a select portion of the electrodes 136 can be activated to target specific neural fibers in a specific region while the other electrodes 136 remain inactive. In certain embodiments, for example, electrodes 136 may be activated across the portion of the second segment 124 that is adjacent to tissue at the target site, and the electrodes 136 that are not proximate to the target tissue can remain inactive to avoid applying energy to non-target tissue. In addition, the electrodes 136 can be individually activated to stimulate or therapeutically modulate certain regions in a specific pattern at different times (e.g., via multiplexing), which facilitates detection of anatomical parameters across a zone of interest and/or regulated therapeutic neuromodulation.

The electrodes 136 can be electrically coupled to the energy generator 106 via wires (not shown) that extend from the electrodes 136, through the shaft 116, and to the energy generator 106. When each of the electrodes 136 is independently controlled, each electrode 136 couples to a corresponding wire that extends through the shaft 116. This allows each electrode 136 to be independently activated for stimulation or neuromodulation to provide precise ablation patterns and/or individually detected via the console 104 to provide information specific to each electrode 136 for neural or anatomical detection and mapping. In other embodiments, multiple electrodes 136 can be controlled together and, therefore, multiple electrodes 136 can be electrically coupled to the same wire extending through the shaft 116. The energy generator 16 and/or components (e.g., a control module) operably coupled thereto can include custom algorithms to control the activation of the electrodes 136. For example, the RF generator can deliver RF power at about 200-100 W to the electrodes 136, and do so while activating the electrodes 136 in a

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predetermined pattern selected based on the position of the end effector 114 relative to the treatment site and/or the identified locations of the target nerves. In other embodiments, the energy generator 106 delivers power at lower levels (e.g., less than 1 W, 1-5 W, 5-15 W, 15-50 W, 50-150 W, etc.) for stimulation and/or higher power levels. For example, the energy generator 106 can be configured to delivery stimulating energy pulses of 1-3 W via the electrodes 136 to stimulate specific targets in the tissue.

As previously described, the end effector 114 can further include one or more temperature sensors disposed on the flexible first and second segments 122, 124 and/or other portions of the end effector 114 and electrically coupled to the console 104 via wires (not shown) that extend through the shaft 116. In various embodiments, the temperature sensors can be positioned proximate to the electrodes 136 to detect the temperature at the interface between tissue at the target site and the electrodes 136. In other embodiments, the temperature sensors can penetrate the tissue at the target site (e.g., a penetrating thermocouple) to detect the temperature at a depth within the tissue. The temperature measurements can provide the operator or the system with feedback regarding the effect of the therapeutic neuromodulation on the tissue. For example, in certain embodiments the operator may wish to prevent or reduce damage to the tissue at the treatment site (e.g., the nasal mucosa), and therefore the temperature sensors can be used to determine if the tissue temperature reaches a predetermined threshold for irreversible tissue damage. Once the threshold is reached, the application of therapeutic neuromodulation energy can be terminated to allow the tissue to remain intact and avoid significant tissue sloughing during wound healing. In certain embodiments, the energy delivery can automatically terminate based on the mapping/evaluation/feedback algorithm 110 stored on the console 104 operably coupled to the temperature sensors.

In certain embodiments, the system 100 can determine the locations and/or morphology of neural structures and/or other anatomical structures before therapy such that the therapeutic neuromodulation can be applied to precise regions including target neural structures, while avoiding negative effects on non-target structures, such as blood vessels. As described in further detail below, the system 100 can detect various bioelectrical parameters in an interest zone (e.g., within in the nasal cavity) to determine the location and morphology of various neural structures (e.g., different types of neural structures, neuronal directionality, etc.) and/or other tissue (e.g., glandular structures, vessels, bony regions, etc.). In some embodiments, the system 100 is

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configured to measure bioelectric potential. To do so, one or more of the electrodes 136 is placed in contact with an epithelial surface at a region of interest (e.g., a treatment site). Electrical stimuli (e.g., constant or pulsed currents at one or more frequencies) are applied to the tissue by one or more electrodes 136 at or near the treatment site, and the voltage and/or current differences at various different frequencies between various pairs of electrodes 136 of the end effector 114 may be measured to produce a spectral profile or map of the detected bioelectric potential, which can be used to identify different types of tissues (e.g., vessels, neural structures, and/or other types of tissue) in the region of interest. For example, current (i.e., direct or alternating current) can be applied to a pair of electrodes 136 adjacent to each other and the resultant voltages and/or currents between other pairs of adjacent electrodes 136 are measured. It will be appreciated that the current injection electrodes 136 and measurement electrodes 136 need not be adjacent, and that modifying the spacing between the two current injection electrodes 136 can affect the depth of the recorded signals. For example, closely-spaced current injection electrodes 136 provided recorded signals associated with tissue deeper from the surface of the tissue than further spaced apart current injection electrodes 136 that provide recorded signals associated with tissue at shallower depths. Recordings from electrode pairs with different spacings may be merged to provide additional information on depth and localization of anatomical structures.

Further, complex impedance and/or resistance measurements of the tissue at the region of interest can be detected directly from current-voltage data provided by the bioelectric potential measurements while differing levels of frequency currents are applied to the tissue (e.g., via the end effector 114), and this information can be used to map the neural and anatomical structures by the use of frequency differentiation reconstruction. Applying the stimuli at different frequencies will target different stratified layers or cellular bodies or clusters. At high signal frequencies (e.g., electrical injection or stimulation), for example, cell membranes of the neural structures do not impede current flow, and the current passes directly through the cell membranes. In this case, the resultant measurement (e.g., impedance, resistance, capacitance, and/or induction) is a function of the intracellular and extracellular tissue and liquids. At low signal frequencies, the membranes impede current flow to provide different defining characteristics of the tissues, such as the shapes of the cells or cell spacing. The stimulation frequencies can be in the megahertz range, in the kilohertz range (e.g., 400-500 kHz, 450-480

kHz, etc.), and/or other frequencies attuned to the tissue being stimulated and the characteristics of the device being used. The detected complex impedance or resistances levels from the zone of interest can be displayed to the user (e.g., via the display 112) to visualize certain structures based on the stimulus frequency.

Further, the inherent morphology and composition of the anatomical structures in the nasal region react differently to different frequencies and, therefore, specific frequencies can be selected to identify very specific structures. For example, the morphology or composition of targeted structures for anatomical mapping may depend on whether the cells of tissue or other structure are membranonic, stratified, and/or annular. In various embodiments, the applied stimulation signals can have predetermined frequencies attuned to specific neural structures, such as the level of myelination and/or morphology of the myelination. For example, second axonal parasympathetic structures are poorly myelinated than sympathetic nerves or other structures and, therefore, will have a distinguishable response (e.g., complex impedance, resistance, etc.) with respect to a selected frequency than sympathetic nerves. Accordingly, applying signals with different frequencies to the target site can distinguish the targeted parasympathetic nerves from the non-targeted sensory nerves, and therefore provide highly specific target sites for neural mapping before or after therapy and/or neural evaluation post-therapy. In some embodiments, the neural and/or anatomical mapping includes measuring data at a region of interest with at least two different frequencies to identify certain anatomical structures such that the measurements are taken first based on a response to an injection signal having a first frequency and then again based on an injection signal having a second frequency different from the first. For example, there are two frequencies at which hypertrophied (i.e., disease-state characteristics) sub-mucosal targets have a different electrical conductivity or permittivity compared to "normal" (i.e., healthy) tissue. Complex conductivity may be determined based on one or more measured physiological parameters (e.g., complex impedance, resistance, dielectric measurements, dipole measurements, etc.) and/or observance of one or more confidently known attributes or signatures. Furthermore, the system 100 can also apply neuromodulation energy via the electrodes 136 at one or more predetermined frequencies attuned to a target neural structure to provide highly targeted ablation of the selected neural structure associated with the frequency(ies). This highly targeted neuromodulation also reduces the collateral effects of neuromodulation therapy to non-target sites/structures (e.g., blood vessels) because the targeted

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signal (having a frequency tuned to a target neural structure) will not have the same modulating effects on the non-target structures.

Accordingly, bioelectric properties, such as complex impedance and resistance, can be used by the system 100 before, during, and/or after neuromodulation therapy to guide one or more treatment parameters. For example, before, during, and/or after treatment, impedance or resistance measurements may be used to confirm and/or detect contact between one or more electrodes 136 and the adjacent tissue. The impedance or resistance measurements can also be used to detect whether the electrodes 136 are placed appropriately with respect to the targeted tissue type by determining whether the recorded spectra have a shape consistent with the expected tissue types and/or whether serially collected spectra were reproducible. In some embodiments, impedance or resistance measurements may be used to identify a boundary for the treatment zone (e.g., specific neural structures that are to be disrupted), anatomical landmarks, anatomical structures to avoid (e.g., vascular structures or neural structures that should not be disrupted), and other aspects of delivering energy to tissue.

The bioelectric information can be used to produce a spectral profile or map of the different anatomical features tissues at the target site, and the anatomical mapping can be visualized in a 3D or 2D image via the display 112 and/or other user interface to guide the selection of a suitable treatment site. This neural and anatomical mapping allows the system 100 to accurately detect and therapeutically modulate the postganglionic parasympathetic neural fibers that innervate the mucosa at the numerous neural entrance points into the nasal cavity. Further, because there are not any clear anatomical markers denoting the location of the SPF, accessory foramen, and microforamina, the neural mapping allows the operator to identify and therapeutically modulate nerves that would otherwise be unidentifiable without intricate dissection of the mucosa. In addition, anatomical mapping also allows the clinician to identify certain structures that the clinician may wish to avoid during therapeutic neural modulation (e.g., certain arteries). The neural and anatomical bioelectric properties detected by the system 100 can also be used during and after treatment to determine the real-time effect of the therapeutic neuromodulation on the treatment site. For example, the mapping/evaluation/feedback algorithms 110 can also compare the detected neural locations and/or activity before and after therapeutic neuromodulation, and compare the change in neural activity to a predetermined

threshold to assess whether the application of therapeutic neuromodulation was effective across the treatment site.

In various embodiments, the system 100 can also be configured to map the expected therapeutic modulation patterns of the electrodes 136 at specific temperatures and, in certain embodiments, take into account tissue properties based on the anatomical mapping of the target site. For example, the system 100 can be configured to map the ablation pattern of a specific electrode ablation pattern at the 45° C. isotherm, the 55° C. isotherm, the 65° C. isotherm, and/or other temperature/ranges (e.g., temperatures ranging from 45° C. to 70° C. or higher) depending on the target site and/or structure.

The system 100 may provide, via the display 112, three-dimensional views of such projected ablation patterns of the electrodes 136 of the end effector 114. The ablation pattern mapping may define a region of influence that each electrode 136 has on the surrounding tissue. The region of influence may correspond to the region of tissue that would be exposed to therapeutically modulating energy based on a defined electrode activation pattern (i.e., one, two, three, four, or more electrodes on any given strut of the first and second segments 122, 124). In other words, the ablation pattern mapping can be used to illustrate the ablation pattern of any number of electrodes 136, any geometry of the electrode layout, and/or any ablation activation protocol (e.g., pulsed activation, multi-polar/sequential activation, etc.).

In some embodiments, the ablation pattern may be configured such that each electrode 136 has a region of influence surrounding only the individual electrode 136 (i.e., a "dot" pattern). In other embodiments, the ablation pattern may be such that two or more electrodes 136 may link together to form a sub-grouped regions of influence that define peanut-like or linear shapes between two or more electrodes 136. In further embodiments, the ablation pattern can result in a more expansive or contiguous pattern in which the region of influence extends along multiple electrodes 136 (e.g., along each strut). In still further embodiments, the ablation pattern may result in different regions of influence depending upon the electrode activation pattern, phase angle, target temperature, pulse duration, device structure, and/or other treatment parameters. The three-dimensional views of the ablation patterns can be output to the display 112 and/or other user interfaces to allow the clinician to visualize the changing regions of influence based on different durations of energy application, different electrode activation sequences (e.g., multiplexing), different pulse sequences, different temperature isotherms, and/or other treatment

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parameters. This information can be used to determine the appropriate ablation algorithm for a patient's specific anatomy. In other embodiments, the three-dimensional visualization of the regions of influence can be used to illustrate the regions from which the electrodes 136 detect data when measuring bioelectrical properties for anatomical mapping. In this embodiment, the three dimensional visualization can be used to determine which electrode activation pattern should be used to determine the desired properties (e.g., impedance, resistance, etc.) in the desired area. In certain embodiments, it may be better to use dot assessments, whereas in other embodiments it may be more appropriate to detect information from linear or larger contiguous regions.

In some embodiments, the mapped ablation pattern is superimposed on the anatomical mapping to identify what structures (e.g., neural structures, vessels, etc.) will be therapeutically modulated or otherwise affected by the therapy. An image may be provided to the surgeon which includes a digital illustration of a predicted or planned neuromodulation zone in relation to previously identified anatomical structures in a zone of interest. For example, the illustration may show numerous neural structures and, based on the predicted neuromodulation zone, identifies which neural structures are expected to be therapeutically modulated. The expected therapeutically modulated neural structures may be shaded to differentiate them from the non-affected neural structures. In other embodiments, the expected therapeutically modulated neural structures can be differentiated from the non-affected neural structures using different colors and/or other indicators. In further embodiments, the predicted neuromodulation zone and surrounding anatomy (based on anatomical mapping) can be shown in a three dimensional view (and/or include different visualization features (e.g., color-coding to identify certain anatomical structures, bioelectric properties of the target tissue, etc.). The combined predicted ablation pattern and anatomical mapping can be output to the display 112 and/or other user interfaces to allow the clinician to select the appropriate ablation algorithm for a patient's specific anatomy.

The imaging provided by the system 100 allows the clinician to visualize the ablation pattern before therapy and adjust the ablation pattern to target specific anatomical structures while avoiding others to prevent collateral effects. For example, the clinician can select a treatment pattern to avoid blood vessels, thereby reducing exposure of the vessel to the therapeutic neuromodulation energy. This reduces the risk of damaging or rupturing vessels and, therefore, prevents immediate or latent bleeding. Further, the selective energy application

provided by the neural mapping reduces collateral effects of the therapeutic neuromodulation, such as tissue sloughing off during wound healing (e.g., 1-3 weeks post ablation), thereby reducing the aspiration risk associated with the neuromodulation procedure.

The system 100 can be further configured to apply neuromodulation energy (via the electrodes 136) at specific frequencies attuned to the target neural structure and, therefore, specifically target desired neural structures over non-target structures. For example, the specific neuromodulation frequencies can correspond to the frequencies identified as corresponding to the target structure during neural mapping. As described above, the inherent morphology and composition of the anatomical structures react differently to different frequencies. Thus, frequency-tuned neuromodulation energy tailored to a target structure does not have the same modulating effects on non-target structures. More specifically, applying the neuromodulation energy at the target-specific frequency causes ionic agitation in the target neural structure, leading to differentials in osmotic potentials of the targeted neural structures and dynamic changes in neuronal membronic potentials (resulting from the difference in intra-cellular and extra-cellular fluidic pressure). This causes degeneration, possibly resulting in vacuolar degeneration and, eventually, necrosis at the target neural structure, but is not expected to functionally affect at least some non-target structures (e.g., blood vessels). Accordingly, the system 100 can use the neural-structure specific frequencies to both (1) identify the locations of target neural structures to plan electrode ablation configurations (e.g., electrode geometry and/or activation pattern) that specifically focus the neuromodulation on the target neural structure; and (2) apply the neuromodulation energy at the characteristic neural frequencies to selectively ablate the neural structures responsive to the characteristic neural frequencies. For example, the end effector 114 of the system 100 may selectively stimulate and/or modulate parasympathetic fibers, sympathetic fibers, sensory fibers, alpha/beta/delta fibers, C-fibers, anoxic terminals of one or more of the foregoing, insulated over non-insulated fibers (regions with fibers), and/or other neural structures. In some embodiments, the system 100 may also selectively target specific cells or cellular regions during anatomical mapping and/or therapeutic modulation, such as smooth muscle cells, sub-mucosal glands, goblet cells, stratified cellular regions within the nasal mucosa. Therefore, the system 100 provides highly selective neuromodulation therapy specific to targeted neural structures, and reduces the collateral effects of neuromodulation therapy to non-target structures (e.g., blood vessels).

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The present disclosure provides a method of anatomical mapping and therapeutic neuromodulation. The method includes expanding an end effector (i.e., end effector 114) at a zone of interest ("interest zone"), such as in a portion of the nasal cavity. For example, the end effector 114 can be expanded such that at least some of the electrodes 136 are placed in contact with mucosal tissue at the interest zone. The expanded device can then take bioelectric measurements via the electrodes 136 and/or other sensors to ensure that the desired electrodes are in proper contact with the tissue at the interest zone. In some embodiments, for example, the system 100 detects the impedance and/or resistance across pairs of the electrodes 136 to confirm that the desired electrodes have appropriate surface contact with the tissue and that all of the electrodes are 136 functioning properly.

The method continues by optionally applying an electrical stimulus to the tissue, and detecting bioelectric properties of the tissue to establish baseline norms of the tissue. For example, the method can include measuring resistance, complex impedance, current, voltage, nerve firing rate, neuromagnetic field, muscular activation, and/or other parameters that are indicative of the location and/or function of neural structures and/or other anatomical structures (e.g., glandular structures, blood vessels, etc.). In some embodiments, the electrodes 136 send one or more stimulation signals (e.g., pulsed signals or constant signals) to the interest zone to stimulate neural activity and initiate action potentials. The stimulation signal can have a frequency attuned to a specific target structure (e.g., a specific neural structure, a glandular structure, a vessel) that allows for identification of the location of the specific target structure. The specific frequency of the stimulation signal is a function of the host permeability and, therefore, applying the unique frequency alters the tissue attenuation and the depth into the tissue the RF energy will penetrate. For example, lower frequencies typically penetrate deeper into the tissue than higher frequencies.

