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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	18411476
	Filing Date	2024-01-12
	First Named Inventor	David Townley
	Art Unit	N/A
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	NEURE-008/03US 35242/151

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Signature	/Matthew P. York/	Date (YYYY-MM-DD)	2024-03-19
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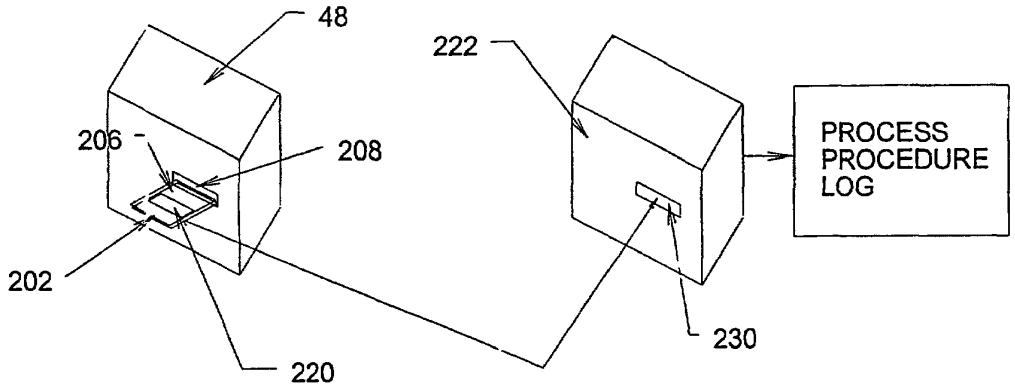
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(54) Title: GRAPHICAL USER INTERFACE FOR MONITORING AND CONTROLLING USE OF MEDICAL DEVICES



(57) Abstract: A device for treating a tissue region is supplied with a separate usage key card (202). The usage key card (202) comprises a storage medium (204), which is formatted to contain an identification code unique to the usage key card (202). The usage key card (202) is adapted to be read by a remote reader (48), to download the identification code for processing by a controller (54) for the device. Processing of the identification code by the controller (54) either enables or disables operation of the device according to prescribed criteria. A viewable image is generated on a display screen (420) that changes in response to processing of the identification code.

WO 01/17450 A1

GRAPHICAL USER INTERFACE FOR MONITORING AND CONTROLLING USE OF MEDICAL DEVICES

RELATED APPLICATION

This application is a continuation-in-part of co-pending United States Patent Application Serial Number 09/026,296, filed February 19, 1998, and entitled "Method for Treating Sphincter." This application is also a continuation-in-part of co-pending United States Patent Application Serial Number 09/495,390, filed January 31, 2000 and entitled "Systems and Methods for Monitoring and Controlling Use of Medical Devices." This application is also a continuation-in-part of co-pending provisional United States Patent Application Serial Number 60/152,749, filed September 8, 1999 and entitled "Systems and Methods for Monitoring and Controlling Use of Medical Devices."

FIELD OF THE INVENTION

The invention is directed to systems and methods for monitoring and controlling use of medical devices.

BACKGROUND OF THE INVENTION

Use of medical devices intended to treat or diagnose conditions of the body can sometimes generate stress on the material or materials from which the devices are made. The material stress can alter the physical characteristics of the devices, making future performance of the devices unpredictable.

In addition, exposure to blood and tissue during use can entrap biological components on or within

many medical devices. Despite cleaning and subsequent sterilization, the presence of entrapped biological components can lead to unacceptable pyrogenic reactions.

The effects of material stress and damage caused during a single use of a medical device, coupled with the possibility of pyrogen reactions even after resterilization, reasonably justify imposing a single use restriction upon many medical devices.

SUMMARY OF THE INVENTION

The invention provides systems and methods for monitoring and controlling use of medical devices. The systems and methods employ a controller to control operation of the device and a reader to download information to the controller. The systems and methods also include a usage key card adapted to be handled separate from the device and comprising a storage medium formatted to contain an identification code unique to the usage key card. Upon reading by the reader, the identification code is downloaded to the controller. The controller includes a processing function for processing the identification code to either enable or disable operation of the device according to prescribed criteria. The systems and methods further include a display screen and an operating system to generate a viewable image on the display screen that changes in response to processing of the identification code by the processing function.

In one embodiment, the processing function causes the controller to create a table by registering unlike identification codes in memory as they are downloaded by the reader. The controller enables operation of the device when a new identification code is registered in the table. In this arrangement, the operating system displays a first image to prompt input to create the table for the device using the processing function.

In one embodiment, the processing function causes the controller to disable operation of the device when the given identification code matches an identification code in the table. In this arrangement, the operating system displays a second image, different than the first image, to prompt exchange of the device when operation of the device is disabled as a result of the processing function.

In one embodiment, the processing function causes the controller to register in the table, a time period of use of the device. In this arrangement, the processing function causes the controller to disable operation of the device when the time of use exceeds a prescribed period. The operating system displays a second image, different than the first image, to prompt exchange of the device when operation of the device is disabled as a result of the processing function.

In one embodiment, the device applies radio frequency energy to the tissue region.

Features and advantages of the inventions are set forth in the following Description and Drawings, as well as in the appended Claims.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a diagrammatic view of a system for treating body sphincters and adjoining tissue regions, which embodies features of the invention;

Fig. 2 is a perspective view, with portions broken away, of a device usable in association with the system shown in Fig. 1 having an operative element for contacting tissue shown in a collapsed condition;

Fig. 3 is a perspective view, with portions broken away, of the device shown in Fig. 2, with the operative element shown in an expanded condition;

Fig. 4 is a perspective view, with portions broken away, of the device shown in Fig. 2, with the

operative element shown in an expanded condition and the electrodes extended for use;

Fig. 5 is an enlarged view of the operative element shown in Fig. 4, with the electrodes extended for use;

Fig. 6 is a perspective view of a kit containing a device, such as shown in Figs. 2 to 5, and a usage key card;

Fig. 7 is an enlarged, mainly schematic view of the usage key card shown in Fig. 6, embodied as a floppy disk, and also showing the pre-formatted files it contains;

Fig. 8 is a schematic view of a controller, which the system shown in Fig. 1 incorporates, showing the pre-programmed rules by which information contained on the usage key card shown in Figs. 6 and 7 is read and processed;

Fig. 9 is a schematic view of another processing device that reads information from the usage key card for further processing;

Fig. 10 is a left perspective views of an integrated generator/controller apparatus for use in association with a disposable treatment device, the apparatus including a graphical user interface (GUI) that aids in monitoring and controlling the incidence of use of the disposable treatment device;

Fig. 11 is a representative SETUP display that can be implemented by the GUI shown in Fig. 10 as part of monitoring and controlling the incidence of use of the disposable treatment device;

Fig. 12 is a representative EXCHANGE display that can be implemented by the GUI shown in Fig. 10 as part of monitoring and controlling the incidence of use of the disposable treatment device; and

Fig. 13 is a flow chart showing the various

states and modes that the apparatus shown in Fig. 10 employs in implementing the GUI in monitoring and controlling the incidence of use of the disposable treatment device.

The invention may be embodied in several forms without departing from its spirit or essential characteristics. The scope of the invention is defined in the appended claims, rather than in the specific description preceding them. All embodiments that fall within the meaning and range of equivalency of the claims are therefore intended to be embraced by the claims.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Fig. 1 shows one embodiment of a system 10, which monitors and controls the use of an operative element 12. The system 10 is well adapted for association with single use, catheter-based devices. Therefore, in the illustrated embodiment, the operative element 12 is part of a catheter-based treatment device 26. It should be appreciated, however, that the system 10 is also adaptable for use with devices and methods that are not necessarily catheter-based.

I. The Treatment Device

In the illustrated embodiment, the device 26 includes a handle 28 made, e.g., from molded plastic. The handle 28 is sized to be conveniently held by a physician, to introduce the catheter tube 30 into the targeted tissue region.

The handle 28 carries a flexible catheter tube 30. The catheter tube 30 can be constructed, for example, using standard flexible, medical grade plastic materials. The catheter tube 30 has a distal end 34, which carries the operative element 12.

The operative element 12 can support, for example, a device for imaging body tissue, such as an endoscope, or an ultrasound transducer. The operative element 12

can also support a device to deliver a drug or therapeutic material to body tissue. The operative element 12 can also support a device for sensing a physiological characteristic in tissue, such as electrical activity, or for transmitting energy to stimulate or form lesions in tissue.

In the illustrated embodiment, the device 26, in use, is intended to treat dysfunction of sphincters and adjoining tissue regions in the upper gastrointestinal tract, e.g., in the lower esophageal sphincter and adjacent cardia of the stomach, as well as in the lower gastrointestinal tract, e.g., in the intestines, rectum and anal canal. Still, it should be appreciated that the system 10 can be used in association with other devices and methods used to treat other dysfunctions elsewhere in the body, which are not necessarily sphincter-related. For example, the various aspects of the invention have application in procedures requiring ablation of tissue throughout the body, or treatment of hemorrhoids, or restoring compliance to or otherwise tightening interior tissue or muscle regions.

In the illustrated embodiment, one function that the operative element 12 is to perform is to apply energy in a selective fashion to a targeted body region, which, for the purpose of illustration, can be the lower esophageal sphincter, or cardia, or both. The applied energy creates one or more lesions, or a prescribed pattern of lesions, below the mucosal surface of the esophagus or cardia. The subsurface lesions are formed in a manner that preserves and protects the mucosal surface against thermal damage.

It has been discovered that natural healing of the subsurface lesions leads to a physical tightening of the sphincter and/or adjoining cardia. The subsurface lesions can also result in the interruption of aberrant

electrical pathways that may cause spontaneous sphincter relaxation. In any event, the treatment can restore normal closure function to the sphincter.

The structure of the operative element 12 to achieve this result can vary. A representative embodiment is shown in Figs. 2 to 4, in which the operative element 12 comprises a three-dimensional basket 56. The basket 56 includes one or more spines 58, and typically includes from four to eight spines 58, which are assembled together by a distal hub 60 and a proximal base 62.

In the illustrated embodiment, an expandable structure 72 comprising a balloon is located within the basket 56. The balloon structure 72 can be made, e.g., from a Polyethylene Terephthalate (PET) material, or a polyamide (non-compliant) material, or a radiation cross-linked polyethylene (semi-compliant) material, or a latex material, or a silicone material, or a C-Flex (highly compliant) material.

The balloon structure 72 presents a normally, generally collapsed condition, as Fig. 2 shows. In this condition, the basket 56 is also normally collapsed about the balloon structure 72, presenting a low profile for deployment into the esophagus 10.

The catheter tube 30 includes an interior lumen, which communicates with the interior of the balloon structure 72. A fitting 76 (e.g., a syringe-activated check valve) is carried by the handle 28. The fitting 76 communicates with the lumen. The fitting 76 couples the lumen to a syringe 78 (see Fig. 3). The syringe 78 injects fluid under pressure through the lumen into the balloon structure 72, causing its expansion.

Expansion of the balloon structure 72 urges the basket 56 to open and expand (see Fig. 3). The force exerted by the balloon structure 72, when expanded, is sufficient to exert an opening force upon the tissue

surrounding the basket 56.

Each spine 58 carries an electrode 66 (see Fig. 4). In the illustrated embodiment, each electrode 66 is carried within the tubular spine 58 for sliding movement. Each electrode 66 slides from a retracted position, withdrawn in the spine 58 (shown in Fig.3) and an extended position, extending outward from the spine 58 (see Fig. 4) through a hole in the spine 58. A push-pull lever 68 on the handle 28 is coupled by one or more interior wires to the sliding electrodes 66. The lever 68 controls movement electrodes between the retracted position (by pulling rearward on the lever 68) and the extended position (by pushing forward on the lever 68). The electrodes 66 have sufficient distal sharpness and strength, when extended, to penetrate a desired depth into tissue the smooth muscle of the esophageal or cardia 20 wall. The desired depth can range from about 4 mm to about 5 mm.

In this arrangement (see Fig. 1), the system 10 includes a generator 38 to supply the treatment energy to the electrodes 66. In the illustrated embodiment, the generator 38 supplies radio frequency energy, e.g., having a frequency in the range of about 400 kHz to about 10 mHz. Of course, other forms of energy can be applied, e.g., coherent or incoherent light; heated or cooled fluid; resistive heating; microwave; ultrasound; a tissue ablation fluid; or cryogenic fluid.

A cable 40 extending from the proximal end of the handle 28 terminates with an electrical connector 42. The cable 40 is electrically coupled to the operative element 12, e.g., by wires that extend through the interior of the handle 28 and catheter tube 30. The connector 42 plugs into the generator 38, to convey the generated energy to the operative element 12.

The electrodes 66 are formed of material that

conducts radio frequency energy, e.g., nickel titanium, stainless steel, e.g., 304 stainless steel, or a combination of nickel titanium and stainless steel.

In the illustrated embodiment (see Fig. 5), an electrical insulating material 70 is coated about the proximal end of each electrode 66. When the distal end of the electrode 66 penetrating the smooth muscle of the esophageal sphincter 18 or cardia 20 transmits radio frequency energy, the material 70 insulates the mucosal surface of the esophagus 10 or cardia 20 from direct exposure to the radio frequency energy. Thermal damage to the mucosal surface is thereby avoided. The mucosal surface can also be actively cooled during application of radio frequency energy, to further protect the mucosal surface from thermal damage.

In the illustrated embodiment (see Fig. 5), at least one temperature sensor 80 is associated with each electrode. One temperature sensor 80 senses temperature conditions near the exposed distal end of the electrode 66, a second temperature sensor 80 is located on the corresponding spine 58, which rests against the muscosal surface when the balloon structure 72 is inflated.

The system 10 (see Fig. 1) can also include certain auxiliary processing equipment, e.g., an external fluid delivery apparatus 44 for supplying cooling liquid to the targeted tissue, e.g., through holes in the spines, and an external aspirating apparatus 46 for conveying liquid from the targeted tissue site, e.g., through other holes in the spine or elsewhere on the basket 56.

The system 10 also includes a controller 52. The controller 52, which preferably includes a central processing unit (CPU), is linked to the generator 38, the fluid delivery apparatus 44, and the aspirating apparatus 46. Alternatively, the aspirating apparatus 46 can comprise a conventional vacuum source typically present

in a physician's suite, which operates continuously, independent of the controller 52. The controller 52 governs the delivery of processing fluid and, if desired, the removal of aspirated material.

The controller 52 also governs the power levels, cycles, and duration that the radio frequency energy is distributed to the electrodes 66, to achieve and maintain power levels appropriate to achieve the desired treatment objectives. The controller 52 can condition the electrodes 66 to operate in a monopolar mode. In this mode, each electrode 66 serves as a transmitter of energy, and an indifferent patch electrode (not shown) serves as a common return for all electrodes 66. Alternatively, the controller 52 can condition the electrodes 66 to operate in a bipolar mode. In this mode, one of the electrodes comprises the transmitter and an other electrode comprises the return for the transmitted energy. The bipolar electrode pairs can electrodes 66 on adjacent spines, or electrodes 66 spaced more widely apart on different spines.

The controller 52 includes an input/output (I/O) device 54. The I/O device 54 allows the physician to input control and processing variables, to enable the controller to generate appropriate command signals. The I/O device 54 also receives real time processing feedback information from the temperature sensors 80, for processing by the controller 52, e.g., to govern the application of energy and the delivery of processing fluid. The I/O device 54 also includes a graphical user interface (GUI), to graphically present processing information to the physician for viewing or analysis.

II. Monitoring and Control of Reuse

The handle 28 and the catheter tube 30 form an integrated construction intended for a single use and subsequent disposal as a unit. Alternatively, the handle

28 can comprise a nondisposable component intended for multiple uses. In this arrangement, the catheter tube 30, and components carried at the end of the catheter tube 30 comprise a disposable assembly, which the physician releasably connects to the handle 28 at time of use and disconnects and discards after use. The catheter tube 30 can, for example, include a male plug connector that couples to a female plug receptacle on the handle 28.

To protect patients from the potential adverse consequences occasioned by multiple use, which include disease transmission, or material stress and instability, or decreased or unpredictable performance, the controller 54 includes a module 48 that controls use of the device 26.

In the illustrated embodiment (see Fig. 6), the device 26 is supplied as part of a kit 200 that includes, together with the device 26, a usage key card 202. The kit 200 packages the device 26 and usage key card 202 as a unitary, single use item in a sterile fashion within peripherally sealed sheets of plastic film material that are torn or peeled away at the instance of use.

The presence of the device 26 and user key card 200 packaged together in the kit 200 verifies to the physician or user that device 26 is sterile and has not be subjected to prior use. The physician or user is thereby assured that the device 26 meets established performance and sterility specifications. No unused device 26 is supplied in the kit 200 without a usage key card 202, and vice versa.

The usage key card 202 incorporates a storage medium 204 that is readable by the module 48. The storage medium 204 contains information that enables at least two use control and monitoring functions.

The first use control and monitoring function of the

usage key card 202 occurs prior to use of the device 26 in association with the generator 38. To enable use of the generator 38 in association with the device 26, the physician must first present the usage key card 202 for reading by the module 48. To enable use of the device 26, the controller 54 must then find that the usage key card 202 meets the criteria necessary for its registration by the controller 54. The criteria are designed to indicate the absence of a prior use, either in absolute terms or in terms of a period of use outside a predetermined time period. If the criteria are not met, the controller 54 will not register the usage key card 202, and the controller 54 will also not enable use of the generator 38 in association with the device 26. Further details of the registration function of the controller 54 will be described later.

The second use control and monitoring function of the usage key card 202 occurs if the criteria are met and registration of the usage key card 202 occurs. During permitted use of the device 26 in association with the generator 38, the storage medium 204 of the usage key card 202 remains in the module 48 and receives, via the module 48, data generated by the controller 54 recording operating parameters and performance of the device 26. The storage medium 204 of the usage key card 202 retains and organizes the data for further off-line storage and processing. Further details of the data retention function will be described later.

The usage key card 202 can be variously configured. In the illustrated embodiment (see Fig. 7), the usage key card 202 comprises a computer-readable storage medium 204 housed within a conventional 3.5 inch floppy disk 206. In this arrangement, the module 48 comprises a conventional floppy disk drive 208 (see Fig. 8) capable of reading data from and downloading data to the storage

medium 204 of the disk 206.

Alternatively, the usage key card 202 can take the form of a PC card, flash memory device, or magnetic card. In these alternative embodiments, the module 48 comprises a data reading and writing device compatible with the storage medium of the card 202.

As Fig. 7 shows, the storage medium 204 of the usage key card 202 contains at least two pre-formatted files 210 and 212. The first file 210 contains a unique identification code 214 capable of being read by the module 48 and registered by the controller 54. The second file 212 is formatted to receive and retain operational and performance data generated by the controller 54 to create from it a procedure log 220.

The identification code 214 contained in the first file 210 is created to be unique to the particular usage key card 202. That is, each usage key card 202 contains its own unique identification code 214. No two usage key cards share the same identification code 214. The unique identification code 214 can comprise, e.g., a serial number uniquely assigned to the particular device 26 found in the kit 200, or any other unique code that is not repeated for any other usage key card 202. The code 214 itself can comprise letters, numbers, or combinations thereof.

As Fig. 8 shows, the module 48 reads the identification code 214 off the usage key card 202 for input to the controller 54. This identification code will be called the "instant identification code."

Following pre-programmed rules, the controller 54 constructs and maintains in non-volatile memory a use table 216. The use table 216 contains all prior identification codes that meet the criteria to be registered by the controller 54. These identification codes will be called the "registered identification

codes."

Following pre-programmed rules, the controller 54 compares the instant identification code 214 to all registered identification codes contained in the table 216. In the absence of a match between the instant identification code and any registered identification code, the controller 54 updates the table, i.e., the controller registers the instant identification code by adding it to the table 216. Upon registering the usage key card 202, the controller 54 also enables use of generator 38 in association with the device.

The presence of a match between the instant identification code and any registered identification code indicates the usage key card 202 has been previously read by the module 48, which reflects a prior use of the device 26 or another device not packaged with the card 202. In this circumstance, the controller 54 does not add the duplicative identification code to the table 216 and does not enable use of the generator 38 in association with any device 26. Preferably, the controller 54 outputs to the GUI notice of prior use.

In an alternative arrangement, the controller 54 maintains for each registered identification code in the table 216 a time record 218. The time record 218 contains a value reflecting the period of time during which energy was applied by the generator 38 during the previous permitted use. In this embodiment, when a match occurs between the instant identification code and a registered identification code, the controller 54 ascertains whether the time period of previous use contained in the record 218 is less than a prescribed maximum time period, e.g., 45 minutes. If so, the controller 54 enables a subsequent operation of the generator 38 in association with the device 26, but only for the time period remaining. The controller 54 updates

the time record 218 as further use occurs. The controller 54 preferably outputs to the GUI the time period of permitted use remaining.