Pairs of the non-stimulating electrodes 136 of the end effector 114 can then detect one or more bioelectric properties of the tissue that occur in response to the stimulus, such as impedance or resistance. For example, an array of electrodes (e.g., the electrodes 136) can be selectively paired together in a desired pattern (e.g., multiplexing the electrodes 136) to detect the bioelectric properties at desired depths and/or across desired regions to provide a high level of spatial awareness at the interest zone. In certain embodiments, the electrodes 136 can be paired together in a time-sequenced manner according to an algorithm (e.g., provided by the

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mapping/evaluation/feedback algorithms 110). In various embodiments, stimuli can be injected into the tissue at two or more different frequencies, and the resultant bioelectric responses (e.g., action potentials) in response to each of the injected frequencies can be detected via various pairs of the electrodes 136. For example, an anatomical or neural mapping algorithm can cause the end effector 114 to deliver pulsed RF energy at specific frequencies between different pairs of the electrodes 136 and the resultant bioelectric response can be recorded in a time sequenced rotation until the desired interest zone is adequately mapped (i.e., "multiplexing"). For example, the end effector 114 can deliver stimulation energy at a first frequency via adjacent pairs of the electrodes 136 for a predetermined time period (e.g., 1-50 milliseconds), and the resultant bioelectric activity (e.g., resistance) can be detected via one or more other pairs of electrodes 136 (e.g., spaced apart from each other to reach varying depths within the tissue). The end effector 114 can then apply stimulation energy at a second frequency different from the first frequency, and the resultant bioelectric activity can be detected via the other electrodes. This can continue when the interest zone has been adequately mapped at the desired frequencies. As described in further detail below, in some embodiments the baseline tissue bioelectric properties (e.g., nerve firing rate) are detected using static detection methods (without the injection of a stimulation signal).

After detecting the baseline bioelectric properties, the information can be used to map anatomical structures and/or functions at the interest zone. For example, the bioelectric properties detected by the electrodes 136 can be amazed via the mapping/evaluation/feedback algorithms 110, and an anatomical map can be output to a user via the display 112. In some embodiments, complex impedance, dielectric, or resistance measurements can be used to map parasympathetic nerves and, optionally, identify neural structures in a diseased state of hyperactivity. The bioelectric properties can also be used to map other non-target structures and the general anatomy, such as blood vessels, bone, and/or glandular structures. The anatomical locations can be provided to a user (e.g., on the display 112) as a two-dimensional map (e.g., illustrating relative intensities, illustrating specific sites of potential target structures) and/or as a three-dimensional image. This information can be used to differentiate structures on a submicron, cellular level and identify very specific target structures (e.g., hyperactive parasympathetic nerves). The method can also predict the ablation patterns of the end effector 114 based on different electrode neuromodulation protocol and, optionally, superimpose the

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predicted neuromodulation patterns onto the mapped anatomy to indicate to the user which anatomical structures will be affected by a specific neuromodulation protocol. For example, when the predicted neuromodulation pattern is displayed in relation to the mapped anatomy, a clinician can determine whether target structures will be appropriately ablated and whether non-target structures (e.g., blood vessels) will be undesirably exposed to the therapeutic neuromodulation energy. Thus, the method can be used for planning neuromodulation therapy to locate very specific target structures, avoid non-target structures, and select electrode neuromodulation protocols.

Once the target structure is located and a desired electrode neuromodulation protocol has been selected, the method continues by applying therapeutic neuromodulation to the target structure. The neuromodulation energy can be applied to the tissue in a highly targeted manner that forms micro-lesions to selectively modulate the target structure, while avoiding non-targeted blood vessels and allowing the surrounding tissue structure to remain healthy for effective wound healing. In some embodiments, the neuromodulation energy can be applied in a pulsed manner, allowing the tissue to cool between modulation pulses to ensure appropriate modulation without undesirably affecting non-target tissue. In some embodiments, the neuromodulation algorithm can deliver pulsed RF energy between different pairs of the electrodes 136 in a time sequenced rotation until neuromodulation is predicted to be complete (i.e., "multiplexing"). For example, the end effector 114 can deliver neuromodulation energy (e.g., having a power of 5-10 W (e.g., 7 W, 8 W, 9 W) and a current of about 50-100 mA) via adjacent pairs of the electrodes 136 until at least one of the following conditions is met: (a) load resistance reaches a predefined maximum resistance (e.g., 350Ω); (b) a thermocouple temperature associated with the electrode pair reaches a predefined maximum temperature (e.g., 80° C.); or (c) a predetermined time period has elapsed (e.g., 10 seconds). After the predetermined conditions are met, the end effector 114 can move to the next pair of electrodes in the sequence, and the neuromodulation algorithm can terminate when all of the load resistances of the individual pairs of electrodes is at or above a predetermined threshold (e.g., 100Ω). In various embodiments, the RF energy can be applied at a predetermined frequency (e.g., 450-500 kHz) and is expected to initiate ionic agitation of the specific target structure, while avoiding functional disruption of non-target structures.

During and/or after neuromodulation therapy, the method continues by detecting and, optionally, mapping the post-therapy bioelectric properties of the target site. This can be performed in a similar manner as described above. The post-therapy evaluation can indicate if the target structures (e.g., hyperactive parasympathetic nerves) were adequately modulated or ablated. If the target structures are not adequately modulated (i.e., if neural activity is still detected in the target structure and/or the neural activity has not decreased), the method can continue by again applying therapeutic neuromodulation to the target. If the target structures were adequately ablated, the neuromodulation procedure can be completed.

Detection of Anatomical Structures and Function

Various embodiments of the present technology can include features that measure bio-electric, dielectric, and/or other properties of tissue at target sites to determine the presence, location, and/or activity of neural structures and other anatomical structures and, optionally, map the locations of the detected neural structures and/or other anatomical structures. For example, the present technology can be used to detect glandular structures and, optionally, their mucoserous functions and/or other functions. The present technology can also be configured to detect vascular structures (e.g., arteries) and, optionally, their arterial functions, volumetric pressures, and/or other functions. The mapping features discussed below can be incorporated into any the system 100 and/or any other devices disclosed herein to provide an accurate depiction of nerves at the target site.

Neural and/or anatomical detection can occur (a) before the application of a therapeutic neuromodulation energy to determine the presence or location of neural structures and other anatomical structures (e.g., blood vessels, glands, etc.) at the target site and/or record baseline levels of neural activity; (b) during therapeutic neuromodulation to determine the real-time effect of the energy application on the neural fibers at the treatment site; and/or (c) after therapeutic neuromodulation to confirm the efficacy of the treatment on the targeted structures (e.g., nerves glands, etc.). This allows for the identification of very specific anatomical structures (even to the micro-scale or cellular level) and, therefore, provides for highly targeted neuromodulation. This enhances the efficacy and efficiency of the neuromodulation therapy. In addition, the anatomical mapping reduces the collateral effects of neuromodulation therapy to non-target sites.

Accordingly, the targeted neuromodulation inhibits damage or rupture of blood vessels (i.e., inhibits undesired bleeding) and collateral damage to tissue that may be of concern during wound healing (e.g., when damage tissue sloughs off of the wall of the nasal wall).

In certain embodiments, the systems disclosed herein can use bioelectric measurements, such as impedance, resistance, voltage, current density, and/or other parameters (e.g., temperature) to determine the anatomy, in particular the neural, glandular, and vascular anatomy, at the target site. The bioelectric properties can be detected after the transmission of a stimulus (e.g., an electrical stimulus, such as RF energy delivered via the electrodes 136; i.e., "dynamic" detection) and/or without the transmission of a stimulus (i.e., "static" detection).

Dynamic measurements include various embodiments to excite and/or detect primary or secondary effects of neural activation and/or propagation. Such dynamic embodiments involve the heightened states of neural activation and propagation and use this dynamic measurement for nerve location and functional identification relative to the neighboring tissue types. For example, a method of dynamic detection can include: (1) delivering stimulation energy to a treatment site via a treatment device (e.g., the end effector 114) to excite parasympathetic nerves at the treatment site; (2) measuring one or more physiological parameters (e.g., resistance, impedance, etc.) at the treatment site via a measuring/sensing array of the treatment device (e.g., the electrodes 136); (4) based on the measurements, identifying the relative presence and position of parasympathetic nerves at the treatment site; and (5) delivering ablation energy to the identified parasympathetic nerves to block the detected para-sympathetic nerves.

Static measurements include various embodiments associated with specific native properties of the stratified or cellular composition at or near the treatment site. The static embodiments are directed to inherent biologic and electrical properties of tissue types at or near the treatment site, the stratified or cellular compositions at or near the treatment site, and contrasting both foregoing measurements with tissue types adjacent the treatment site (and that are not targeted for neuromodulation). This information can be used to localize specific targets (e.g., parasympathetic fibers) and non-targets (e.g., vessels, sensory nerves, etc.). For example, a method of static detection can include: (1) before ablation, utilizing a measuring/sensing array of a treatment device (e.g., the electrodes 136) to determine one or more baseline physiological parameters; (2) geometrically identifying inherent tissue properties within a region of interest based on the measured physiological parameters (e.g., resistance, impedance, etc.); (3) delivering

ablation energy to one or more nerves within the region of via treatment device interest; (4) during the delivery of the ablation energy, determining one or more mid-procedure physiological parameters via the measuring/sensing array; and (5) after the delivery of ablation energy, determining one or more post-procedure physiological parameters via the measurement/sensing array to determine the effectiveness of the delivery of the ablation energy on blocking the nerves that received the ablation energy.

After the initial static and/or dynamic detection of bioelectric properties, the location of anatomical features can be used to determine where the treatment site(s) should be with respect to various anatomical structures for therapeutically effective neuromodulation of the targeted parasympathetic nasal nerves. The bioelectric and other physiological properties described herein can be detected via electrodes (e.g., the electrodes 136 of the end effector 114), and the electrode pairings on a device (e.g., end effector 114) can be selected to obtain the bioelectric data at specific zones or regions and at specific depths of the targeted regions. The specific properties detected at or surrounding target neuromodulation sites and associated methods for obtaining these properties are described below. These specific detection and mapping methods discussed below are described with reference to the system 100 , although the methods can be implemented on other suitable systems and devices that provide for anatomical identification, anatomical mapping and/or neuromodulation therapy.

Neural Identification and Mapping

In many neuromodulation procedures, it is beneficial to identify the portions of the nerves that fall within a zone and/or region of influence (referred to as the "interest zone") of the energy delivered by a neuromodulation device 102, as well as the relative three-dimensional position of the neural structures relative to the neuromodulation device 102. Characterizing the portions of the neural structures within the interest zone and/or determining the relative positions of the neural structures within the interest zone enables the clinician to (1) selectively activate target neural structures over non-target structures (e.g., blood vessels), and (2) sub-select specific targeted neural structures (e.g., parasympathetic nerves) over non-target neural structures (e.g., sensory nerves, subgroups of neural structures, neural structures having certain compositions or morphologies). The target structures (e.g., parasympathetic nerves) and non-target structures

(e.g., blood vessels, sensory nerves, etc.) can be identified based on the inherent signatures of specific structures, which are defined by the unique morphological compositions of the structures and the bioelectrical properties associated with these morphological compositions. For example, unique, discrete frequencies can be associated with morphological compositions and, therefore, be used to identify certain structures. The target and non-target structures can also be identified based on relative bioelectrical activation of the structures to sub-select specific neuronal structures. Further, target and non-target structures can be identified by the differing detected responses of the structures to a tailored injected stimuli. For example, the systems described herein can detect the magnitude of response of structures and the difference in the responses of anatomical structures with respect to differing stimuli (e.g., stimuli injected at different frequencies).

At least for purposes of this disclosure, a nerve can include the following portions that are defined based on their respective orientations relative to the interest zone: terminating neural structures (e.g., terminating axonal structures), branching neural structures (e.g., branching axonal structures), and travelling neural structures (e.g., travelling axonal structures). For example, terminating neural structures enter the zone but do not exit. As such, terminating neural structures are terminal points for neuronal signaling and activation. Branching neural structures are nerves that enter the interest zone and increase number of nerves exiting the interest zone. Branching neural structures are typically associated with a reduction in relative geometry of nerve bundle. Travelling neural structures are nerves that enter the interest zone and exit the zone with no substantially no change in geometry or numerical value.

The system 100 can be used to detect voltage, current, complex impedance, resistance, permittivity, and/or conductivity, which are tied to the compound action potentials of nerves, to determine and/or map the relative positions and proportionalities of nerves in the interest zone. Neuronal cross-sectional area ("CSA") is expected to be due to the increase in axonic structures. Each axon is a standard size. Larger nerves (in cross-sectional dimension) have a larger number of axons than nerves having smaller cross-sectional dimensions. The compound action responses from the larger nerves, in both static and dynamic assessments, are greater than smaller nerves. This is at least in part because the compound action potential is the cumulative action response from each of the axons. When using static analysis, for example, the system 100 can directly measure and map impedance or resistance of nerves and, based on the determined

impedance or resistance, determine the location of nerves and/or relative size of the nerves. In dynamic analysis, the system 100 can be used to apply a stimulus to the interest zone and detect the dynamic response of the neural structures to the stimulus. Using this information, the system 100 can determine and/or map impedance or resistance in the interest zone to provide information related to the neural positions or relative nerve sizes. Neural impedance mapping can be illustrated by showing the varying complex impedance levels at a specific location at differing cross-sectional depths. In other embodiments, neural impedance or resistance can be mapped in a three-dimensional display.

Identifying the portions and/or relative positions of the nerves within the interest zone can inform and/or guide selection of one or more treatment parameters (e.g., electrode ablation patterns, electrode activation plans, etc.) of the system 100 for improving treatment efficiency and efficacy. For example, during neural monitoring and mapping, the system 100 can identify the directionality of the nerves based at least in part on the length of the neural structure extending along the interest zone, relative sizing of the neural structures, and/or the direction of the action potentials. This information can then be used by the system 100 or the clinician to automatically or manually adjust treatment parameters (e.g., selective electrode activation, bipolar and/or multipolar activation, and/or electrode positioning) to target specific nerves or regions of nerves. For example, the system 100 can selectively activate specific electrodes 136, electrode combinations (e.g., asymmetric or symmetric), and/or adjust the bi-polar or multi-polar electrode configuration. In some embodiments, the system 100 can adjust or select the waveform, phase angle, and/or other energy delivery parameters based on the nerve portion/position mapping and/or the nerve proportionality mapping. In some embodiments, structure and/or properties of the electrodes 136 themselves (e.g., material, surface roughening, coatings, cross-sectional area, perimeter, penetrating, penetration depth, surface-mounted, etc.) may be selected based on the nerve portion and proportionality mapping.

In various embodiments, treatment parameters and/or energy delivery parameters can be adjusted to target on-axis or near axis travelling neural structures and/or avoid the activation of traveling neural structures that are at least generally perpendicular to the end effector 114. Greater portions of the on-axis or near axis travelling neural structures are exposed and susceptible to the neuromodulation energy provided by the end effector 114 than a perpendicular travelling neural structure, which may only be exposed to therapeutic energy at a discrete cross-

section. Therefore, the end effector 114 is more likely to have a greater effect on the on-axis or near axis travelling neural structures. The identification of the neural structure positions (e.g., via complex impedance or resistance mapping) can also allow targeted energy delivery to travelling neural structures rather than branching neural structures (typically downstream of the travelling neural structures) because the travelling neural structures are closer to the nerve origin and, therefore, more of the nerve is affected by therapeutic neuromodulation, thereby resulting in a more efficient treatment and/or a higher efficacy of treatment. Similarly, the identification of neural structure positions can be used to target travelling and branching neural structures over terminal neural structures. In some embodiments, the treatment parameters can be adjusted based on the detected neural positions to provide a selective regional effect. For example, a clinician can target downstream portions of the neural structures if only wanting to influence partial effects on very specific anatomical structures or positions.

In various embodiments, neural locations and/or relative positions of nerves can be determined by detecting the nerve-firing voltage and/or current over time. An array of the electrodes 136 can be positioned in contact with tissue at the interest zone, and the electrodes 136 can measure the voltage and/or current associated with nerve-firing. This information can optionally be mapped (e.g., on a display 112) to identify the location of nerves in a hyper state (i.e., excessive parasympathetic tone). Rhinitis is at least in part the result of over-firing nerves because this hyper state drives the hyper-mucosal production and hyper-mucosal secretion. Therefore, detection of nerve firing rate via voltage and current measurements can be used to locate the portions of the interest region that include hyper-parasympathetic neural function (i.e., nerves in the diseased state). This allows the clinician to locate specific nerves (i.e., nerves with excessive parasympathetic tone) before neuromodulation therapy, rather than simply targeting all parasympathetic nerves (including non-diseased state parasympathetic nerves) to ensure that the correct tissue is treated during neuromodulation therapy. Further, nerve firing rate can be detected during or after neuromodulation therapy so that the clinician can monitor changes in nerve firing rate to validate treatment efficacy. For example, recording decreases or elimination of nerve firing rate after neuromodulation therapy can indicate that the therapy was effective in therapeutically treating the hyper/diseased nerves.

In various embodiments, the system 100 can detect neural activity using dynamic activation by injecting a stimulus signal (i.e., a signal that temporarily activates nerves) via one

or more of the electrodes 136 to induce an action potential, and other pairs of electrodes 136 can detect bioelectric properties of the neural response. Detecting neural structures using dynamic activation involves detecting the locations of action potentials within the interest zone by measuring the discharge rate in neurons and the associated processes. The ability to numerically measure, profile, map, and/or image fast neuronal depolarization for generating an accurate index of activity is a factor in measuring the rate of discharge in neurons and their processes. The action potential causes a rapid increase in the voltage across nerve fiber and the electrical impulse then spreads along the fiber. As an action potential occurs, the conductance of a neural cell membrane changes, becoming about 40 times larger than it is when the cell is at rest. During the action potential or neuronal depolarization, the membrane resistance diminishes by about 80 times, thereby allowing an applied current to enter the intracellular space as well. Over a population of neurons, this leads to a net decrease in the resistance during coherent neuronal activity, such as chronic para-sympathetic responses, as the intracellular space will provide additional conductive ions. The magnitude of such fast changes has been estimated to have local resistivity changes with recording near DC is 2.8-3.7% for peripheral nerve bundles (e.g., including the nerves in the nasal cavity).

Detecting neural structures using dynamic activation includes detecting the locations of action potentials within the interest zone by measuring the discharge rate in neurons and the associated processes. The basis of each this discharge is the action potential, during which there is a depolarization of the neuronal membrane of up to 110 mV or more, lasting approximately 2 milliseconds, and due to the transfer of micromolar quantities of ions (e.g., sodium and potassium) across the cellular membrane. The complex impedance or resistance change due to the neuronal membrane falls from 1000 to 25 Ωcm. The introduction of a stimulus and subsequent measurement of the neural response can attenuate noise and improve signal to noise ratios to precisely focus on the response region to improve neural detection, measurement, and mapping.

In some embodiments, the difference in measurements of physiological parameters (e.g., complex impedance, resistance, voltage) over time, which can reduce errors, can be used to create a neural profiles, spectrums, or maps. For example, the sensitivity of the system 100 can be improved because this process provides repeated averaging to a stimulus. As a result, the mapping function outputs can be a unit-less ratio between the reference and test collated data at a

single frequency and/or multiple frequencies and/or multiple amplitudes. Additional considerations may include multiple frequency evaluation methods that consequently expand the parameter assessments, such as resistivity, admittivity, center frequency, or ratio of extra- to intracellular resistivity.

In some embodiments, the system 100 may also be configured to indirectly measure the electrical activity of neural structures to quantify the metabolic recovery processes that accompany action potential activity and act to restore ionic gradients to normal. These are related to an accumulation of ions in the extracellular space. The indirect measurement of electrical activity can be approximately a thousand times larger (in the order of millimolar), and thus are easier to measure and can enhance the accuracy of the measured electrical properties used to generate the neural maps.

The system 100 can perform dynamic neural detection by detecting nerve-firing voltage and/or current and, optionally, nerve firing rate over time, in response to an external stimulation of the nerves. For example, an array of the electrodes 136 can be positioned in contact with tissue at the interest zone, one or more of the electrodes 136 can be activated to inject a signal into the tissue that stimulates the nerves, and other electrodes 136 of the electrode array can measure the neural voltage and/or current due to nerve firing in response to the stimulus. This information can optionally be mapped (e.g., on a display 112) to identify the location of nerves and, in certain embodiments, identify parasympathetic nerves in a hyper state (e.g., indicative of Rhinitis or other diseased state). The dynamic detection of neural activity (voltage, current, firing rate, etc.) can be performed before neuromodulation therapy to detect target nerve locations to select the target site and treatment parameters to ensure that the correct tissue is treated during neuromodulation therapy. Further, dynamic detection of neural activity can be performed during or after neuromodulation therapy to allow the clinician to monitor changes in neural activity to validate treatment efficacy. For example, recording decreases or elimination of neural activity after neuromodulation therapy can indicate that the therapy was effective in therapeutically treating the hyper/diseased nerves.

In some embodiments, a stimulating signal can be delivered to the vicinity of the targeted nerve via one or more penetrating electrodes (e.g., microneedles that penetrate tissue) associated with the end effector 114 and/or a separate device. The stimulating signal generates an action potential, which causes smooth muscle cells or other cells to contract. The location and strength

of this contraction can be detected via the penetrating electrode(s) and, thereby, indicate to the clinician the distance to the nerve and/or the location of the nerve relative to the stimulating needle electrode. In some embodiments, the stimulating electrical signal may have a voltage of typically 1-2 mA or greater and a pulse width of typically 100-200 microseconds or greater. Shorter pulses of stimulation result in better discrimination of the detected contraction, but may require more current. The greater the distance between the electrode and the targeted nerve, the more energy is required to stimulate. The stimulation and detection of contraction strength and/or location enables identification of how close or far the electrodes are from the nerve, and therefore can be used to localize the nerve spatially. In some embodiments, varying pulse widths may be used to measure the distance to the nerve. As the needle becomes closer to the nerve, the pulse duration required to elicit a response becomes less and less.

To localize nerves via muscle contraction detection, the system 100 can vary pulse-width or amplitude to vary the energy (Energy=pulse-width*amplitude) of the stimulus delivered to the tissue via the penetrating electrode(s). By varying the stimulus energy and monitoring muscle contraction via the penetrating electrodes and/or other type of sensor, the system 100 can estimate the distance to the nerve. If a large amount of energy is required to stimulate the nerve/contract the muscle, the stimulating/penetrating electrode is far from the nerve. As the stimulating/penetrating electrode, moves closer to the nerve, the amount of energy required to induce muscle contraction will drop. For example, an array of penetrating electrodes can be positioned in the tissue at the interest zone and one or more of the electrodes can be activated to apply stimulus at different energy levels until they induce muscle contraction. Using an iterative process, localize the nerve (e.g., via the mapping/evaluation/feedback algorithm 110).

In some embodiments, the system 100 can measure the muscular activation from the nerve stimulus (e.g., via the electrodes 136) to determine neural positioning for neural mapping, without the use of penetrating electrodes. In this embodiment, the treatment device targets the smooth muscle cells' varicosities surrounding the submucosal glands and the vascular supply, and then the compound muscle action potential. This can be used to summate voltage response from the individual muscle fiber action potentials. The shortest latency is the time from stimulus artifact to onset of the response. The corresponding amplitude is measured from baseline to negative peak and measured in millivolts (mV). Nerve latencies (mean±SD) in adults typically range about 2-6 milliseconds, and more typically from about 3.4±0.8 to about 4.0±0.5

milliseconds. A comparative assessment may then be made which compares the outputs at each time interval (especially pre- and post-energy delivery) in addition to a group evaluation using the alternative nasal cavity. This is expected to provide an accurate assessment of the absolute value of the performance of the neural functioning because muscular action/activation may be used to infer neural action/activation and muscle action/activation is a secondary effect or by-product whilst the neural function is the absolute performance measure.

In some embodiments, the system 100 can record a neuromagnetic field outside of the nerves to determine the internal current of the nerves without physical disruption of the nerve membrane. Without being bound by theory, the contribution to the magnetic field from the current inside the membrane is two orders of magnitude larger than that from the external current, and that the contribution from current within the membrane is substantially negligible. Electrical stimulation of the nerve in tandem with measurements of the magnetic compound action fields ("CAFs") can yield sequential positions of the current dipoles such that the location of the conduction change can be estimated (e.g., via the least-squares method). Visual representation (e.g., via the display 112) using magnetic contour maps can show normal or non-normal neural characteristics (e.g., normal can be equated with a characteristic quadrupolar pattern propagating along the nerve), and therefore indicate which nerves are in a diseases, hyperactive state and suitable targets for neuromodulation.

During magnetic field detection, an array of the electrodes 136 can be positioned in contact with tissue at the interest zone and, optionally, one or more of the electrodes 136 can be activated to inject an electrical stimulus into the tissue. As the nerves in the interest zone fire (either in response to a stimulus or in the absence of it), the nerve generates a magnetic field (e.g., similar to a current carrying wire), and therefore changing magnetic fields are indicative of the nerve nerve-firing rate. The changing magnetic field caused by neural firing can induce a current detected by nearby sensor wire (e.g., the sensor 314) and/or wires associated with the nearby electrodes 136. By measuring this current, the magnetic field strength can be determined. The magnetic fields can optionally be mapped (e.g., on a display 112) to identify the location of nerves and select target nerves (nerves with excessive parasympathetic tone) before neuromodulation therapy to ensure that the desired nerves are treated during neuromodulation therapy. Further, the magnetic field information can be used during or after neuromodulation

therapy so that the clinician can monitor changes in nerve firing rate to validate treatment efficacy.

In other embodiments, the neuromagnetic field is measured with a Hall Probe or other suitable device, which can be integrated into the end effector 114 and/or part of a separate device delivered to the interest zone. Alternatively, rather than measuring the voltage in the second wire, the changing magnetic field can be measured in the original wire (i.e. the nerve) using a Hall probe. A current going through the Hall probe will be deflected in the semi-conductor. This will cause a voltage difference between the top and bottom portions, which can be measured. In some aspects of this embodiments, three orthogonal planes are utilized.

In some embodiments, the system 100 can be used to induce electromotive force ("EMF") in a wire (i.e., a frequency-selective circuit, such as a tunable/LC circuit) that is tunable to resonant frequency of a nerve. In this embodiment, the nerve can be considered to be a current carrying wire, and the firing action potential is a changing voltage. This causes a changing current which, in turn, causes a changing magnetic flux (i.e., the magnetic field that is perpendicular to the wire). Under Faraday's Law of Induction/Faraday's Principle, the changing magnetic flux induces EMF (including a changing voltage) in a nearby sensor wire (e.g., integrated into the end effector 114, the sensor 314, and/or other structure), and the changing voltage can be measured via the system 100.

In further embodiments, the sensor wire (e.g., the sensor 314) is an inductor and, therefore, provides an increase of the magnetic linkage between the nerve (i.e., first wire) and the sensor wire (i.e., second wire), with more turns for increasing effect. (e.g., $V_{2,rms}=V_{1,rms}(N2/N1)$). Due to the changing magnetic field, a voltage is induced in the sensor wire, and this voltage can be measured and used to estimate current changes in the nerve. Certain materials can be selected to enhance the efficiency of the EMF detection. For example, the sensor wire can include a soft iron core or other high permeability material for the inductor.

During induced EMF detection, the end effector 114 and/or other device including a sensor wire is positioned in contact with tissue at the interest zone and, optionally, one or more of the electrodes 136 can be activated to inject an electrical stimulus into the tissue. As the nerves in the interest zone fire (either in response to a stimulus or in the absence of it), the nerve generates a magnetic field (e.g., similar to a current carrying wire) that induces a current in the sensor wire (e.g., the sensor 314). This information can be used to determine neural location

and/or map the nerves (e.g., on a display 112) to identify the location of nerves and select target nerves (nerves with excessive parasympathetic tone) before neuromodulation therapy to ensure that the desired nerves are treated during neuromodulation therapy. EMF information can also be used during or after neuromodulation therapy so that the clinician can monitor changes in nerve firing rate to validate treatment efficacy.

In some embodiments, the system 100 can detect magnetic fields and/or EMF generated at a selected frequency that corresponds to a particular type of nerve. The frequency and, by extension, the associated nerve type of the detected signal can be selected based on an external resonant circuit. Resonance occurs on the external circuit when it is matched to the frequency of the magnetic field of the particular nerve type and that nerve is firing. In manner, the system 100 can be used to locate a particular sub-group/type of nerves.

In some embodiments, the system 100 can include a variable capacitor frequency-selective circuit to identify the location and/or map specific nerves (e.g., parasympathetic nerve, sensory nerve, nerve fiber type, nerve subgroup, etc.). The variable capacitor frequency-selective circuit can be defined by the sensor 314 and/or other feature of the end effector 114. Nerves have different resonant frequencies based on their function and structure. Accordingly, the system 100 can include a tunable LC circuit with a variable capacitor (C) and/or variable inductor (L) that can be selectively tuned to the resonant frequency of desired nerve types. This allows for the detection of neural activity only associated with the selected nerve type and its associated resonant frequency. Tuning can be achieved by moving the core in and out of the inductor. For example, tunable LC circuits can tune the inductor by: (i) changing the number of coils around the core; (ii) changing the cross-sectional area of the coils around the core; (iii) changing the length of the coil; and/or (iv) changing the permeability of the core material (e.g., changing from air to a core material). Systems including such a tunable LC circuit provide a high degree of dissemination and differentiation not only as to the activation of a nerve signal, but also with respect to the nerve type that is activated and the frequency at which the nerve is firing.

Anatomical Mapping

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In various embodiments, the system 100 is further configured to provide minimally-invasive anatomical mapping that uses focused energy current/voltage stimuli from a spatially localized source (e.g., the electrodes 136) to cause a change in the conductivity of the of the tissue at the interest zone and detect resultant biopotential and/or bioelectrical measurements (e.g., via the electrodes 136). The current density in the tissue changes in response to changes of voltage applied by the electrodes 136, which creates a change in the electric current that can be measured with the end effector 114 and/or other portions of the system 100. The results of the bioelectrical and/or biopotential measurements can be used to predict or estimate relative absorption profilometry to predict or estimate the tissue structures in the interest zone. More specifically, each cellular construct has unique conductivity and absorption profiles that can be indicative of a type of tissue or structure, such as bone, soft tissue, vessels, nerves, types of nerves, and/or certain neural structures. For example, different frequencies decay differently through different types of tissue. Accordingly, by detecting the absorption current in a region, the system 100 can determine the underlying structure and, in some instances, to a sub-microscale, cellular level that allows for highly specialized target localization and mapping. This highly specific target identification and mapping enhances the efficacy and efficiency of neuromodulation therapy, while also enhancing the safety profile of the system 100 to reduce collateral effects on non-target structures.

To detect electrical and dielectric tissue properties (e.g., resistance, complex impedance, conductivity, and/or, permittivity as a function of frequency), the electrodes 136 and/or another electrode array is placed on tissue at an interest region, and an internal or external source (e.g., the generator 106) applies stimuli (current/voltage) to the tissue. The electrical properties of the tissue between the source and the receiver electrodes 136 are measured, as well as the current and/or voltage at the individual receiver electrodes 136. These individual measurements can then be converted into an electrical map/image/profile of the tissue and visualized for the user on the display 112 to identify anatomical features of interest and, in certain embodiments, the location of firing nerves. For example, the anatomical mapping can be provided as a color-coded or gray-scale three-dimensional or two-dimensional map showing differing intensities of certain bioelectric properties (e.g., resistance, impedance, etc.), or the information can be processed to map the actual anatomical structures for the clinician. This information can also be used during neuromodulation therapy to monitor treatment progression with respect to the anatomy, and after

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neuromodulation therapy to validate successful treatment. In addition, the anatomical mapping provided by the bioelectrical and/or biopotential measurements can be used to track the changes to non-target tissue (e.g., vessels) due to neuromodulation therapy to avoid negative collateral effects. For example, a clinician can identify when the therapy begins to ligate a vessel and/or damage tissue, and modify the therapy to avoid bleeding, detrimental tissue ablation, and/or other negative collateral effects.

Furthermore, the threshold frequency of electric current used to identify specific targets can subsequently be used when applying therapeutic neuromodulation energy. For example, the neuromodulation energy can be applied at the specific threshold frequencies of electric current that are target neuronal-specific and differentiated from other non-targets (e.g., blood vessels, non-target nerves, etc.). Applying ablation energy at the target-specific frequency results in an electric field that creates ionic agitation in the target neural structure, which leads to differentials in osmotic potentials of the targeted neural structures. These osmotic potential differentials cause dynamic changes in neuronal membronic potentials (resulting from the difference in intra-cellular and extra-cellular fluidic pressure) that lead to vacuolar degeneration of the targeted neural structures and, eventually, necrosis. Using the highly targeted threshold neuromodulation energy to initiate the degeneration allows the system 100 to delivery therapeutic neuromodulation to the specific target, while surrounding blood vessels and other non-target structures are functionally maintained.

In some embodiments, the system 100 can further be configured to detect bioelectrical properties of tissue by non-invasively recording resistance changes during neuronal depolarization to map neural activity with electrical impedance, resistance, bio-impedance, conductivity, permittivity, and/or other bioelectrical measurements. Without being bound by theory, when a nerve depolarizes, the cell membrane resistance decreases (e.g., by approximately 80×) so that current will pass through open ion channels and into the intracellular space. Otherwise the current remains in the extracellular space. For non-invasive resistance measurements, tissue can be stimulated by applying a current of less than 100 Hz, such as applying a constant current square wave at 1 Hz with an amplitude less than 25% (e.g., 10%) of the threshold for stimulating neuronal activity, and thereby preventing or reducing the likelihood that the current does not cross into the intracellular space or stimulating at 2 Hz. In either case,

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the resistance and/or complex impedance is recorded by recording the voltage changes. A complex impedance or resistance map or profile of the area can then be generated.

For impedance/conductivity/permittivity detection, the electrodes 136 and/or another electrode array are placed on tissue at an interest region, and an internal or external source (e.g., the generator 106) applies stimuli to the tissue, and the current and/or voltage at the individual receiver electrodes 136 is measured. The stimuli can be applied at different frequencies to isolate different types of nerves. These individual measurements can then be converted into an electrical map/image/profile of the tissue and visualized for the user on the display 112 to identify anatomical features of interest. The neural mapping can also be used during neuromodulation therapy to select specific nerves for therapy, monitor treatment progression with respect to the nerves and other anatomy, and validate successful treatment.

In some embodiments of the neural and/or anatomical detection methods described above, the procedure can include comparing the mid-procedure physiological parameter(s) to the baseline physiological parameter(s) and/or other, previously-acquired mid-procedure physiological parameter(s) (within the same energy delivery phase). Such a comparison can be used to analyze state changes in the treated tissue. The mid-procedure physiological parameter(s) may also be compared to one or more predetermined thresholds, for example, to indicate when to stop delivering treatment energy. In some embodiments of the present technology, the measured baseline, mid-, and post-procedure parameters include a complex impedance. In some embodiments of the present technology, the post-procedure physiological parameters are measured after a pre-determined time period to allow the dissipation of the electric field effects (ionic agitation and/or thermal thresholds), thus facilitating accurate assessment of the treatment.

In some embodiments, the anatomical mapping methods described above can be used to differentiate the depth of soft tissues within the nasal mucosa. The depth of mucosa on the turbinates is great whilst the depth off the turbinate is shallow and, therefore, identifying the tissue depth in the present technology also identifies positions within the nasal mucosa and where precisely to target. Further, by providing the micro-scale spatial impedance mapping of epithelial tissues as described above, the inherent unique signatures of stratified layers or cellular bodies can be used as identifying the region of interest. For example, different regions have

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larger or small populations of specific structures, such as submucosal glands, so target regions can be identified via the identification of these structures.

In some embodiments, the system 100 includes additional features that can be used to detect anatomical structures and map anatomical features. For example, the system 100 can include an ultrasound probe for identification of neural structures and/or other anatomical structures. Higher frequency ultrasound provides higher resolution, but less depth of penetration. Accordingly, the frequency can be varied to achieve the appropriate depth and resolution for neural/anatomical localization. Functional identification may rely on the spatial pulse length ("SPL") (wavelength multiplied by number of cycles in a pulse). Axial resolution (SPL/2) may also be determined to locate nerves.

In some embodiments, the system 100 can further be configured to emit stimuli with selective parameters that suppress rather than fully stimulate neural activity. for example, in embodiments where the strength-duration relationship for extracellular neural stimulation is selected and controlled, a state exists where the extracellular current can hyperpolarize cells, resulting in suppression rather than stimulation spiking behavior (i.e., a full action potential is not achieved). Both models of ion channels, HH and RGC, suggest that it is possible to hyperpolarize cells with appropriately designed burst extracellular stimuli, rather than extending the stimuli. This phenomenon could be used to suppress rather than stimulate neural activity during any of the embodiments of neural detection and/or modulation described herein.