If the controller 54 ascertains that the time period of previous use equals or exceeds the prescribed maximum time period, the controller 54 does not enable use of the generator 38. Preferably, the controller 54 outputs to the GUI notice of prior use.

As Fig. 9 shows, the second file 212 contained on the storage medium 204 of the usage key card 202 is formatted to receive, via the module 48, data that is generated by the controller 54 during permitted use of the device 26 in association with the generator 38. The file 212 retains the data in a formatted array according to pre-programmed rules to create a procedure log 220.

The content of the formatted log 220 can vary. For example, the log 220 can document, by date of treatment and number of treatments, the coagulation level (i.e., the depth at which the electrodes are inserted), the time duration of energy application, the magnitude of energy delivered by each electrode, and the coolant flow rate. The procedure log 220 can also record at pre-established intervals (e.g., every 5 seconds) the temperatures of the electrodes and surrounding tissue, along other parameters, e.g., sensed impedance and power delivered by each electrode.

The procedure log 220 preferably records these values in a pre-formatted data base format, to enable import of the values as data base items for storage, processing, and retrieval by an off-line data processing device 222 having a compatible data base processing application. The off-line data processing device 222 reads processing log data from the usage key card 202 (via a floppy disk drive 230 or otherwise compatible reading device).

The device 222 can process the data in various ways according to the rules of the data processing application. The device 222 can, e.g., create a print-formatted record of the procedure log 220 for printing in a hard copy version. The device 222 can also, e.g., process the procedure logs for multiple devices and patients, to create historical patient treatment records, patient reimbursement records, and the like for storage or retrieval. The device 222 thereby makes possible the establishment and maintenance of an archival patient data base by processing individual procedure logs.

As Fig. 6 shows, the kit 200 can also include a label 224 that is pre-applied or that can be applied by the physician to the usage key card 202. The label 224 receives manually transcribed, visually readable information pertaining to the usage key card 202, e.g., the name of the patient being treated by the device 26, the date of treatment, and the like. In this way, usage key cards 202 can itself be physically stored and indexed.

As Fig. 6 also shows, the kit 200 can also include instructions 232 for using the usage key card 202 in the fashion described. For example, the instructions 232 can instruct the physician as to the need for having the usage key card 202 read by the module 48, in order to enable use of the device 26 in association with the generator 38. The instructions 232 can also instruct the physician regarding the content of the procedure log and the subsequent off-line processing options that are available.

As Fig. 7 shows, the storage medium 204 of the usage key card 202 can also contain at least one additional formatted file 226 that provides device information 228, which characterizes the device 26 supplied in the kit 200. For example, the device information 228, when read

by the module 48, can identify the type of device 26 in terms of its operational characteristics, the inclusion of temperature sensing, and reuse criteria (e.g., no reuse after a single use, or multiple uses permitted up a prescribed maximum number of uses, or multiple uses permitted up to a maximum time period of use, or multiple uses permitted up to a maximum application of RF energy). The file 226 can also condition the GUI to display the desired images and data formats, which change depending upon the treatment procedure using the device (e.g, treatment of GERD, fecal incontinence, or urinary incontinence). In one arrangement, the controller 54 can compare the device characteristics with the operational characteristics of the controller 54 and generator 38, and disable operation of the device 26 should the characteristics of the device 26 be incompatible with the characteristics of the controller 54 and/or generator 38.

III. Graphical User Interface (GUI) For Monitoring and Controlling Reuse

In the illustrated embodiment (see Fig. 10), the radio frequency generator 38, the controller 52 with I/O device 54, and the fluid delivery apparatus 44 (e.g., for the delivery of cooling liquid) are integrated within a single housing 400. The I/O device 54 includes input connectors 402, 404, and 406. The connector 402 accepts an electrical connector 408, to which the connector 42 of the selected treatment device 26 is electrically coupled for use. The connector 404 accepts an electrical connector 410 coupled to a patch electrode 412 (for mono-polar operation). The connector 406 accepts an pneumatic connector 414 coupled to a conventional foot pedal 416, when, when depressed, causes the delivery of radio frequency energy to the electrodes 66 on the device 26. These connectors 402, 404, and 406 couple these external devices to the controller 52.

The I/O device 54 also couples the controller 54 to an array of membrane keypads 422 and other indicator lights on the housing 400, for entering and indicating parameters governing the operation of the controller 52.

The I/O device 54 also couples the controller 52 to a display microprocessor 474. In the illustrated embodiment, the microprocessor 474 comprises, e.g., a dedicated Pentium®-based central processing unit. The controller 52 transmits data to the microprocessor 474, and the microprocessor 474 acknowledges correct receipt of the data and formats the data for meaningful display to the physician. In the illustrated embodiment, the dedicated display microprocessor 474 exerts no control over the controller 52.

In the illustrated embodiment, the controller 52 comprises an 68HC11 processor having an imbedded operating system. Alternatively, the controller 52 can comprise another style of processor, and the operating system can reside as process software on a hard drive coupled to the CPU, which is down loaded to the CPU during system initialization and startup.

The display microprocessor 474 is coupled to a graphics display monitor 420 in the housing 400. The controller 52 implements through the display microprocessor 474 the graphical user interface, or GUI, which is displayed on the display monitor 420.

The GUI can be realized, e.g., as a "C" language program implemented by the microprocessor 474 using the MS WINDOWS™ or NT application and the standard WINDOWS 32 API controls, e.g., as provided by the WINDOWS™ Development Kit, along with conventional graphics software disclosed in public literature.

The display microprocessor 474 is also itself coupled to the floppy disk drive 208, previously described. The display microprocessor 474 can also be

coupled to a keyboard, printer, and include one or more parallel port links and one or more conventional serial RS-232C port links or Ethernet™ communication links.

Upon boot-up of the CPU (see Fig. 13), the operating system implements the START-UP function 510 for the GUI 424. The GUI 424 displays an appropriate start-up logo and title image (not shown), while the controller 52 performs a self-test.

Upon completion of the START-UP function (see Fig. 13), the controller 54 conducts a CHECK function 512. The function 512 checks for the presence of a usage key card 202 in the floppy disk drive 208. As before described, a valid usage key card 202 is a prerequisite for using a given treatment device 26.

The absence of a usage key card 202 causes the controller 54 to command the display microprocessor 474 to generate a SETUP prompt 500 on the graphics display monitor 420. Fig. 11 shows a representative SETUP prompt 500. When graphically implemented, as shown in Fig. 11, the SETUP prompt 500 leads the operator in a step-wise fashion through the tasks required to enable use of the generator 38. A first graphic field displays one or more icons and/or alpha-numeric indicia 502 that prompt the operator to connect the electrical connector 42 of the treatment device 26 to the connector cable 408. A second graphic field displays one or more icons and/or alpha-numeric indicia 504 that prompt the operator to insert a valid user key card 202 (i.e., floppy disk). A third graphic field displays one or more icons and/or alpha-numeric indicia 506 that prompt the user to select the standby-ready button 430 on the housing 400 (see Fig. 10).

With the treatment device 26 connected and a user key card 202 inserted in the floppy disk drive 208, the actuation of the standby-ready button 430 causes the

controller 52 to enter the STAND-BY mode 508(see Fig. 13). In the STAND-BY mode 508, the controller 52 executes the REGISTRATION function 514, to determine whether the user key card 202 inserted in the drive 208 contains a valid identification code 214.

The identification code 214 will not be deemed valid when the code already exists in the use table 216 of the controller 52 with a time record 218 equal to or greater than the prescribed maximum, thereby indicating a completed prior use of the device 26. When the identification code 214 is not valid, the REGISTRATION function 514 commands the display microprocessor 474 to generate an EXCHANGE prompt 516 on the graphics display monitor 420. Fig. 12 shows a representative EXCHANGE prompt 516. When graphically implemented, as shown in Fig. 12, the EXCHANGE prompt 516 leads the operator in a step-wise fashion through the tasks of replacing the previously used device 26 and its key card 202 with a new device 26 and its associated key card 202.

As shown in Fig. 12, a first graphic field displays one or more icons and/or alpha-numeric indicia 518 that prompt the operator to disconnect the electrical connector 42 of the previously used treatment device 26 and to connect a new treatment device 26. A second graphic field displays one or more icons and/or alpha-numeric indicia 520 that prompt the operator to remove the old user key card 202 and insert the new key card 202 that accompanied the new treatment device 26 in the kit 200. A third graphic field displays one or more icons and/or alpha-numeric indicia 522 that prompt the user to again select the standby-ready button 430 on the housing 400.

With the new treatment device 26 connected and the new user key card 202 inserted in the floppy disk drive 208, selection of the standby-ready button 430 causes the

controller 52 to again enter the STAND-BY mode 508, and again execute the REGISTRATION function 514 (see Fig. 13).

The presence of a valid identification code 214 on the user card 202 causes the controller 52 to enter the READY mode 524. The operator deploys the treatment device 26 to the intended treatment site. The operator locates the electrodes 66 in the desired orientation. When delivery of radio frequency energy is desired, the operator depresses the foot pedal 416 (or selects the standby-ready button 430). In the illustrated embodiment, the controller 52 executes a prescribed PAUSE state 528 (e.g., 8 seconds), and then commands the generator 38 to apply radio frequency energy through the electrodes 66 carried by the treatment device 26.

The controller 52 includes an UPDATE function 526 (see Fig. 13). The UPDATE function 526 registers the time period during which radio frequency energy is applied using the device 26. The time is entered into the time record 218 of the use table 216 maintained by the controller 52. After a prescribed maximum period of use is registered (e.g., sixty minutes), the UPDATE function 526 interrupts application of radio frequency energy to the electrodes 66, and prevents further delivery by the generator 38 to the particular device 26.

In this circumstance, the UPDATE function 526 causes the controller 52 to generate the EXCHANGE prompt 516. As previously described, the EXCHANGE prompt 516 requires the operator to replace the existing device 26 and its key card 200 with a new device 26 and its associated key card 200.