In various embodiments, the system 100 could apply the anatomical mapping techniques disclosed herein to locate or detect the targeted vasculature and surrounding anatomy before, during, and/or after treatment.

Reference throughout this specification to "one embodiment" or "an embodiment" means that a particular feature, structure, or characteristic described in connection with the embodiment is included in at least one embodiment. Thus, appearances of the phrases "in one embodiment" or "in an embodiment" in various places throughout this specification are not necessarily all referring to the same embodiment. Furthermore, the particular features, structures, or characteristics may be combined in any suitable manner in one or more embodiments.

The terms and expressions which have been employed herein are used as terms of description and not of limitation, and there is no intention, in the use of such terms and expressions, of excluding any equivalents of the features shown and described (or portions

thereof), and it is recognized that various modifications are possible within the scope of the claims. Accordingly, the claims are intended to cover all such equivalents.

Incorporation by Reference

References and citations to other documents, such as patents, patent applications, patent publications, journals, books, papers, web contents, have been made throughout this disclosure. All such documents are hereby incorporated herein by reference in their entirety for all purposes.

Equivalents

Various modifications of the invention and many further embodiments thereof, in addition to those shown and described herein, will become apparent to those skilled in the art from the full contents of this document, including references to the scientific and patent literature cited herein. The subject matter herein contains important information, exemplification and guidance that can be adapted to the practice of this invention in its various embodiments and equivalents thereof.

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Claims

What is claimed is:

1. A method for improving a patient's sleep by treating at least one of rhinitis, congestion, and rhinorrhea within a sino-nasal cavity of a patient, the method comprising:

delivering energy to one or more target sites within a sino-nasal cavity of the patient to disrupt multiple neural signals to, and/or result in local hypoxia of, mucus producing and/or mucosal engorgement elements, thereby reducing production of mucus and/or mucosal engorgement within a nose of the patient and reducing or eliminate one or more symptoms associated with at least one of rhinitis, congestion, and rhinorrhea to improve nasal breathability of the patient.

2. The method of claim 1, wherein delivering energy results in ablation of targeted tissue at one or more locations to thereby disrupt the multiple neural signals to, and/or result in local hypoxia of, the mucus producing and/or mucosal engorgement elements within the nose.

3. The method of claim 2, wherein the targeted tissue is associated with one or more target sites proximate or inferior to a sphenopalatine foramen.

4. The method of claim 3, wherein energy is delivered at a level sufficient to therapeutically modulate postganglionic parasympathetic nerves innervating nasal mucosa at foramina and or microforamina of a palatine bone of the patient

5. The method of claim 4, wherein delivering energy causes multiple points of interruption of neural branches extending through foramina and microforamina of palatine bone.

6. The method of claim 2, wherein ablation of targeted tissue causes thrombus formation within one or more blood vessels associated with mucus producing and/or mucosal engorgement elements within the nose.

7. The method of claim 6, wherein the resulting local hypoxia of the mucus producing and/or mucosal engorgement elements results in decreased mucosal engorgement to thereby increase volumetric flow through a nasal passage of the patient.

8. The method of claim 2, wherein the ablation is thermal ablation.

9. The method of claim 8, wherein the thermal ablation is cyro-ablation.

10. The method of claim 2, wherein the ablation is caused by delivery of radiofrequency (RF) energy.

11. The method of claim 2, wherein the ablation is caused by a treatment device comprising a handle, an elongate body extending therefrom, and a retractable and expandable end effector operably associated with the elongate body.

12. The method of claim 11, wherein the end effector is advanced into the sino-nasal cavity under image guidance.

13. The method of claim 11, wherein the handle controls transformation of the end effector from a retracted state to an expanded state.

14. The method of claim 13, wherein the end effector comprises a plurality of energy delivery elements provided thereon.

15. The method of claim 14, wherein, when in the expanded state, the end effector positions one or more of the plurality of energy delivery elements relative to the one or more target sites.

16. The method of claim 15, wherein the end effector comprises a proximal segment that is spaced apart from a separate distal segment.

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17. The method of claim 16, wherein:

the proximal segment comprises a first set of flexible support elements arranged in a deployed configuration to fit around at least a portion of a middle turbinate at an anterior position relative to a lateral attachment and a posterior-inferior edge of the middle turbinate and position one or more energy delivery elements into contact with one or more respective tissue locations associated with the middle turbinate; and

the distal segment comprises a second set of flexible support elements configured in a deployed configuration to position one or more energy delivery elements into contact with one or more respective tissue locations in a cavity at a posterior position relative to the lateral attachment and posterior-inferior edge of the middle turbinate.

18. The method of claim 11, wherein the elongate body comprises a shaft to which the end effector is coupled, wherein the shaft comprises an outer sheath surrounding a hypotube or metallic member, wherein at least one of the outer sheath and hypotube and metallic member includes the one or more energy delivering elements provided thereon.

19. The method of claim 18, wherein the energy delivering elements are configured to deliver energy at one or more target sites associated with an inferior or middle turbinate within the sino-nasal cavity of the patient at a level sufficient to reduce engorgement of tissue associated therewith to thereby increase volumetric flow through a nasal passage of the patient.

20. The method of claim 1, wherein the one or more symptoms associated with at least one of rhinitis, congestion, and rhinorrhea are selected from the group consisting of nasal congestion, coughing, sneezing, and nasal or throat irritation and itching.

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Abstract

The invention generally relates to systems and methods for improving sleep by treating at least one of rhinitis, congestion, and/or rhinorrhea to thereby reduce or eliminate symptoms associated therewith, including, but not limited to, nasal congestion, coughing, sneezing, and nasal or throat irritation and itching.

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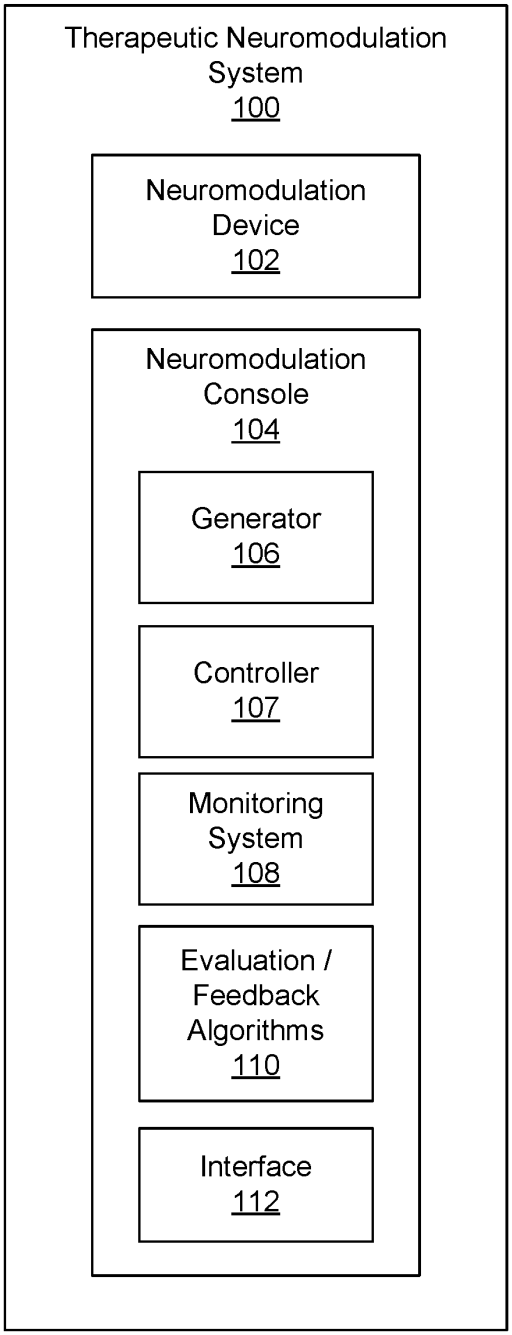

Therapeutic Neuromodulation System
100
Neuromodulation Device
102
Neuromodulation Console
104
Generator
106
Controller
107
Monitoring System
108
Evaluation / Feedback Algorithms
110
Interface
112

FIG. 1A

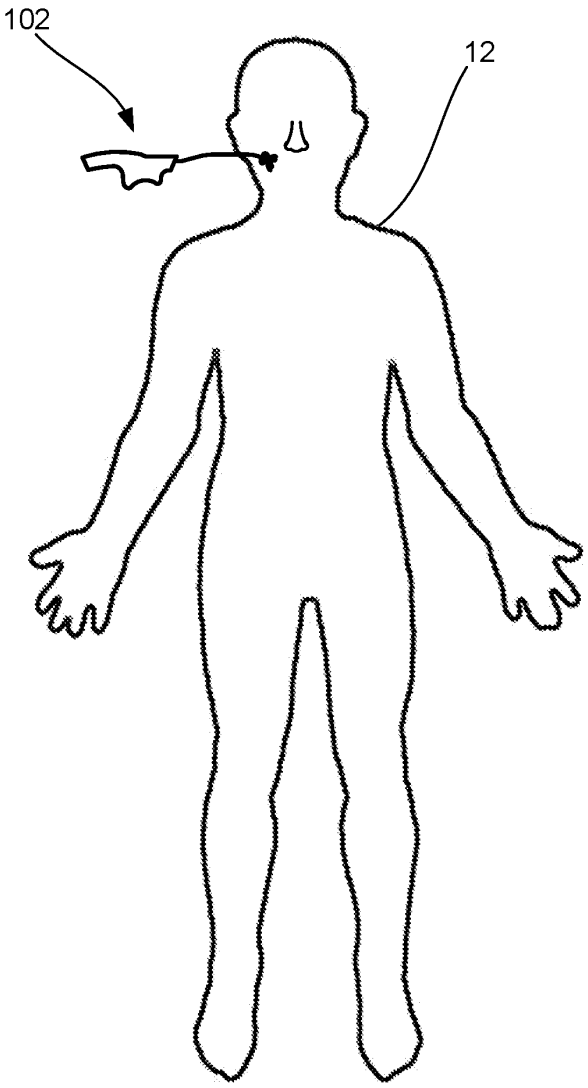

102
12

FIG. 1B

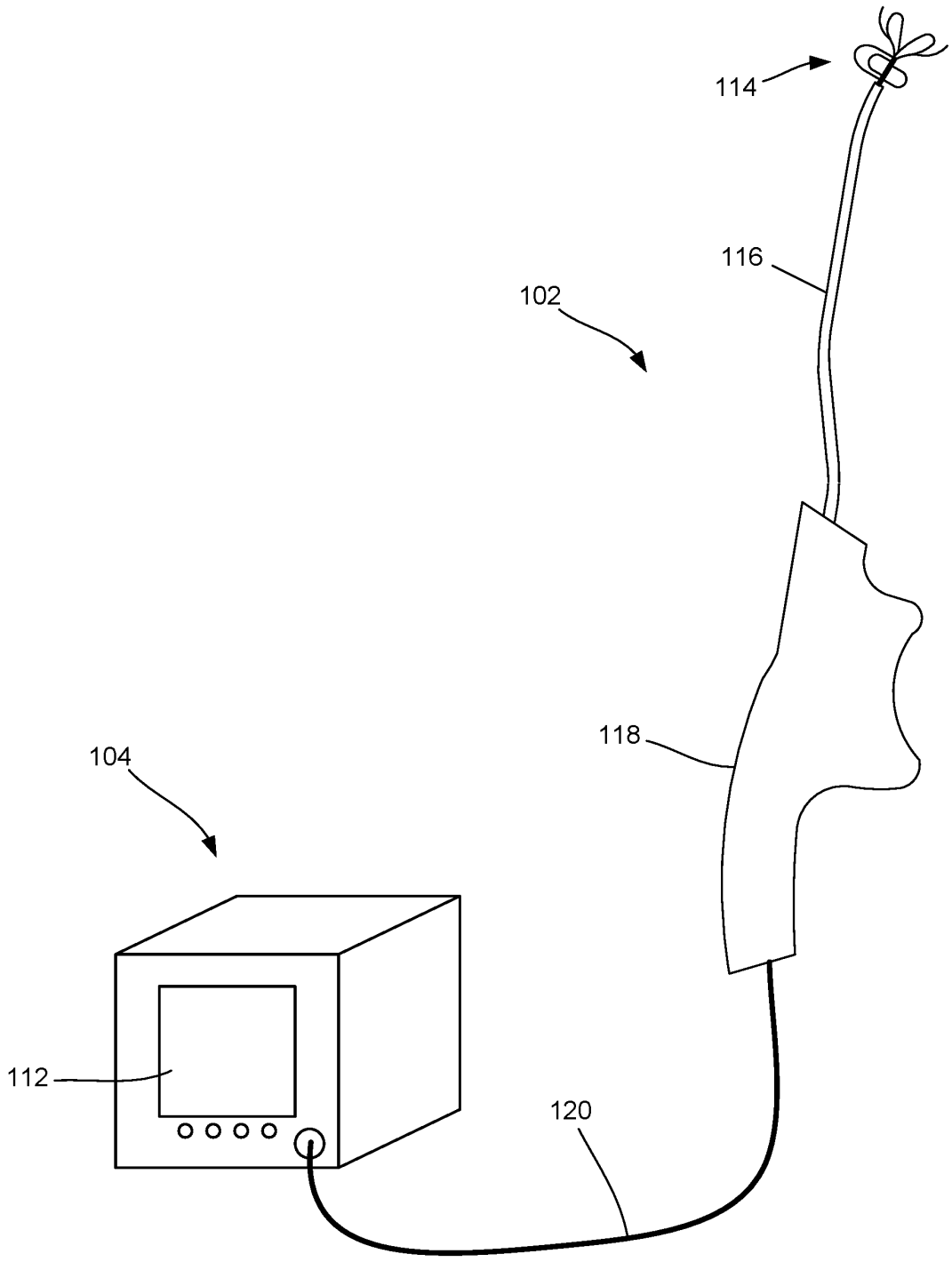


FIG. 2

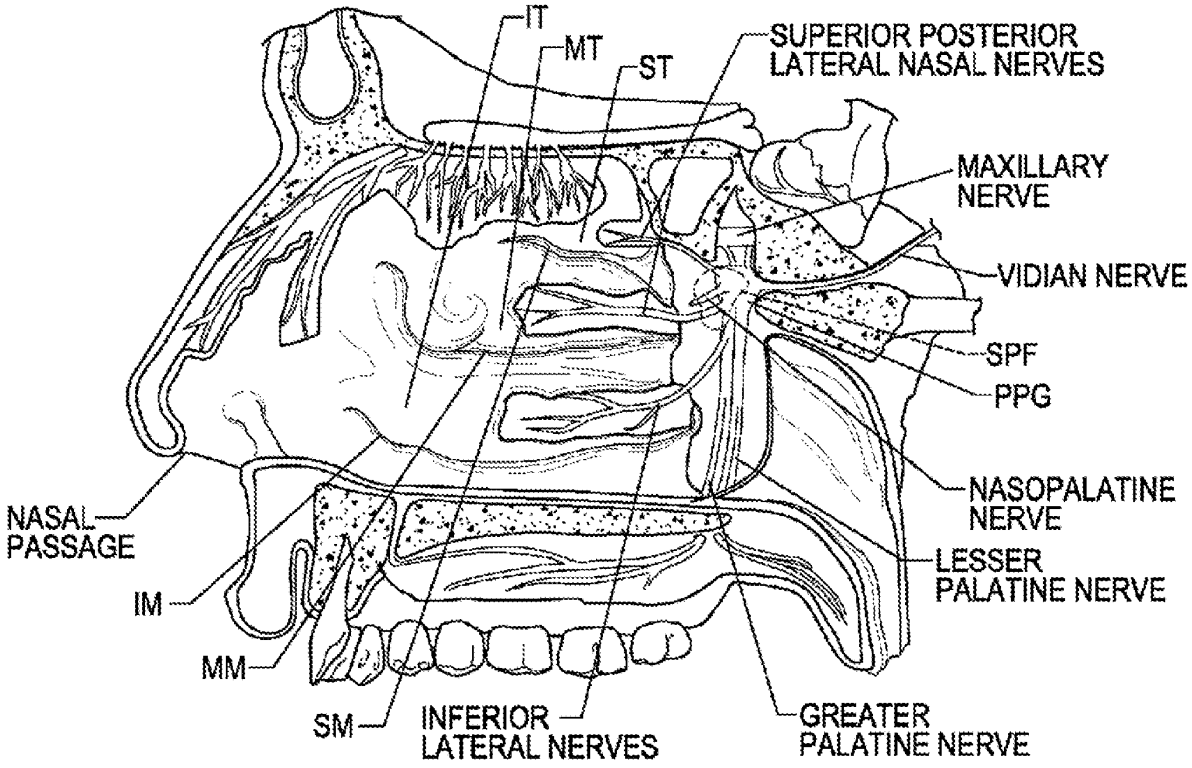

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LESSER
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INFERIOR
LATERAL NERVES
GREATER
PALATINE NERVE

FIG. 3A

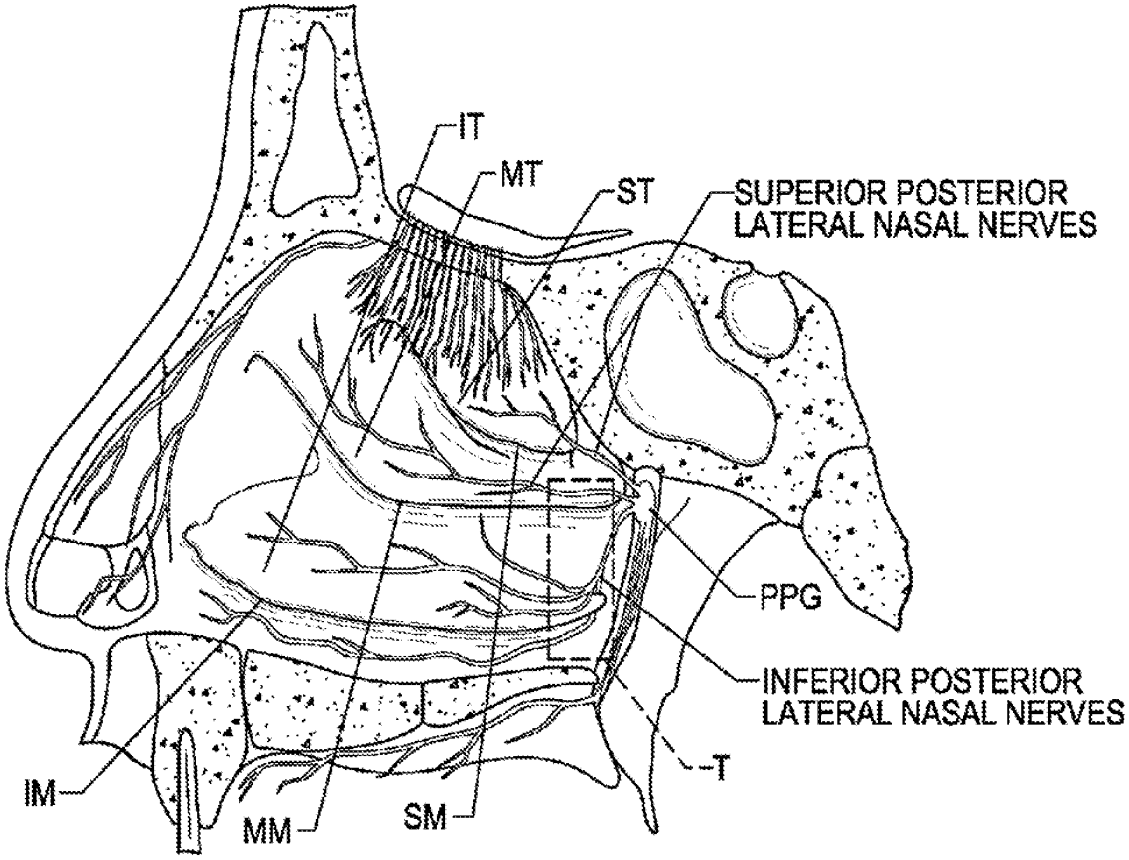

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FIG. 3B

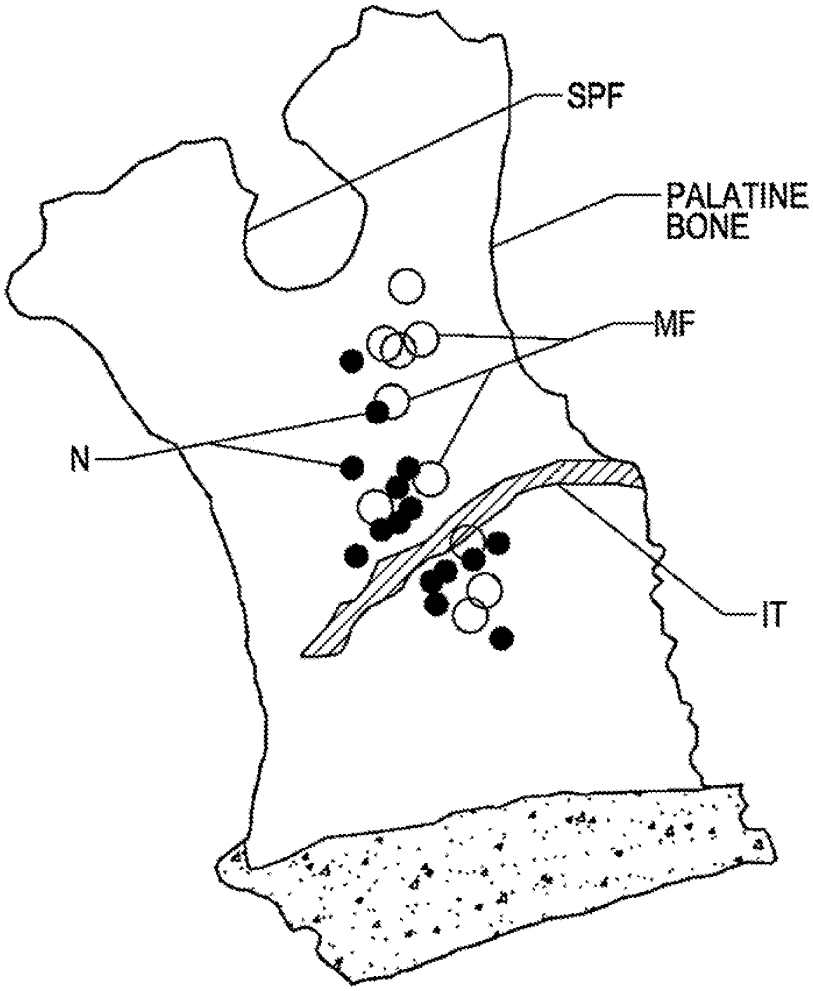


FIG. 3C

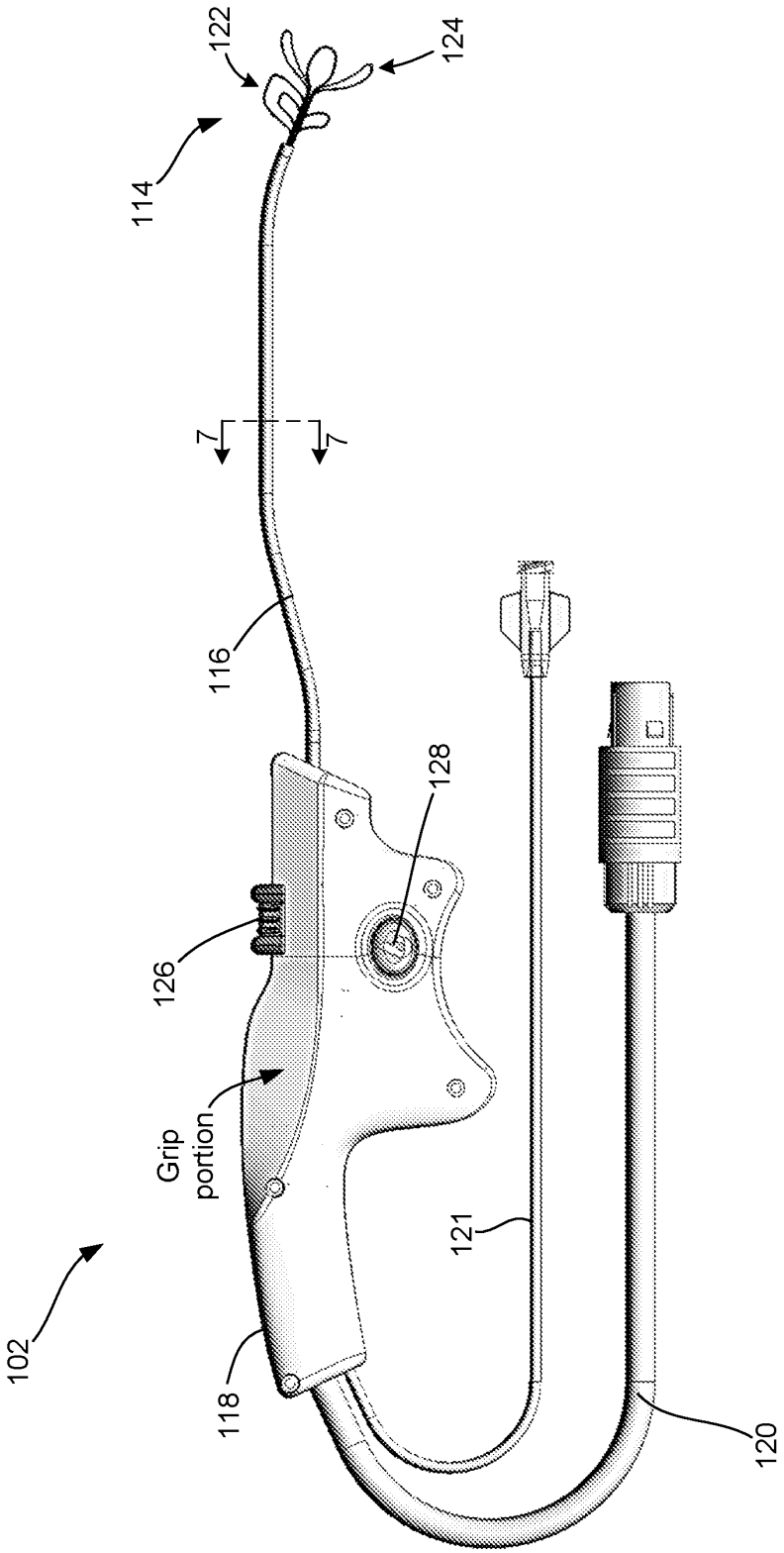


FIG. 4

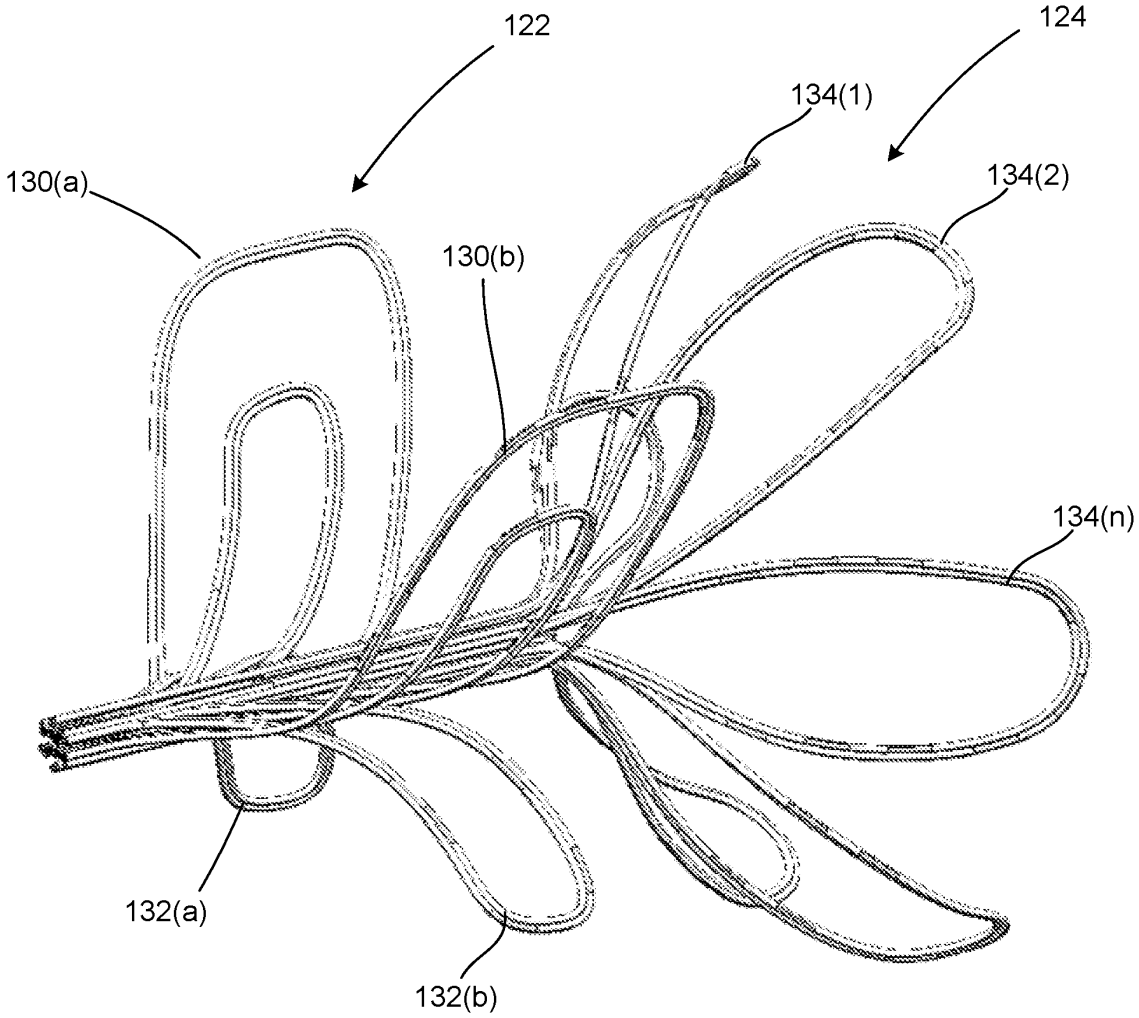


FIG. 5A

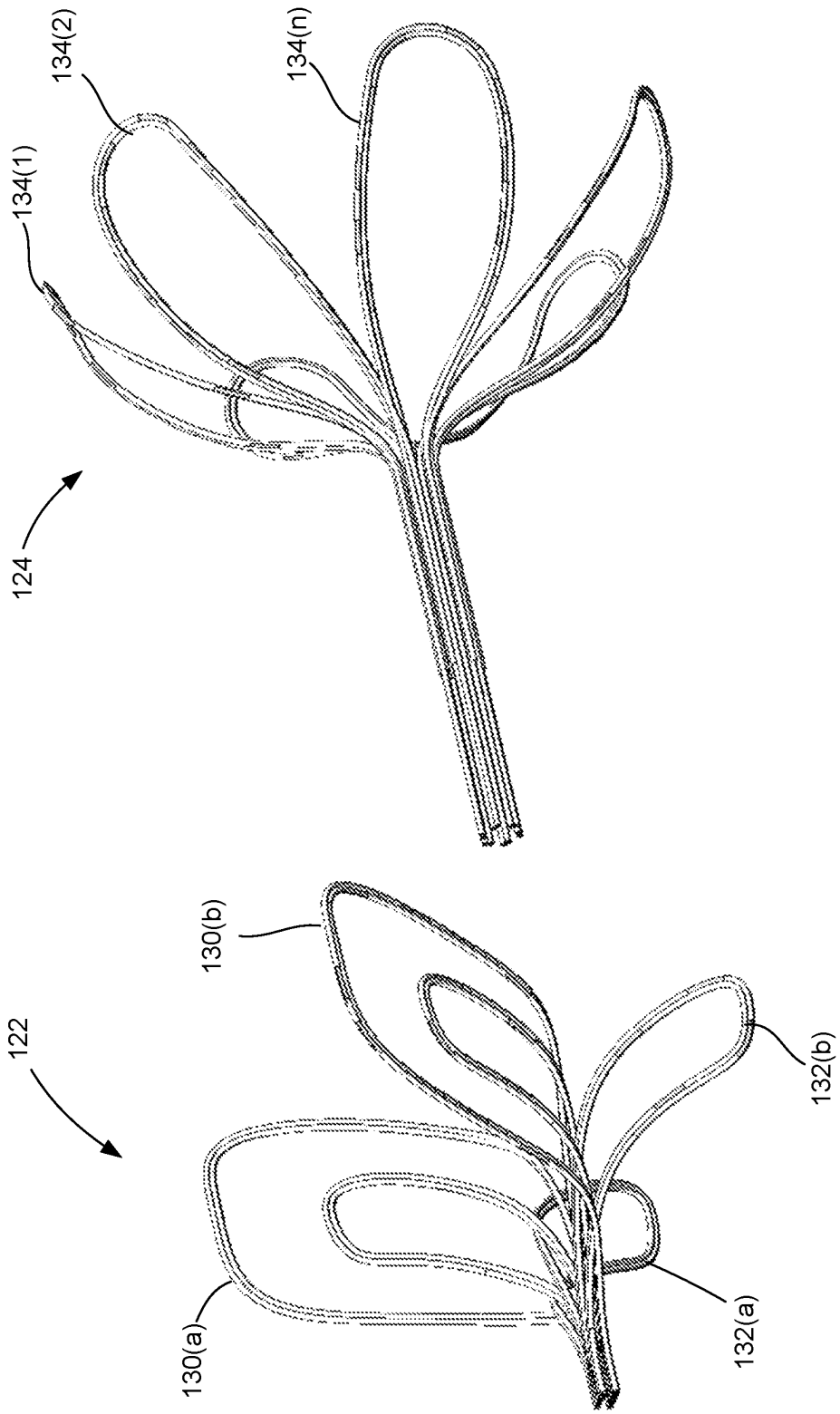


FIG. 5B

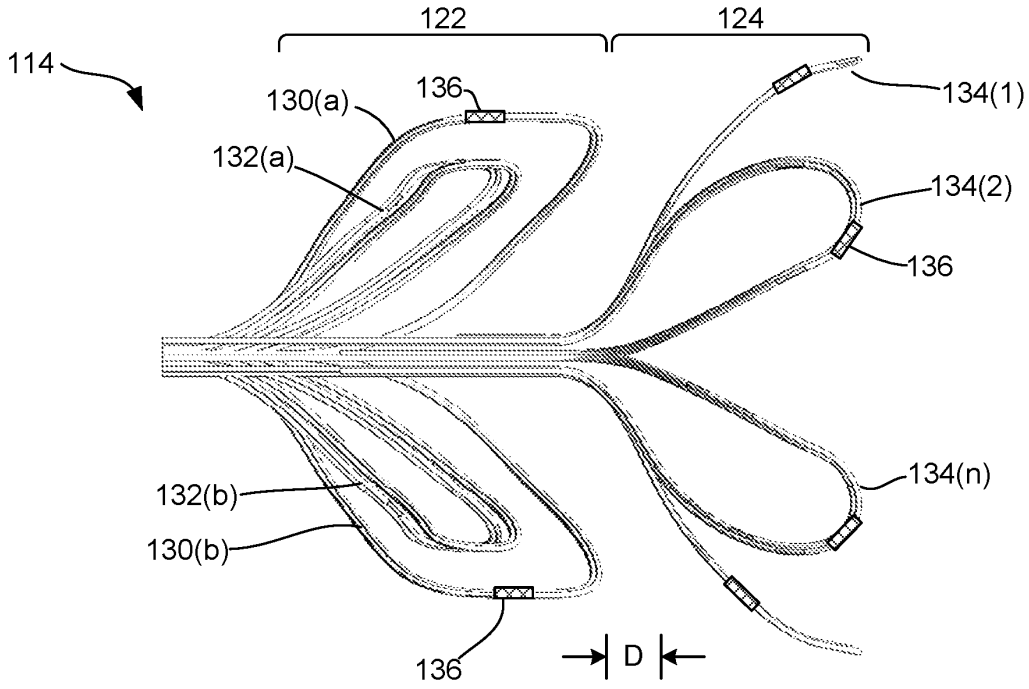

122
124
114
130(a)
136
134(1)
132(a)
134(2)
136
134(n)
132(b)
130(b)
136
D

FIG. 5C

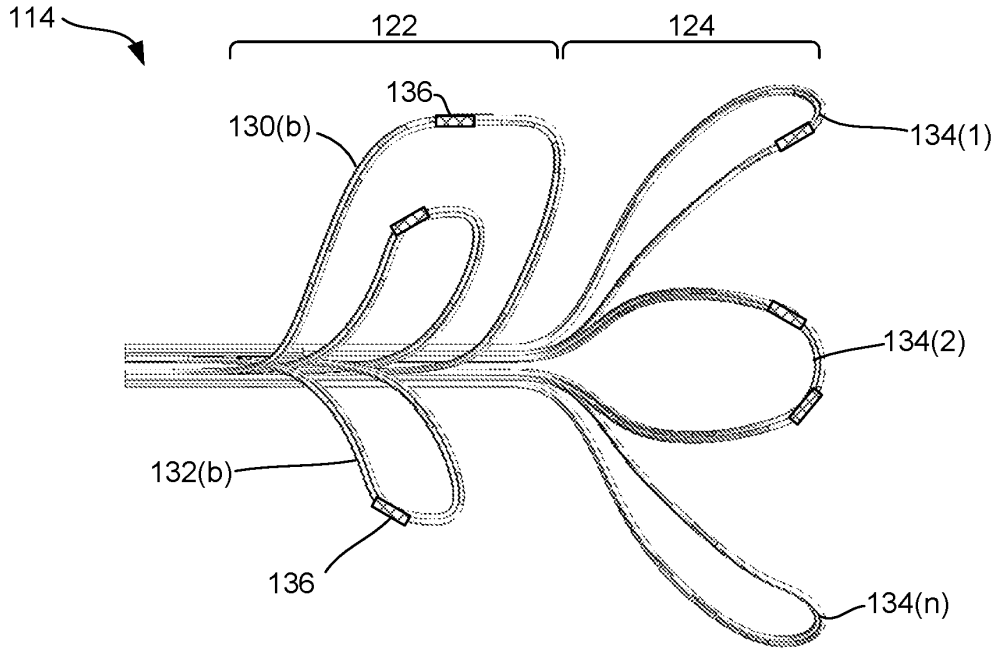

114
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124
136
130(b)
134(1)
134(2)
132(b)
136
134(n)