In the illustrated embodiment, while radio frequency energy is being applied during the READY mode 524, the controller 52 preferably monitors impedance and/or temperature conditions at the treatment site. The

controller 52 enters a DEFAULT mode 530 and returns to the PAUSE state 528 when certain localized impedance and/or temperature conditions are sensed, e.g., when impedance is outside a prescribed range (for example, less than 50 ohms or greater than 1000 ohms); or electrode tip temperature exceeds 100 degrees C; or tissue surface temperature exceeds 50 degrees C. In the PAUSE state 528, the controller 52 prevents the application of radio frequency energy through the electrodes 66 for a prescribed period of time (e.g., 8 seconds), after which operation of the generator 38 using the foot pedal 416 or standby-ready button 430 is restored.

Other details of the GUI during operation of the device 26 can be found in co-pending United States Patent Application Serial No. 09/305,123, filed May 4, 1999 and entitled "Graphical User Interface for Association with an Electrode Structure Deployed in Contact with a Tissue Region," which is incorporated herein by reference.

Various features of the invention are set forth in the following claims.

We Claim:

1. A system for controlling use of a device for treating a tissue region comprising

a controller to control operation of the device,

a reader to download information to the controller,

a usage key card adapted to be handled separate from the device and comprising a storage medium formatted to contain an identification code unique to the usage key card that, upon reading by the reader, is downloaded to the controller,

the controller including a processing function for processing the identification code to either enable or disable operation of the device according to prescribed criteria,

a display screen, and

an operating system to generate a viewable image on the display screen that changes in response to processing of the identification code by the processing function.

2. A system according to claim 1

wherein the processing function causes the controller to create a table by registering unlike identification codes in memory as they are downloaded by the reader and to enable operation of the device when a new identification code is registered in the table, and

wherein the operating system displays a first image to prompt input to create the table for the device using the processing function.

3. A system according to claim 2

wherein the processing function causes the controller to disable operation of the device when the given identification code matches an identification code in the table, and

wherein the operating system displays a second image, different than the first image, to prompt exchange of the device when operation of the device is disabled as a result of the processing function.

4. A system according to claim 2

wherein the processing function causes the controller to register in the table, a time period of use of the device.

5. A system according to claim 4

wherein the processing function causes the controller to disable operation of the device when the time period of use exceeds a prescribed period, and

wherein the operating system displays a second image, different than the first image, to prompt exchange of the device when operation of the device is disabled as a result of the processing function.

6. A system according to claim 1

wherein the device applies radio frequency energy to the tissue region.

7. A method for controlling use of a device for treating a tissue region comprising the steps of

providing a usage key card for the device adapted to be handled separate from the device and comprising a storage medium formatted to contain an identification code unique to the usage key card,

reading the usage key card by a reader separate from the device to download the identification code to a controller for the device,

causing the controller to process the identification code by pre-programmed rules to either enable or disable operation of the device, and

generating a viewable image on a display screen that changes in response to processing of the identification code according to the pre-programmed rules.

8. A method according to claim 7

wherein the viewable image generating step generates a first image to prompt input to process the identification code for a given device according to the pre-programmed rules and a second image, different than the first image, to prompt exchange of the device when operation of the device is disabled by the pre-programmed rules.

9. A method according to claim 7

wherein the pre-programmed rules register a time period of use of the device.

10. A method according to claim 9

wherein the pre-programmed rules causes the controller to disable operation of the device when the time period of use exceeds a prescribed period.

11. A method according to claim 7

wherein the device, during use, applies radio frequency energy to the tissue region.