FIG. 5D

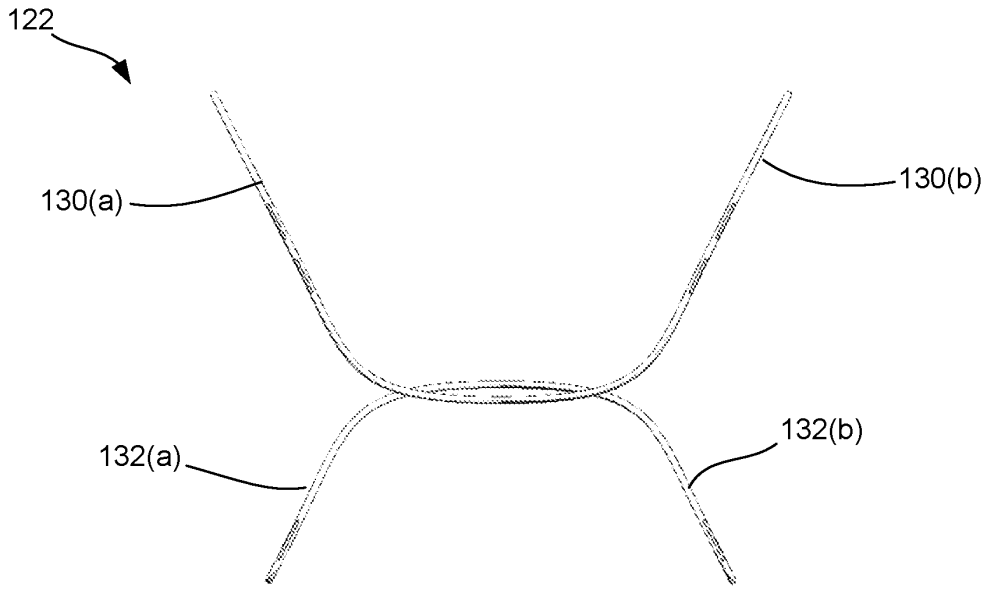


FIG. 5E

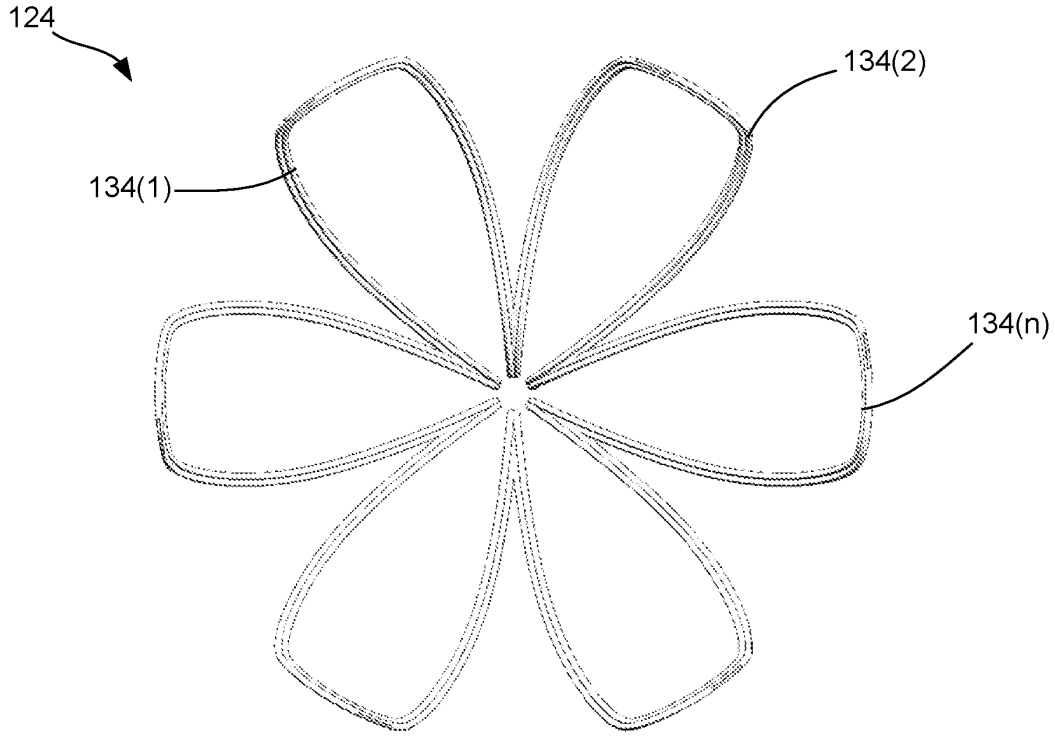


FIG. 5F

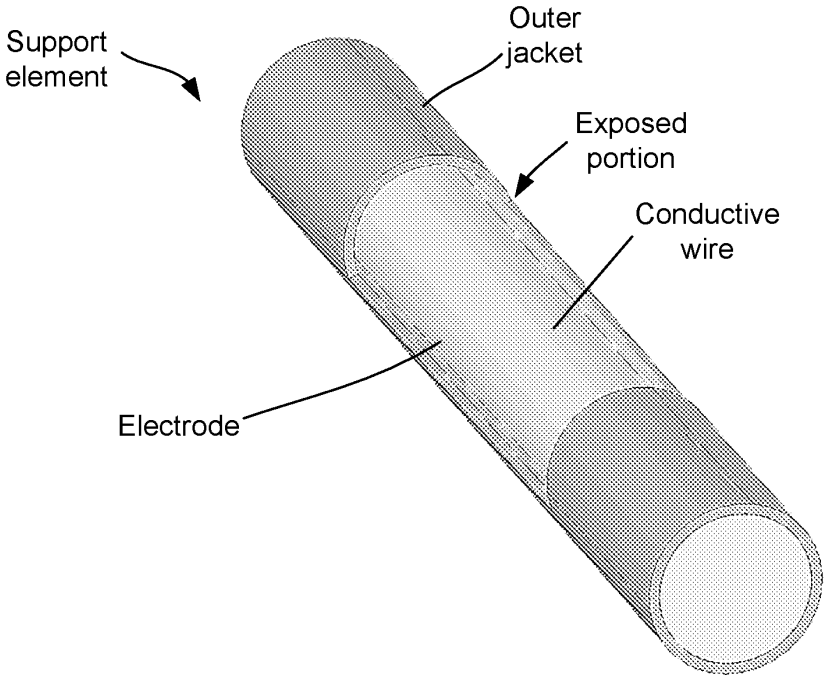

Support element
Outer jacket
Exposed portion
Conductive wire
Electrode

FIG. 6

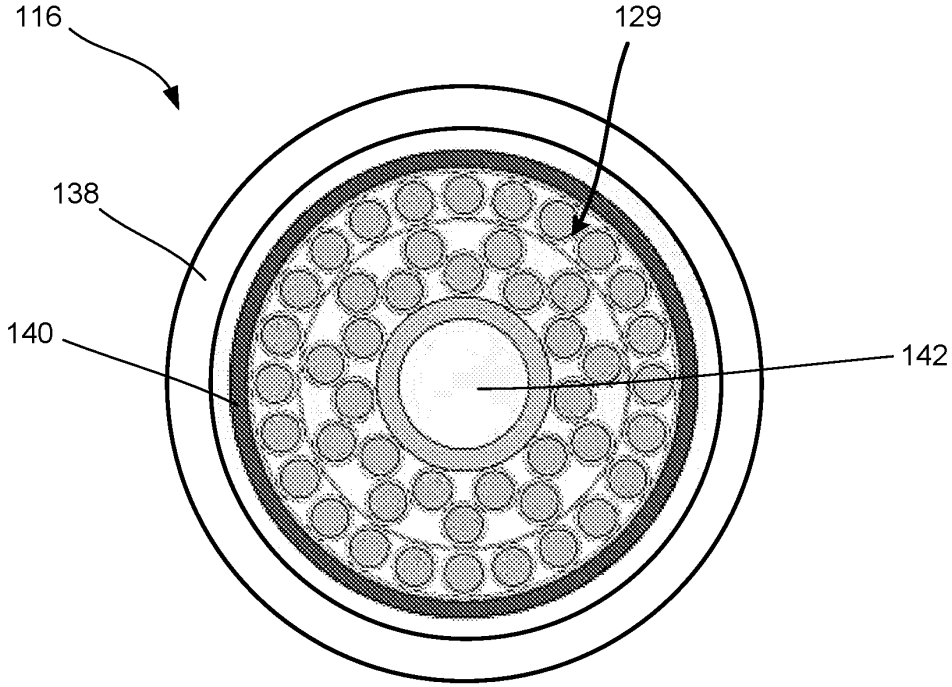

116
129
138
140
142

FIG. 7

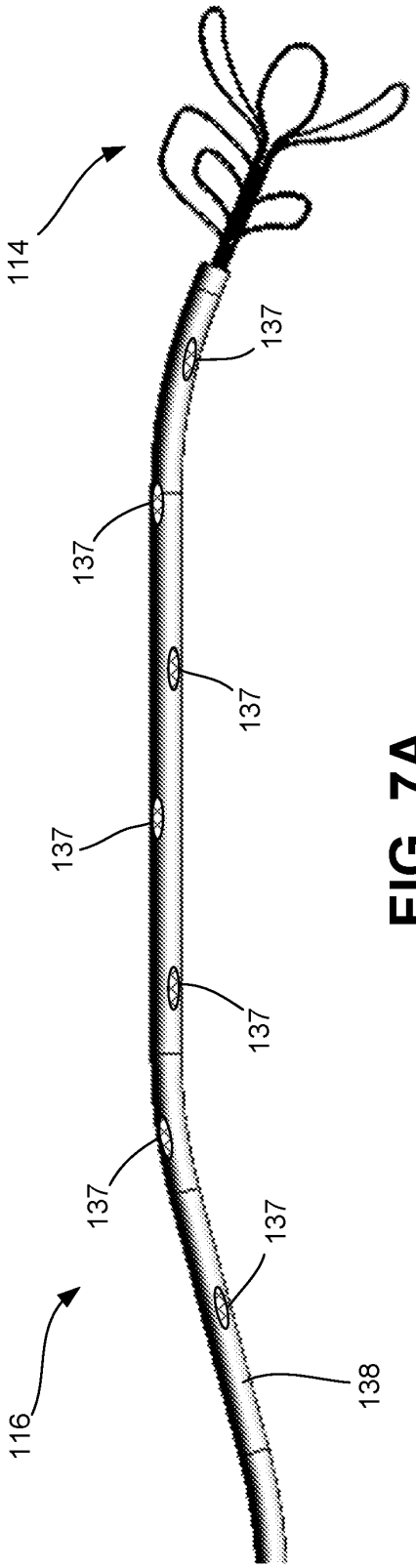


FIG. 7A

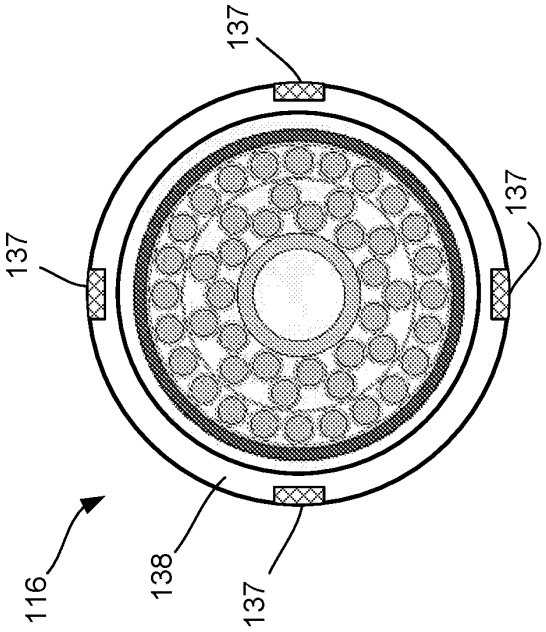


FIG. 7B

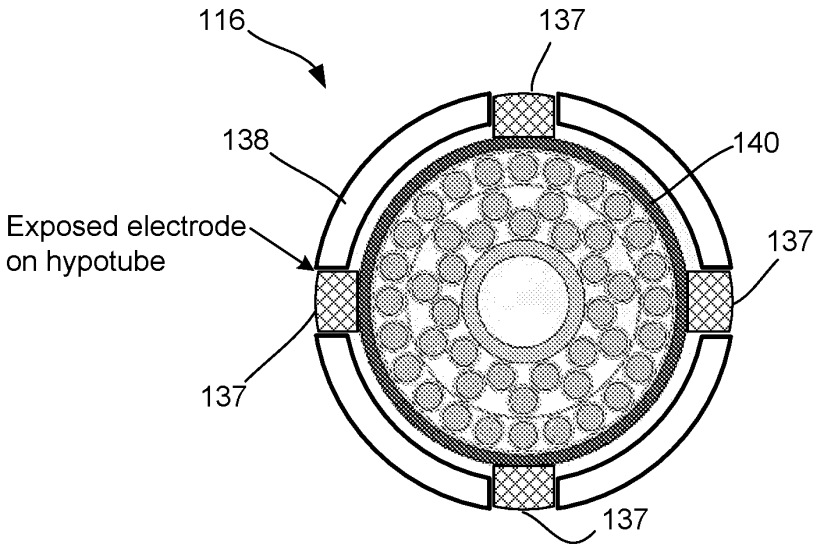

116
137
138
140
Exposed electrode
on hypotube
137
137
137

FIG. 7C

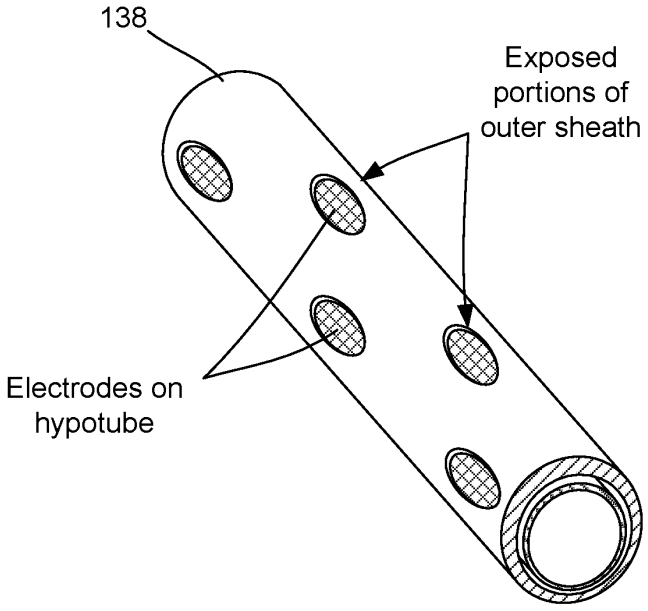

138
Exposed
portions of
outer sheath
Electrodes on
hypotube

FIG. 7D

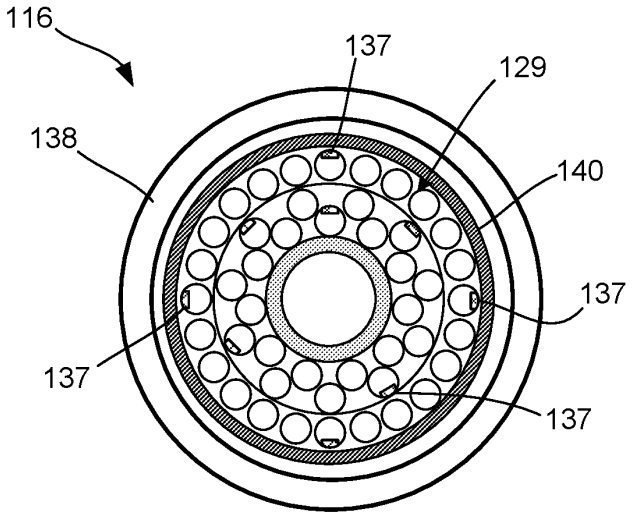


FIG. 7E

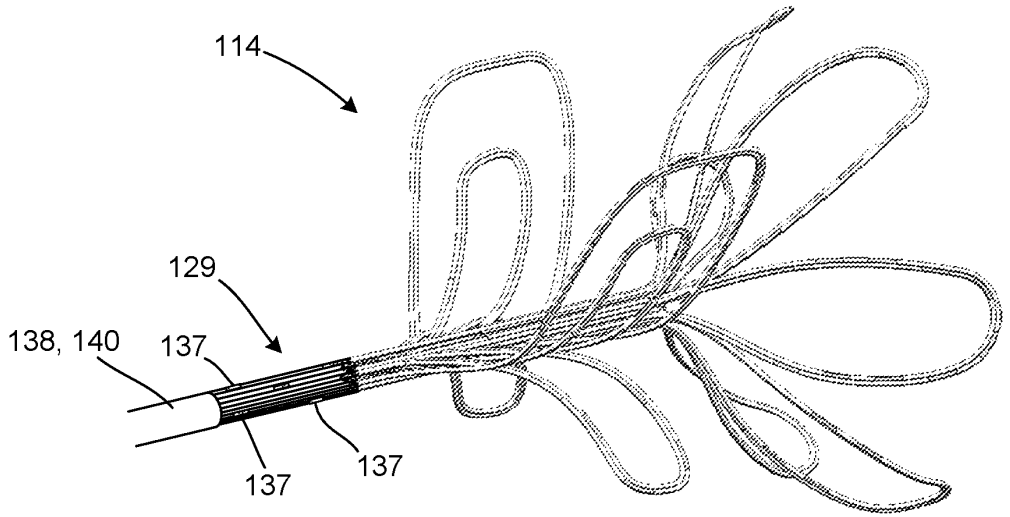


FIG. 7F

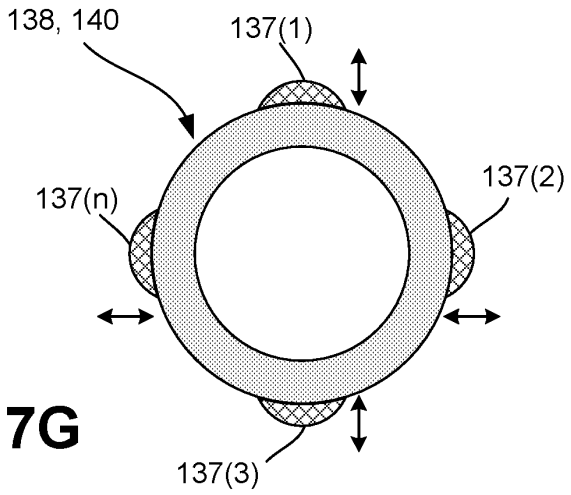


FIG. 7G

Aerin Exhibit 1009, Page 2057 of 2072
Aerin Medical Inc. v. Neurent Medical Ltd.
IPR2025-01124

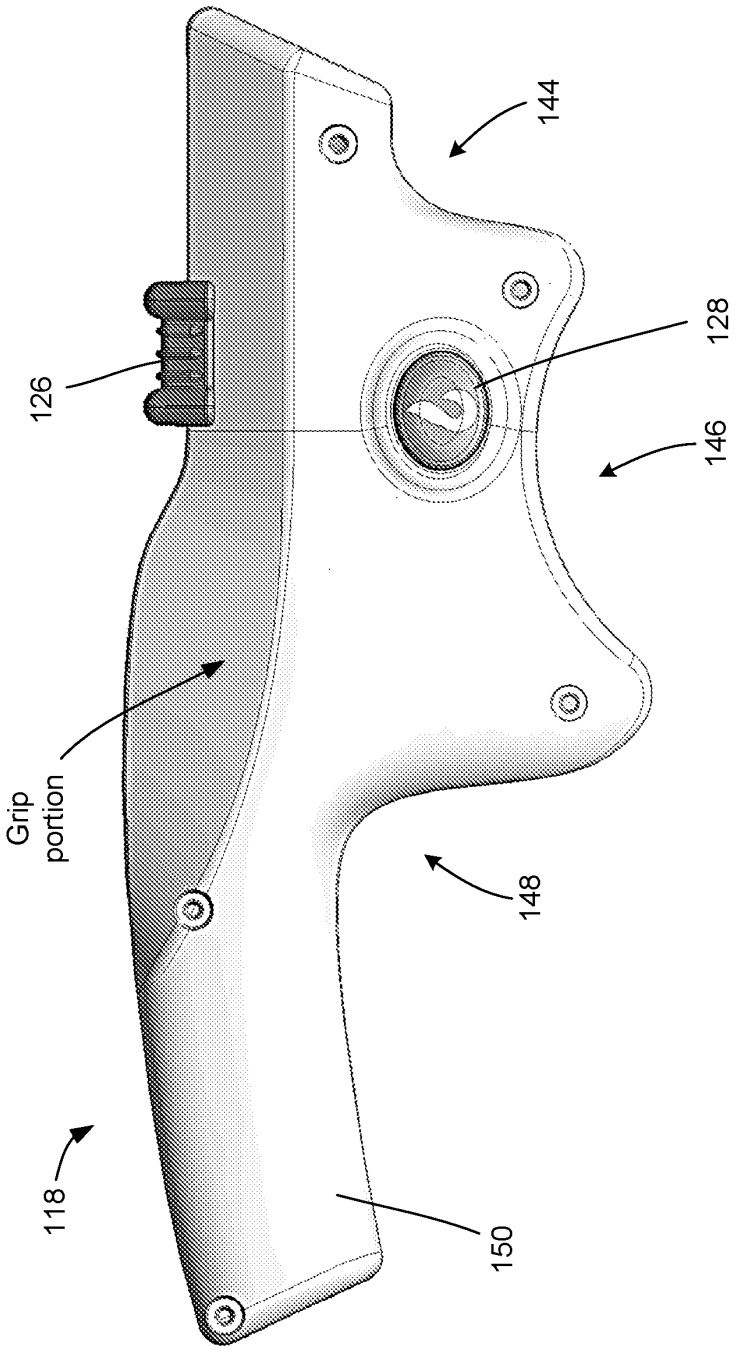


FIG. 8

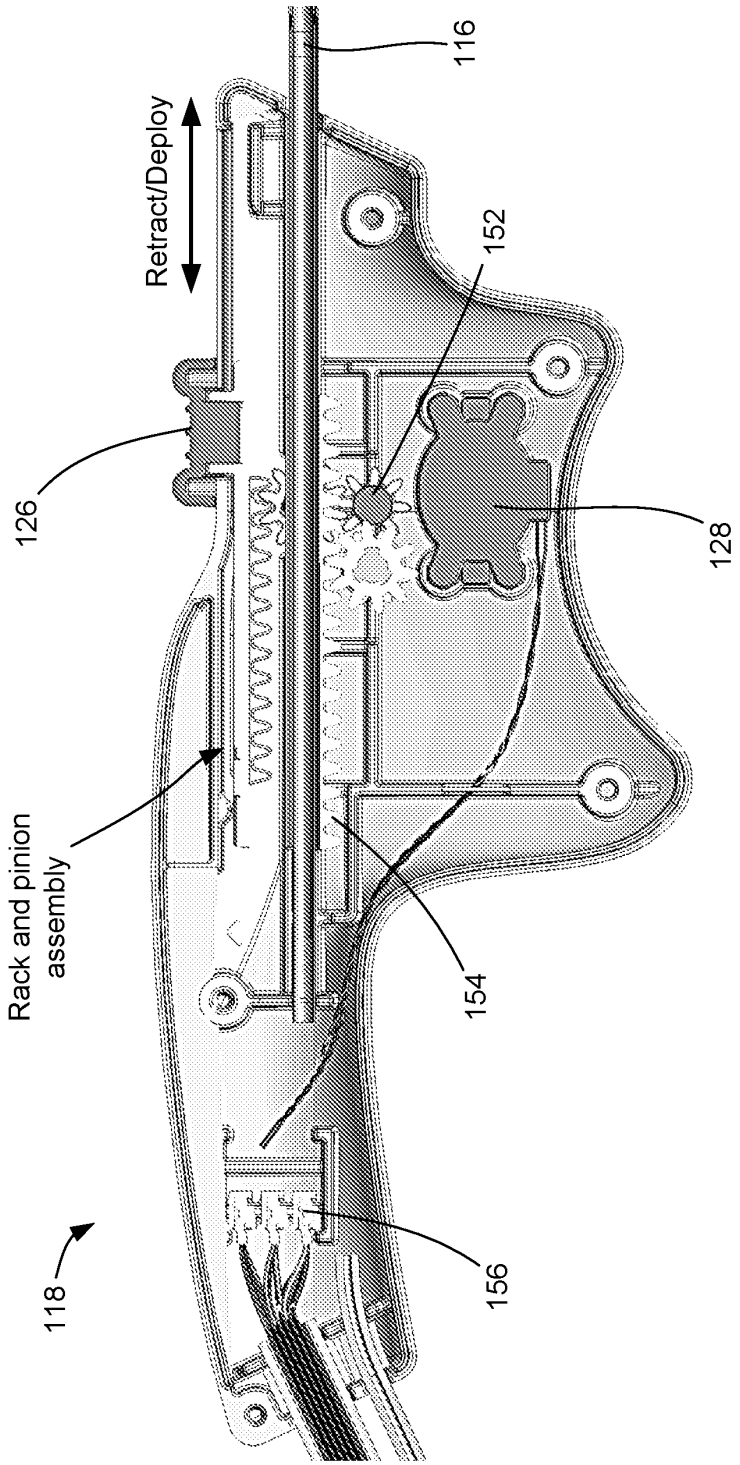

116
Retract/Deploy
152
126
128
Rack and pinion assembly
154
156
118

FIG. 9

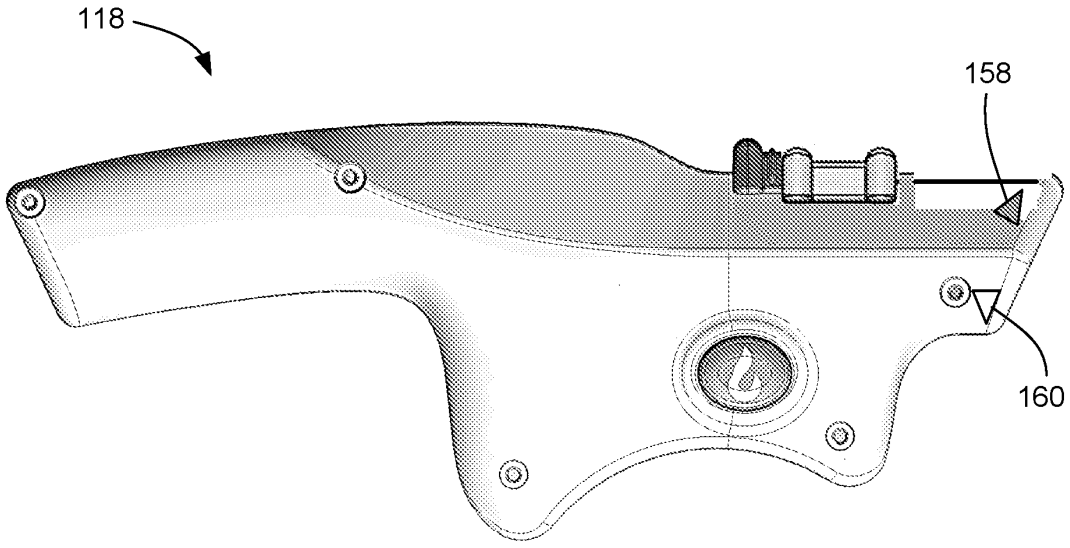


FIG. 10

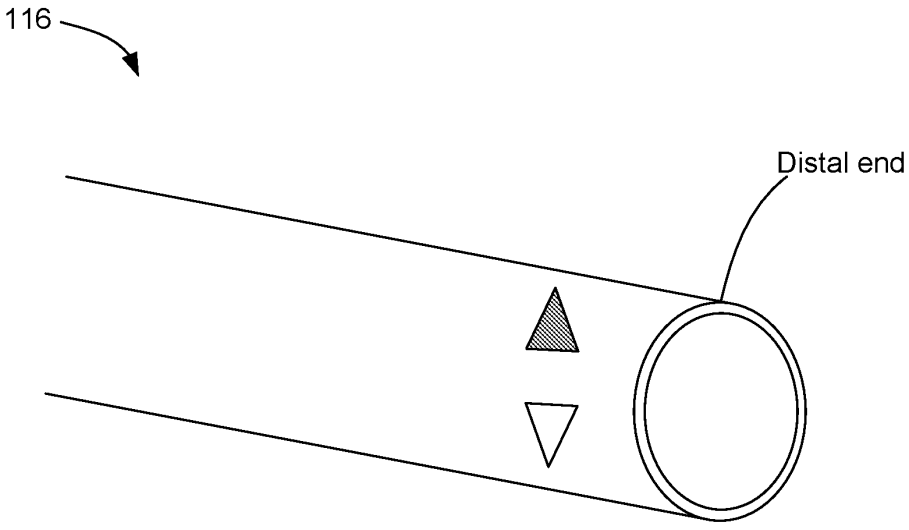


FIG. 11

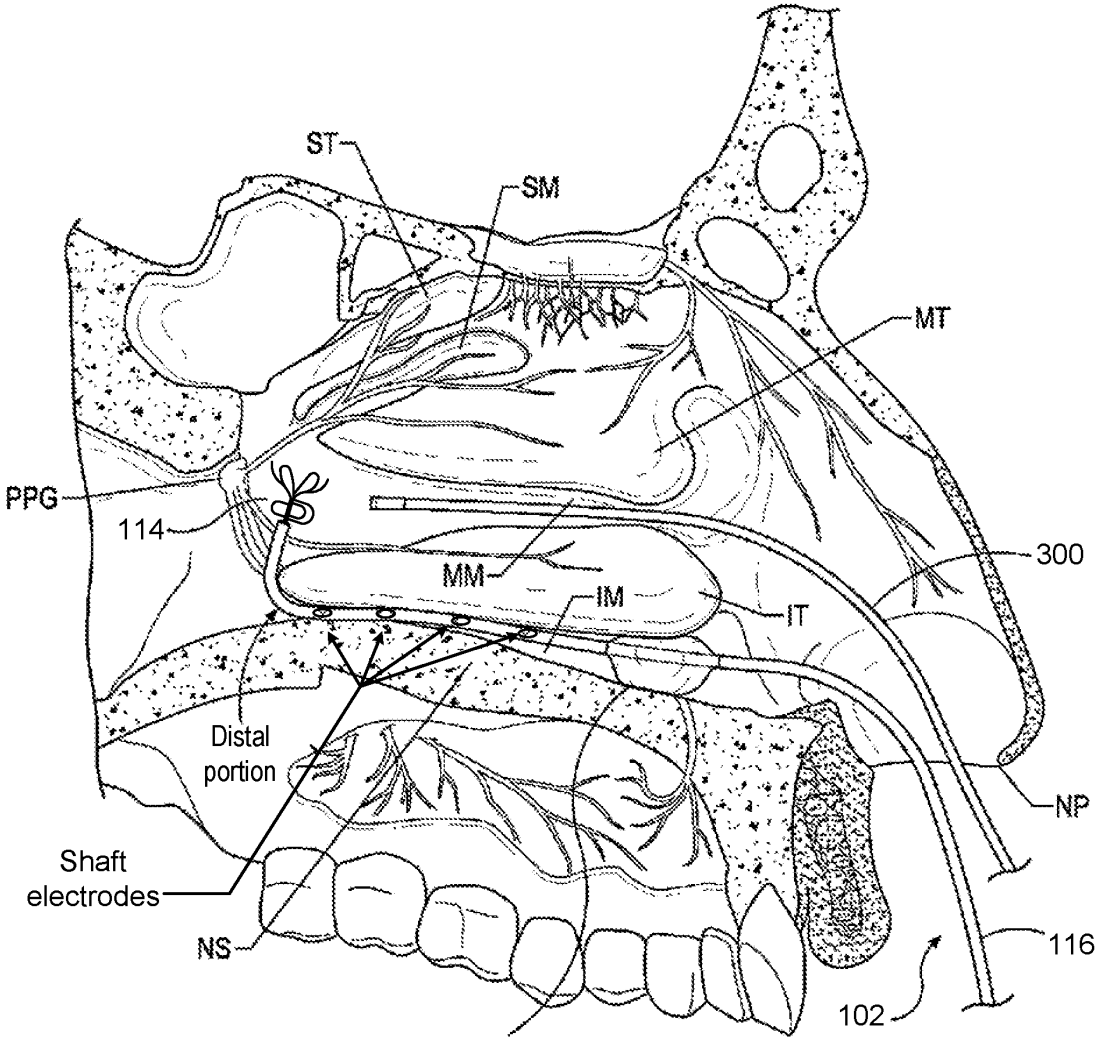

ST
SM
MT
PPG
114
300
MM
IM
IT
Distal
portion
NP
Shaft
electrodes
NS
116
102

FIG. 12

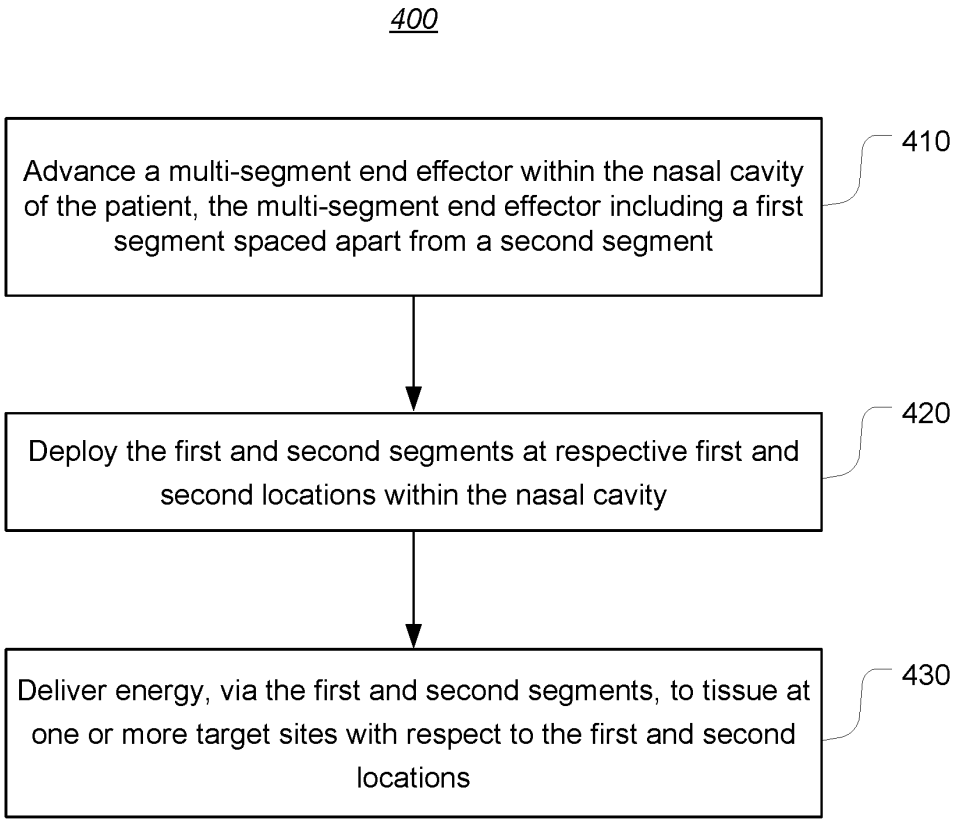

400
Advance a multi-segment end effector within the nasal cavity of the patient, the multi-segment end effector including a first segment spaced apart from a second segment
410
Deploy the first and second segments at respective first and second locations within the nasal cavity
420
Deliver energy, via the first and second segments, to tissue at one or more target sites with respect to the first and second locations
430