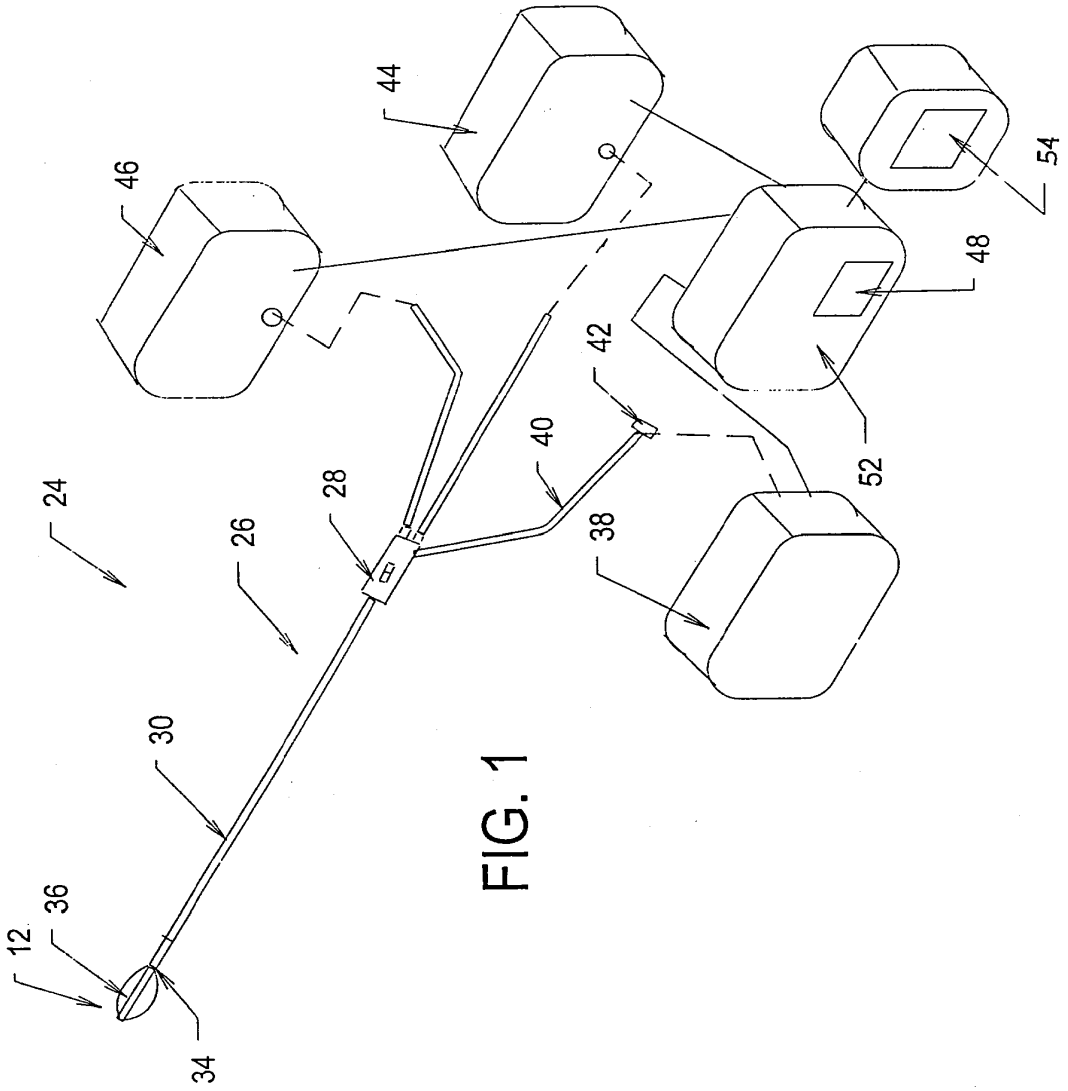


FIG. 1

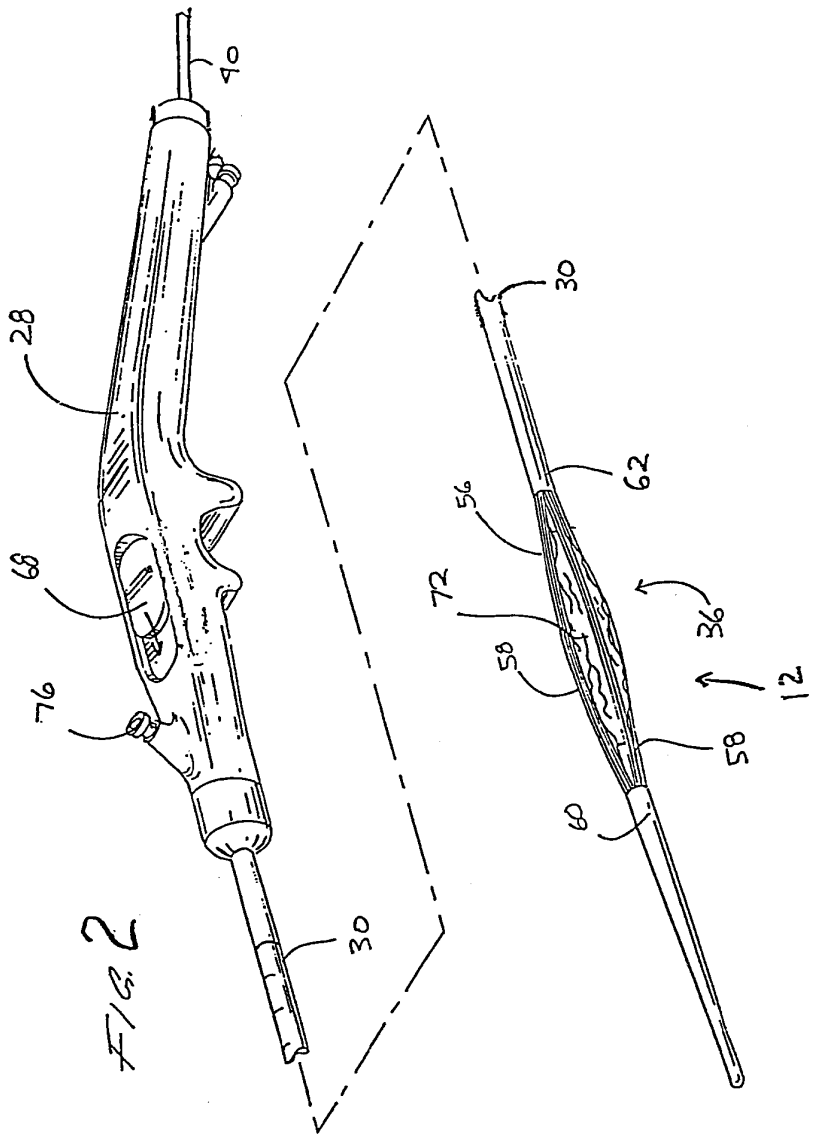


FIG. 2

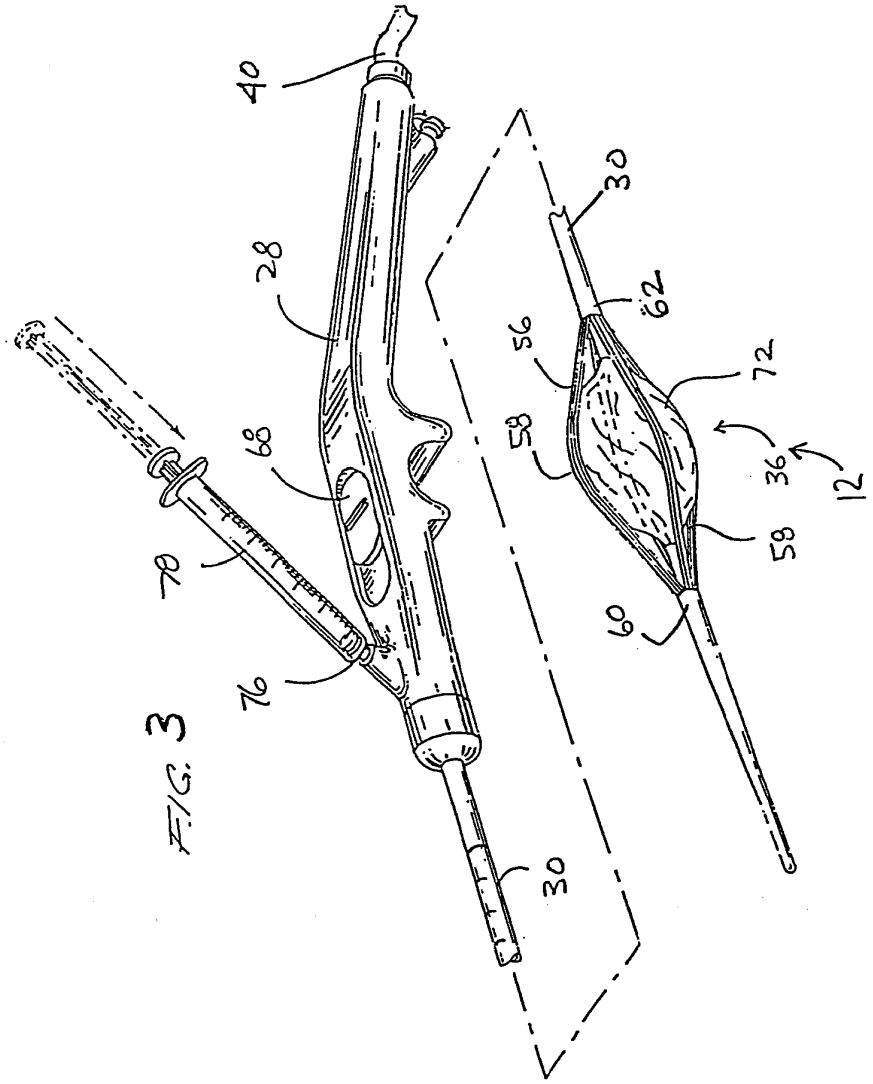


FIG. 3

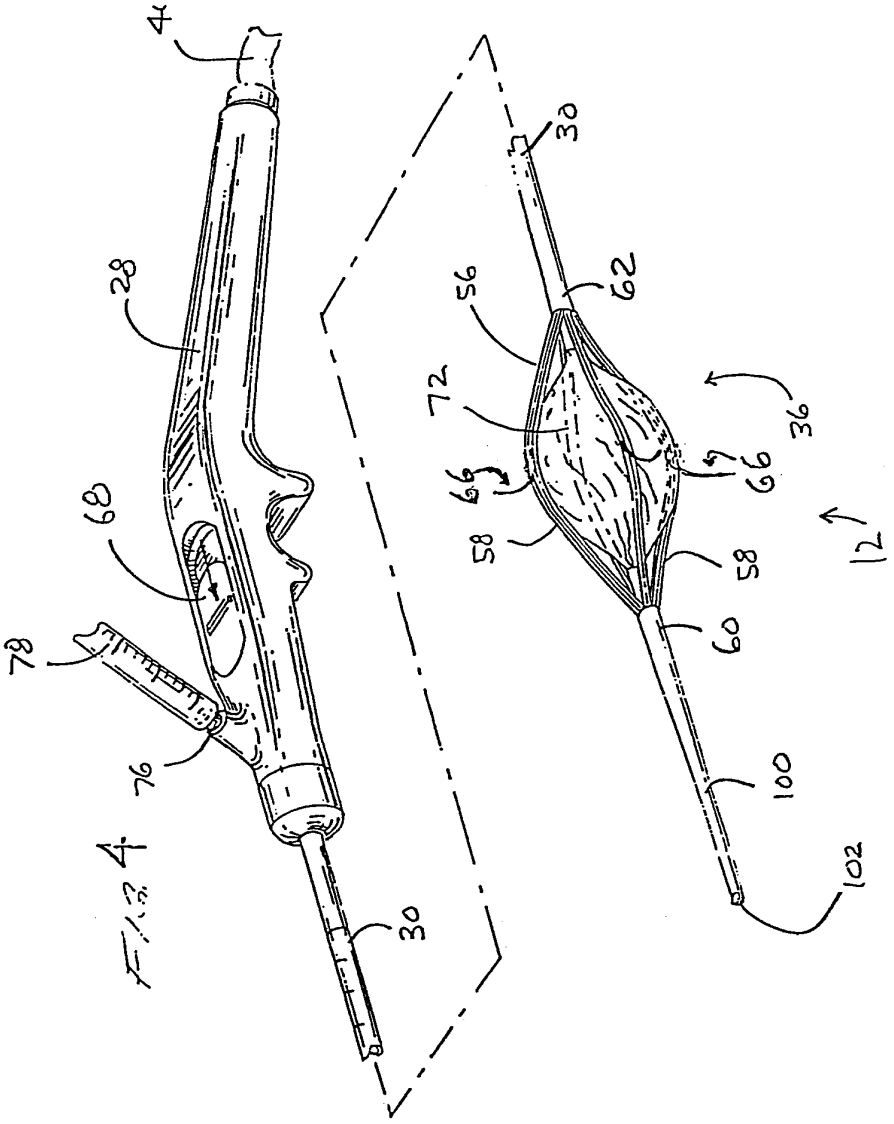


Fig. 4

Fig. 5

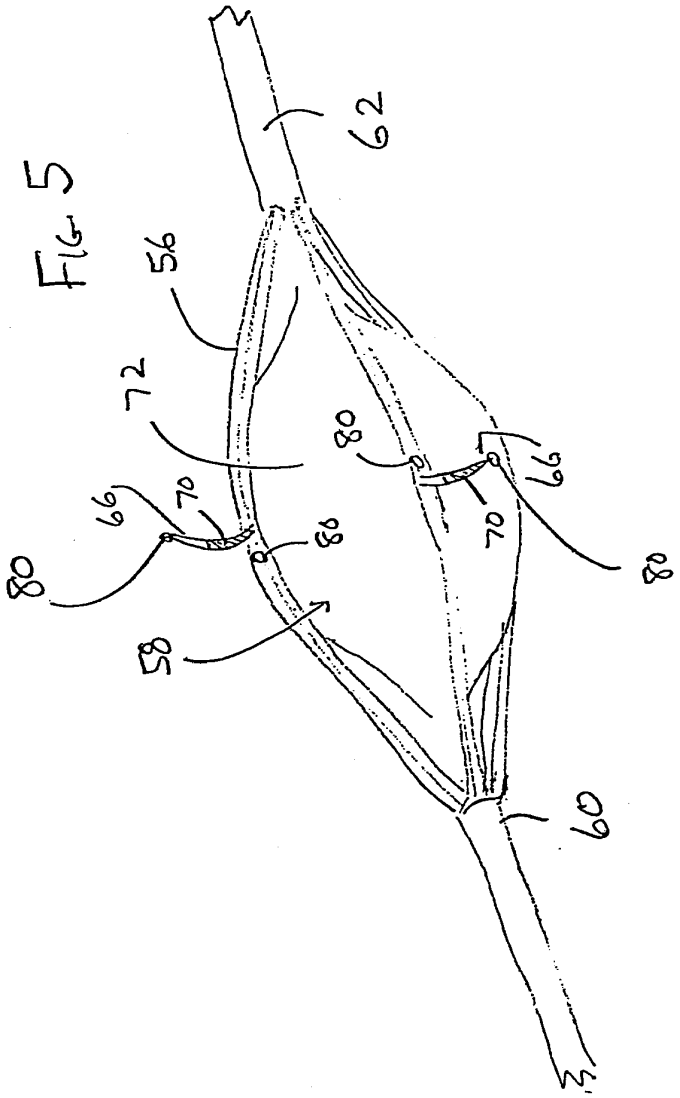


FIG. 6

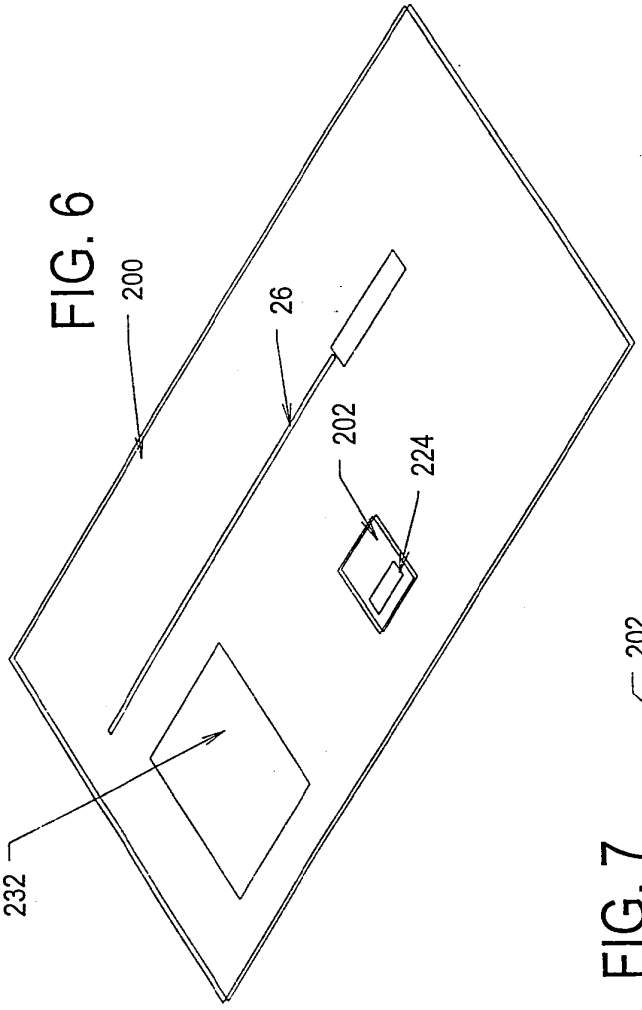
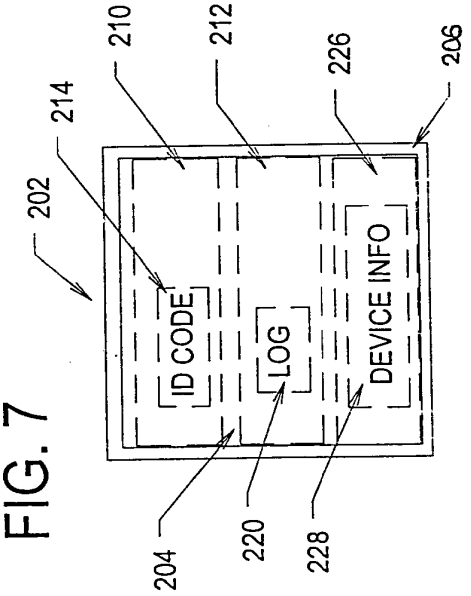

200
26
202
224
232

FIG. 7


210
212
226
206
214
202
ID CODE
LOG
DEVICE INFO
204
220
228

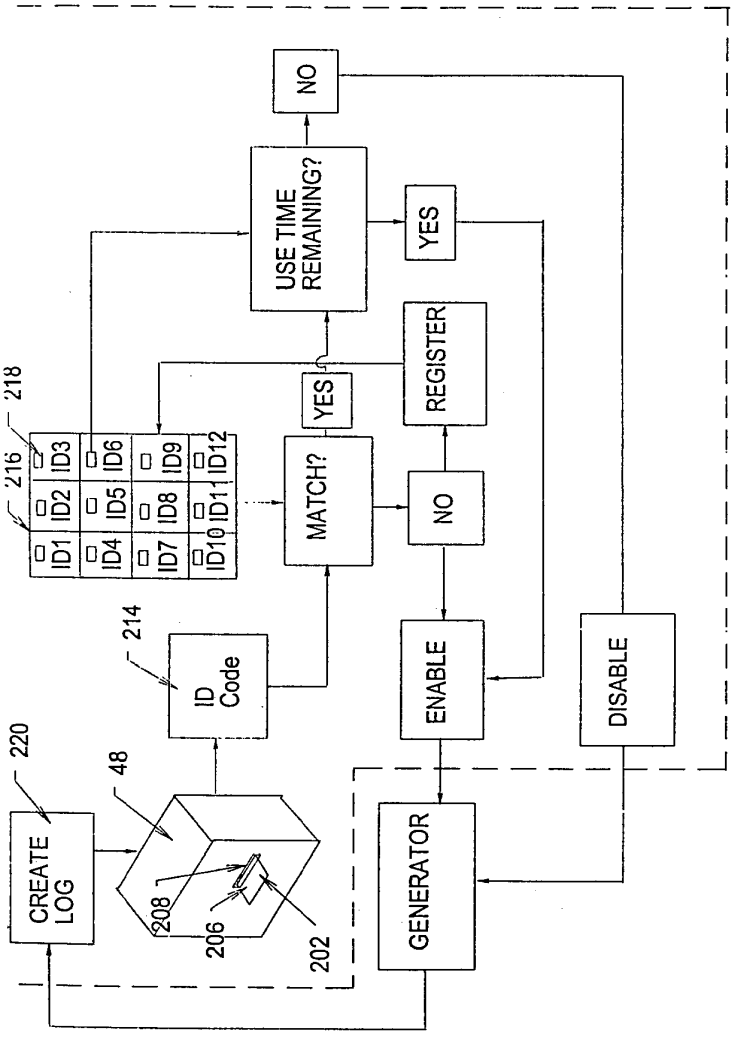
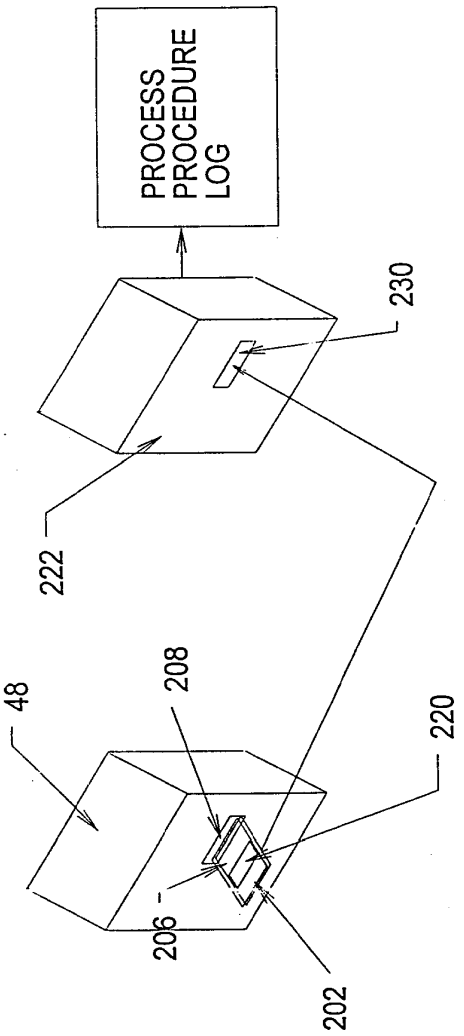

NO
USE TIME REMAINING?
YES
REGISTER
YES
218
216
ID1 ID2 ID3
ID4 ID5 ID6
ID7 ID8 ID9
ID10 ID11 ID12
MATCH?
NO
214
ID Code
ENABLE
DISABLE
220
48
CREATE LOG
208
206
202
GENERATOR