FIG. 13

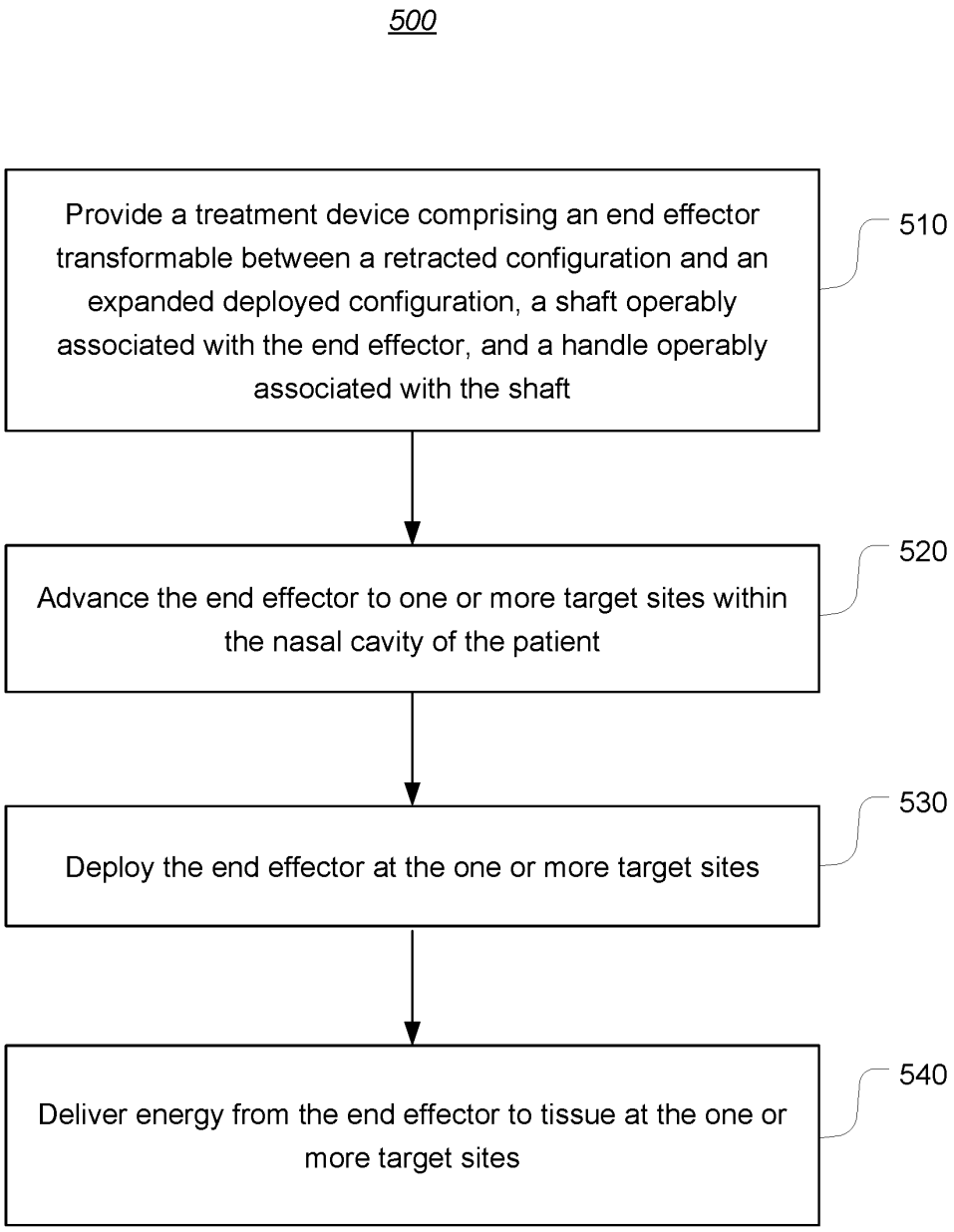

500
Provide a treatment device comprising an end effector transformable between a retracted configuration and an expanded deployed configuration, a shaft operably associated with the end effector, and a handle operably associated with the shaft
510
Advance the end effector to one or more target sites within the nasal cavity of the patient
520
Deploy the end effector at the one or more target sites
530
Deliver energy from the end effector to tissue at the one or more target sites
540

FIG. 14

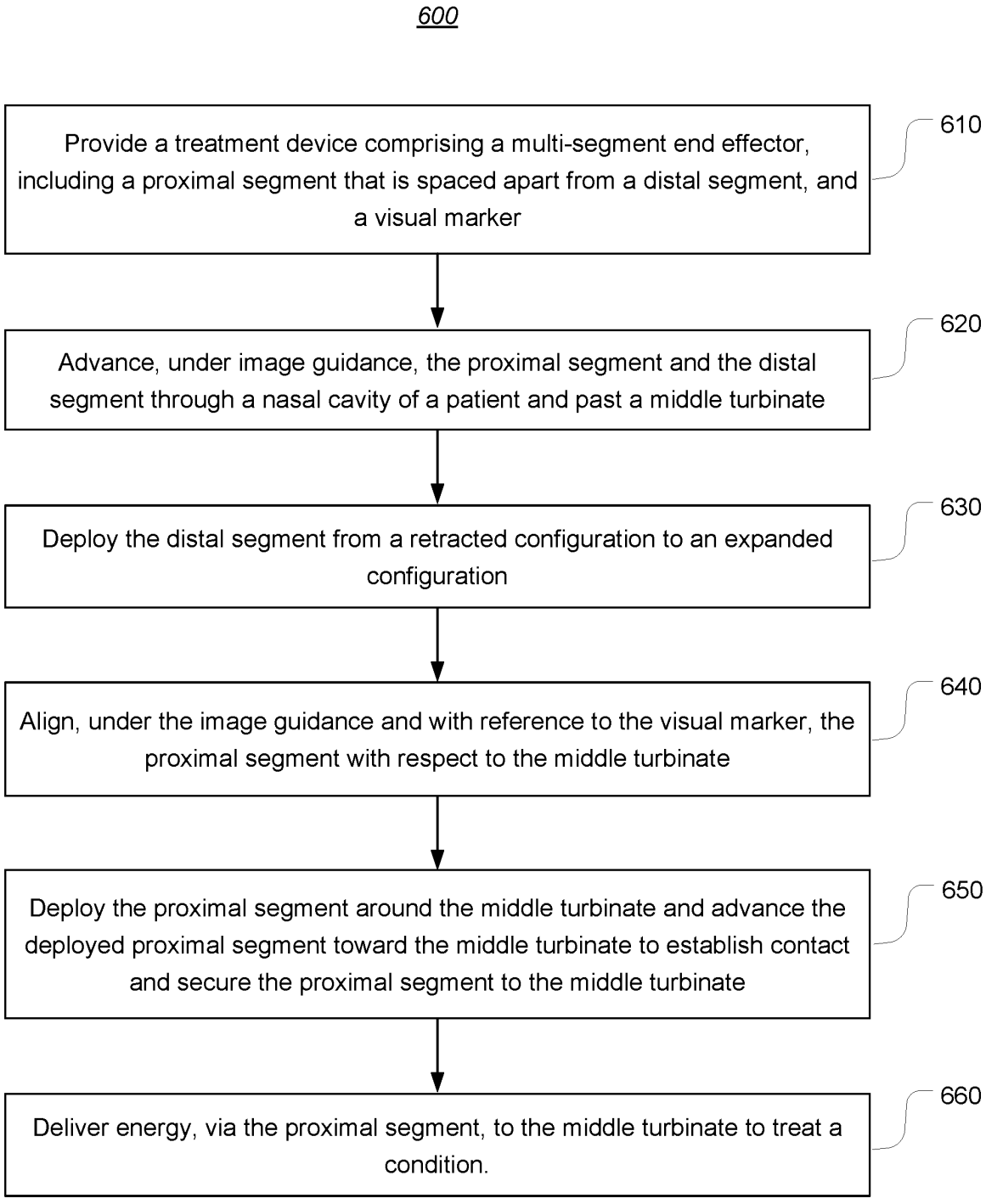

600
Provide a treatment device comprising a multi-segment end effector, including a proximal segment that is spaced apart from a distal segment, and a visual marker
610
Advance, under image guidance, the proximal segment and the distal segment through a nasal cavity of a patient and past a middle turbinate
620
Deploy the distal segment from a retracted configuration to an expanded configuration
630
Align, under the image guidance and with reference to the visual marker, the proximal segment with respect to the middle turbinate
640
Deploy the proximal segment around the middle turbinate and advance the deployed proximal segment toward the middle turbinate to establish contact and secure the proximal segment to the middle turbinate
650
Deliver energy, via the proximal segment, to the middle turbinate to treat a condition.
660

FIG. 15

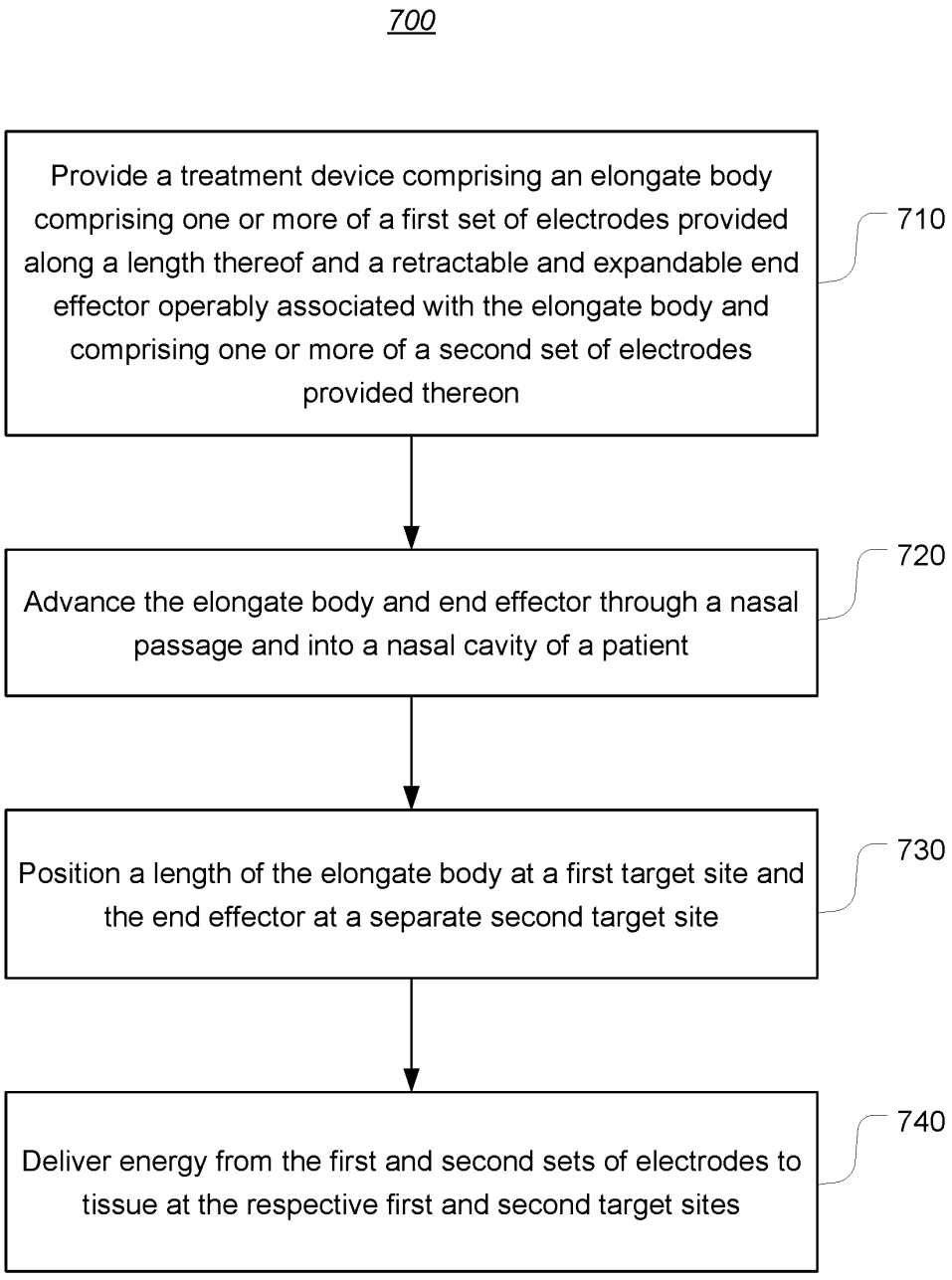

700
Provide a treatment device comprising an elongate body comprising one or more of a first set of electrodes provided along a length thereof and a retractable and expandable end effector operably associated with the elongate body and comprising one or more of a second set of electrodes provided thereon
710
Advance the elongate body and end effector through a nasal passage and into a nasal cavity of a patient
720
Position a length of the elongate body at a first target site and the end effector at a separate second target site
730
Deliver energy from the first and second sets of electrodes to tissue at the respective first and second target sites
740

FIG. 16

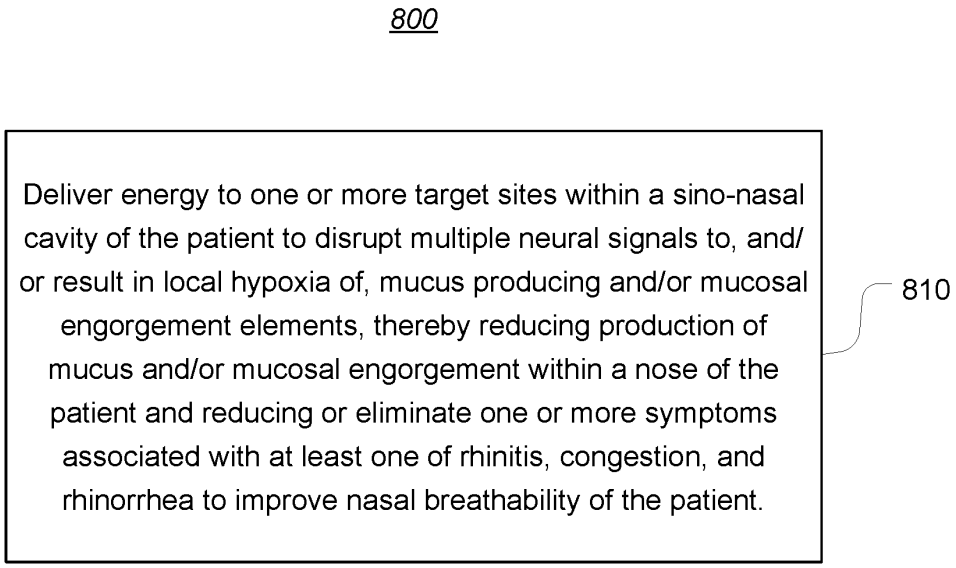

800
Deliver energy to one or more target sites within a sino-nasal cavity of the patient to disrupt multiple neural signals to, and/or result in local hypoxia of, mucus producing and/or mucosal engorgement elements, thereby reducing production of mucus and/or mucosal engorgement within a nose of the patient and reducing or eliminate one or more symptoms associated with at least one of rhinitis, congestion, and rhinorrhea to improve nasal breathability of the patient.
810

FIG. 17

Electronic Patent Application Fee Transmittal

Application Number:	
Filing Date:	
Title of Invention:	SYSTEMS AND METHODS FOR IMPROVING SLEEP WITH THERAPEUTIC NASAL TREATMENT
First Named Inventor/Applicant Name:	David Townley
Filer:	Adam M Schoen/Michelle Aiello
Attorney Docket Number:	NEURE-008/01US 35242/69

Filed as Small Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
UTILITY FILING FEE (ELECTRONIC FILING)	4011	1	80	80
UTILITY SEARCH FEE	2111	1	350	350
UTILITY EXAMINATION FEE	2311	1	400	400
Pages:				
Claims:				
Miscellaneous-Filing:				
LATE FILING FEE FOR OATH OR DECLARATION	2051	1	80	80
Petition:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**910**

Electronic Acknowledgement Receipt

EFS ID:	42400418
Application Number:	17225560
International Application Number:	
Confirmation Number:	9752
Title of Invention:	SYSTEMS AND METHODS FOR IMPROVING SLEEP WITH THERAPEUTIC NASAL TREATMENT
First Named Inventor/Applicant Name:	David Townley
Customer Number:	21710
Filer:	Adam M Schoen/Michelle Aiello
Filer Authorized By:	Adam M Schoen
Attorney Docket Number:	NEURE-008/01US 35242/69
Receipt Date:	08-APR-2021
Filing Date:	
Time Stamp:	15:19:29
Application Type:	Utility under 35 USC 111(a)

Payment information:

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Payment Type	DA
Payment was successfully received in RAM	$910
RAM confirmation Number	E202148F21271503
Deposit Account	
Authorized User	
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Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Application Data Sheet	NEURE-008-01US-ADS.pdf	1255657 4497df5d9701fbef4c06d15be618a192ff91e66a	no	8
Warnings:					
Information:					
2		NEURE-008-01US-Application.pdf	330949 9912c366435297a77d383f705dee54098d648282	yes	85

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Specification	1	81
	Claims	82	84
	Abstract	85	85

Warnings:					
Information:					
3	Drawings-only black and white line drawings	NEURE-008-01US-Drawings.pdf	6263899 dcb212e9893c568b11a3ce448697ccb5a39e8541	no	23
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Information:					
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		Total Files Size (in bytes):	7887304		

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National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

DocCode – SCORE

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