FIG. 8

FIG. 9



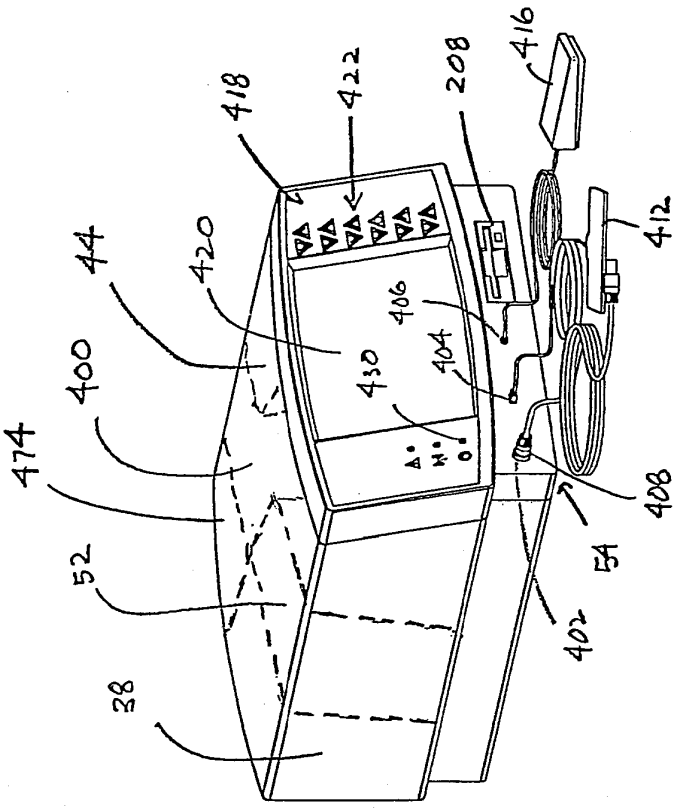


Fig. 10

Fig. 11

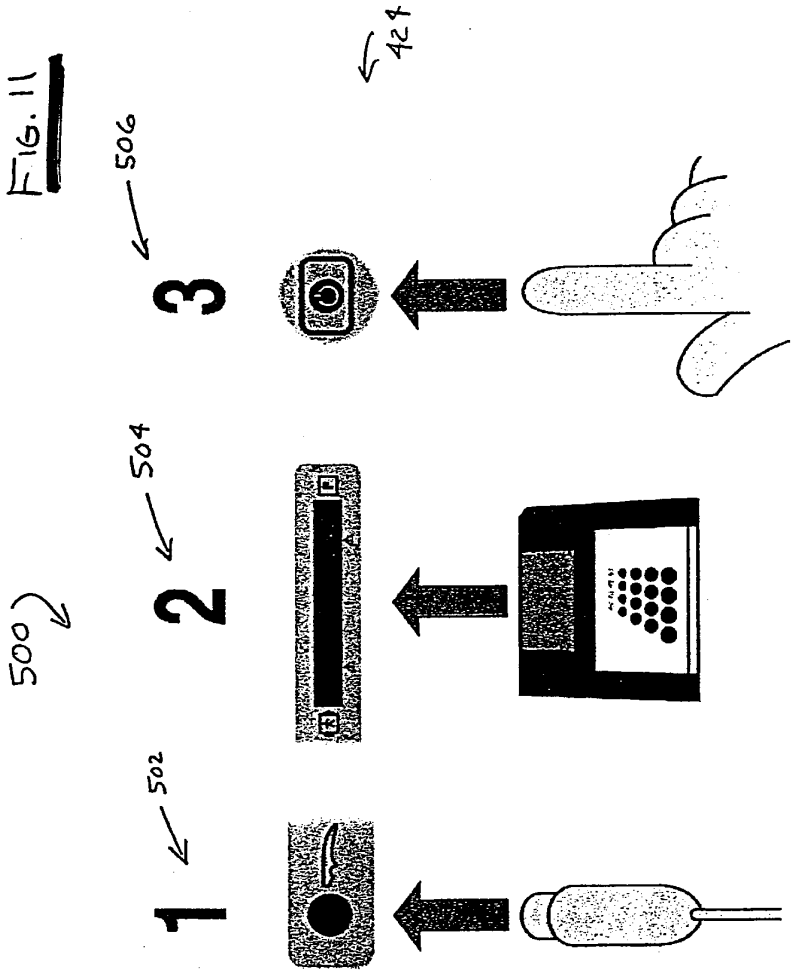


Fig. 12

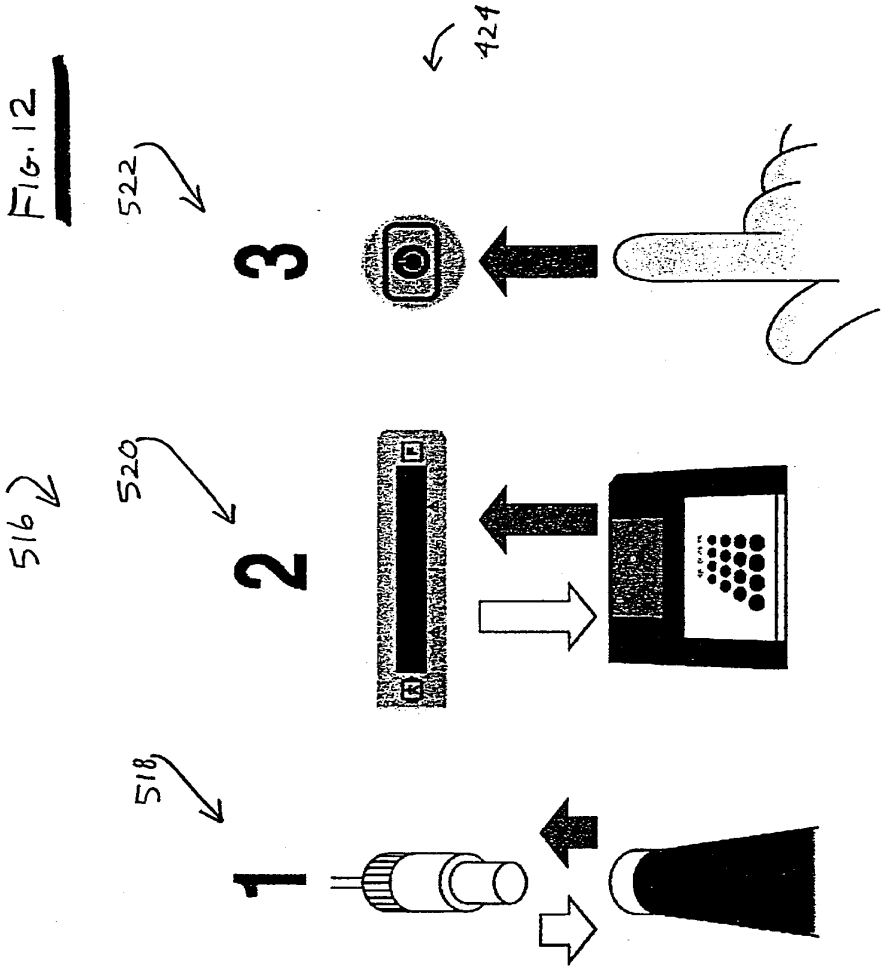
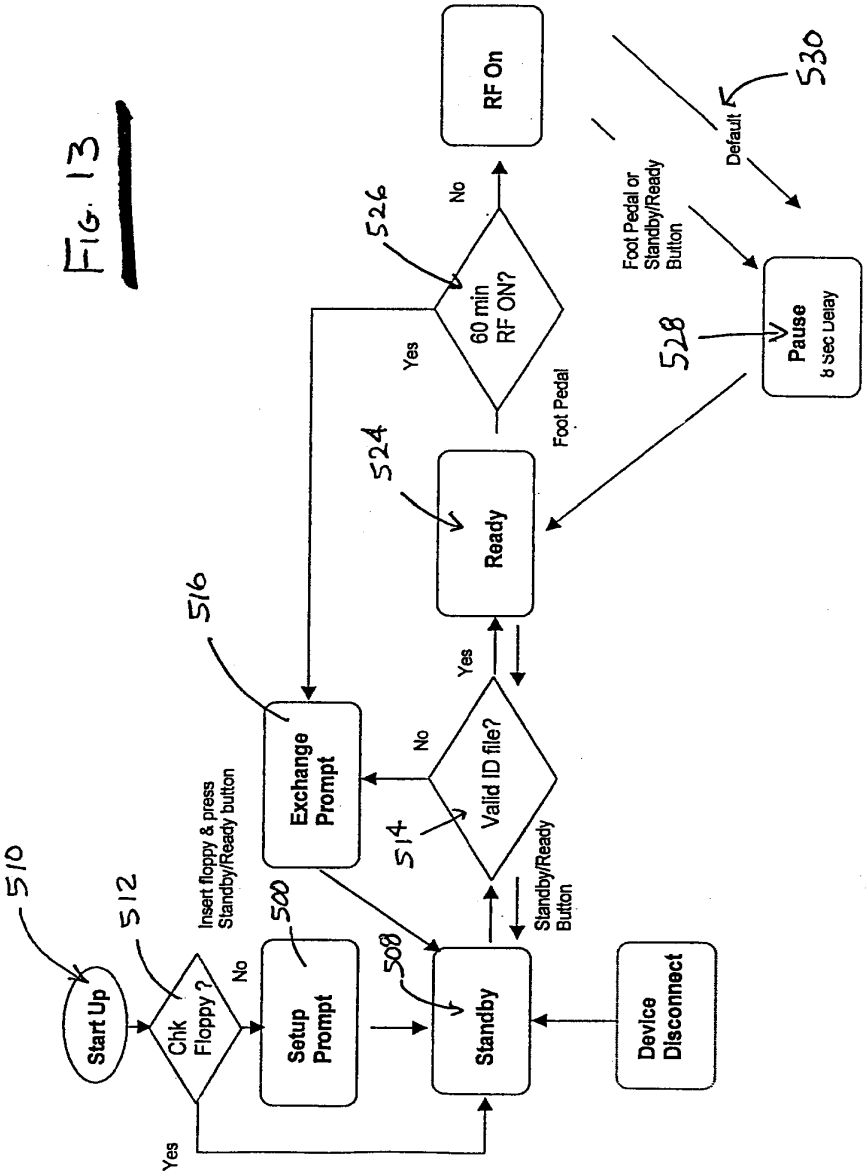


Fig. 13


Start Up
510
Chk Floppy ?
512
No
Yes
Insert floppy & press Standby/Ready button
Setup Prompt
500
Exchange Prompt
516
Valid ID file?
514
No
Yes
Standby/Ready Button
Standby
508
Device Disconnect
Ready
524
Foot Pedal
60 min RF ON?
526
No
Yes
RF On
Foot Pedal or Standby/Ready Button
Pause
6 sec Delay
528
Default
530

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/24461

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :A61B 18/18
US CL :606/41

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)

U.S. : 606/34,41,42; 607/101,102; 600/300,372,374; 128/920; 345/10,11,24,27,156

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

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EAST

search terms: key card, identification code, surgical, GUI

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,848,969 A (Panescu et al) 15 Dec 1998, whole document	1-11
Y	US 5,742,718 A (Harman et al) 21 April 1998, whole document	1-11
A,P	US 6,106,460 A (Panescu et al) 22 Aug 2000, whole document	1-11

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"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
"A"	document defining the general state of the art which is not considered to be of particular relevance	"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
"E"	earlier document published on or after the international filing date	"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
"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)	"&"	document member of the same patent family
"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		

Date of the actual completion of the international search 09 NOVEMBER 2000	Date of mailing of the international search report 22 JAN 2001
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer MICHAEL PEFFLEY Telephone No. (703) 308-0858

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Espacenet

Bibliographic data: WO2015013252 (A1) — 2015-01-29

TREATMENT OF ALZHEIMER'S DISEASE

Inventor(s): SHANTHA TOTADA R [US] ± (SHANTHA, TOTADA R)

Applicant(s): WEDGE THERAPEUTICS LLC [US] ± (WEDGE THERAPEUTICS, LLC)

Classification: - international: ***A61N1/30***
- cooperative: **A61M25/10 (EP)**; **A61M31/00 (EP)**; **A61M37/00 (EP)**; **A61N1/0546 (EP)**; **A61N1/36017 (EP)**; **A61N1/36025 (EP)**; A61M2025/105 (EP); A61M2025/1054 (EP); A61N1/36082 (EP)

Application number: WO2014US47566 20140722 Global Dossier

Priority number (s): US201361857008P 20130722

Abstract of WO2015013252 (A1)

A safe and effective electrical impulses delivering device to stimulate the CNS by transmitting electrical impulses through olfactory nerves, sphenopalatine ganglion and its branches; cranial nerve III, IV, V, VI,; pituitary gland, hypothalamo hypophysial tract, thalamus, thalamic radiation, brain stem, and cerebellum for the treatment of Alzheimer's diseases is described.

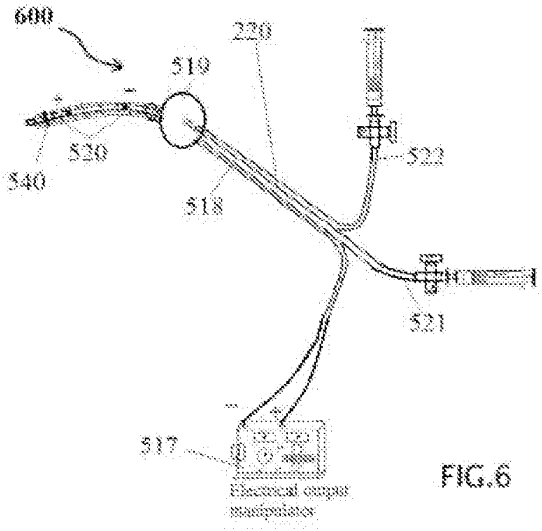


FIG.6

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Aerin Medical Inc. v. Neurent Medical Ltd.
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(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, LT, 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, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK,

[Continued on next page]

(54) Title: TREATMENT OF ALZHEIMER'S DISEASE

(57) Abstract: A safe and effective electrical impulses delivering device to stimulate the CNS by transmitting electrical impulses through olfactory nerves, sphenopalatine ganglion and its branches; cranial nerve III, IV, V, VI,; pituitary gland, hypothalamo hypophysial tract, thalamus, thalamic radiation, brain stem, and cerebellum for the treatment of Alzheimer's diseases is described.

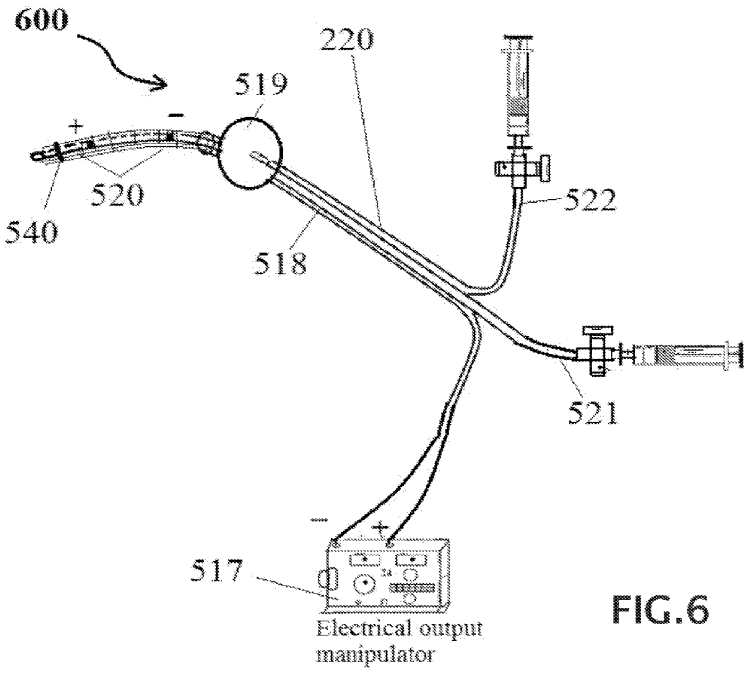


FIG.6

WO 2015/013252 A1

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).

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

TREATMENT OF ALZHEIMER'S DISEASE

PRIORITY

This application claims the benefit of priority to U.S. Provisional Application No. 61/857,008 filed July 22, 2013 entitled "TREATMENT OF ALZHEIMER`S DISEASE" the entire disclosure of which is incorporated herein by reference for all purposes.

FIELD OF THE INVENTION

This invention disclosure relates to methods of treating Alzheimer's disease (AD) and other neurodegenerative diseases by electrical impulses delivered to the central nervous system (CNS) through one or more of the olfactory nerves (ORE), trigeminal nerve branches, sphenoid sinus with its 10 (five on each side) cranial nerves surrounding it, and pituitary-hypothalamic-hypophysis complex; and sphenopalatine ganglion, such as to be received at the central nervous system. The present disclosure involves a medical device and medical procedures that stimulate nerves by transmitting electrical energy to adjacent nerves From there the energy is transmitted to the central nervous system non-invasively to treat Alzheimer's and other neurodegenerative diseases. This medical procedure is defined as being non-invasive when no break in the skin (or other surface of the body, such as a wound bed) is created through use of the method, and when there is no contact with an internal body cavity beyond a body orifice (Examples: mouth, anus, external auditory meatus of the ear, nasal passages and its air sinuses). As compared to non-invasive methods described herein, invasive (including minimally invasive procedures) procedures do involve inserting a substance or device into, through the skin, or into an internal body cavity beyond a body orifice.

BACKGROUND OF THE INVENTION

Neural activity is controlled by electrical impulses or "action potentials" generated in and propagated by neurons. In an inactive dormant state, a neuron is negatively polarized, and exhibits a resting membrane potential that is typically between -70 and -60 mV. Through electrical or chemical connections known as synapses, any given neuron receives from other neurons excitatory and inhibitory input signals or stimuli. A neuron integrates the excitatory and inhibitory input signals it receives, and generates or fires a series of action potentials in the event that

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the integration exceeds a threshold potential. A neural firing threshold may be, for example, approximately -55 mV Action potentials propagated to the neuron's synapses, then conveyed to other neurons to which the neuron is connected through the synapses connected by axons and dendrites.

Neural activity in the brain is influenced by electrical energy supplied from a waveform generator type of device as explained in this invention. Nerve stimulation is accomplished directly or indirectly by depolarizing a nerve membrane, causing the discharge of an action potential; or by hyperpolarization of a nerve membrane, preventing the discharge of an action potential. Such stimulation may occur after electrical energy, or also other forms of energy, transmitted to the vicinity of a nerve [Rattay, F. The basic mechanism for the electrical stimulation of the nervous system. Neuroscience Vol. 89, No.2, pp. 335-346,1999; Heimbur, T. G, Andrew D. Jackson. On soliton propagation in biomembranes and nerves. PNAS vol. 102 (no. 28, Jul. 12, 2005):9790-9795]. Nerve stimulation is measured directly as an increase, decrease, or modulation (inflection) of the activity of nerve fibers. It may be also secondary from the physiological effects that follow the transmission of electrical energy to the nerve fibers, its connected neurons, glia, and neuropil.

Electrical stimulation of the brain with implanted electrodes has been approved for the treatment of essential tremor and Parkinson's disease. The principle underlying these approaches involves disruption and modulation of hyperactive neuronal circuit transmission at specific sites in the brain by electrical stimulation by implanting electrodes at these sites. These electrical stimulation procedures are expensive, may not work as desired, and are invasive procedure conducted with the patient conscious and a participant in the surgery. Our method is used while the patient is awake and without invasive surgical procedure. The successful applications of modem electrophysiology are the cardiac pacemaker, electrical stimulation of nerves for the treatment of radiating pain in the lower extremities by stimulating the sacral nerve roots at the bottom of the spinal cord, and electrical stimulation of the vagus nerves for treatment of epilepsy and depression (U.S. Pat. No. 4, 702, 254).

Neural stimulation systems encompass a pulse generator and an electrode assembly as described here in this invention. The present disclosure involves such a

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device and medical procedures that stimulate nerves (nerve fibers and neurons) by transmitting energy to nerves and tissue (neuropil) non-invasively with no break in the skin or mucus membrane. The neurons of the brain (central nervous system-CNS) communicate via a relay system (through synapses and nerve fibers) of electrical impulses and specialized molecules that play an important role in the generation and conduction of these conductive electrical pulses called neurotransmitters. A neuron generates an electrical impulse, causing the cell to release its neurotransmitters, which in turn, bind to adjacent neurons or synapses. Then the recipient neurons (through synapses) generate their own electrical impulses and release their neurotransmitters, triggering the process in more neurons and the processes continues until the impulse becomes to weak to be conducted, or no longer produced. This is how messages to and from the CNS to various structures are propagated with their effect felt all over the body. Researchers have found that the electrical stimulation causes the neurons to release adenosine triphosphate (ATP), a high-energy molecule essential to many biological processes including myelinization and nerve conduction. The invention described herein is intended to increase the ATP levels, which will in turn enhance all the activities of the neuron, its extensions, and synapses.

Insulin and other therapeutic agents are incorporated in the treatment of Alzheimer's disease, along with the inventive device described here as illustrated in U. S. Patent Application Publication Number US 2012/0323214 Al (Pub. Date: Dec. 20, 2012; Alzheimer's Disease Treatment With Multiple Therapeutic Agents Delivered To The Olfactory Region Through A Special Delivery Catheter And Iontophoresis by Totada R. Shantha). Other therapeutic agents to treat Alzheimer's disease along with electrical stimulation of the nerves (nerve fibers and neurons) by transmitting energy to nerve tissue non-invasively as described will augment and amplify each other's effect besides its own effects to increase the memory and cognition in AD. Both electrical energy and insulin have a trophic effect on the neurons, and the insulin is a mitogenic. They promote the glucose metabolism within the neuronal mitochondria, which increases the ATP production aerobically. The ATP enhances the protein, peptides, amino acid synthesis, and their output by the nucleus and endoplasmic reticulum by using the ATP energy provided by the

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mitochondria. Thus, the combination enhances the protein-peptide-amino acid complex production of every kind, including tau proteins involved in the construction and maintenance of neurotubules, neurotrophic factors, neurotransmitters, enzymes, and hormones, that are also involved in memory and cognition. Electrical impulses and insulin augment the production of substrates needed to assemble neurotransmitters; and protein complexes to maintain the cell wall, the integrity of the neurons, and their extensions and synapses. Thus, electrical energy with insulin along with other therapeutic agents described in this invention prevents or delays further decay of the neurons afflicted by this disease, reduces the ROS damage to the remaining healthy nerve tissue, improves synaptogenesis, enhances the output of glutathione, and augments the production of acetylcholine and their functions as memory enhancer and neurotransmitter.

The cited patent publication, U. S. Patent Application Publication Number US 2012/0323214 Al (the '214 publication) contains information that overlaps with certain aspects of the present disclosure. But the present description includes certain additional features. The '214 publication involves stimulation to produce electroporation and inontphoresis, to cause membranes of nerve or other tissue more permeable to therapeutic agents, allowing improved delivery of therapeutic agents to the central nervous system by passing the blood-brain-barrier. Methods of and devices of the description may cause this same effect, but in a distinct manner transmit impulses to nerve fibers of up to fourteen nerve trunks, which cause or allow the impulse to spread to various centers of the brain and wake the brain to enhance memory, increase memory, and cure or curtail AD and other neurological diseases or one or more symptom thereof. The electrical activity generated may be similar to electrical activity associated with biological release of a neurotransmitter such acetyl choline, generating electrical activity that is translated into various neurological activities including memory and recall.

Electrical synapsis is the term used to describe the reaction in which the membranes of the two neurons or cells touch and share proteins. This allows the action potential to pass directly from one neuronal cell membrane to the next. Our invention will enhance the mechanism of electrical synapse.

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Action potentials occur in several types of animal cells. Such cells are called excitable cells; for example neurons, muscle cells, and endocrine cells, and some plant cells. In neurons, action potential plays a fundamental role in cell-to-cell communication. In muscle cells, for instance, an action potential is the first step in the chain of events leading to contraction. Action potentials in the neurons are known as "nerve impulses" or "spikes", and the temporal sequence of action potentials generated by a neuron is called its "spike train". A neuron that emits an action potential is said to "fire".

Action potentials in neurons (other cells) are generated by special types of voltage-gated ion channels embedded in a cell's plasma membrane (Barnett MW, Larkman PM (June 2007). "The action potential". Pract Neurol 7 (3): 192–7). These channels shut when the membrane potential is near the resting potential of the cell, but they rapidly begin to open if the membrane potential increases to a precisely defined threshold value. When the channels open, they allow an inward flow of sodium ions, which changes the electrochemical gradient, which in turn produces a further rise in the membrane potential. This then causes more channels to open, producing a greater electric current, and so on. The process proceeds explosively until all of the available ion channels are open, resulting in a large upswing in the membrane potential. The rapid influx of sodium ions causes the polarity of the plasma membrane to reverse, and the ion channels then rapidly inactivate. As the sodium channels close, sodium ions can no longer enter the neuron, and they are actively transported out of the plasma membrane. Potassium channels are then activated, and there is an outward current of potassium ions, returning the electrochemical gradient to the resting state. After an action potential has occurred, there is a transient negative shift, called the after hyper-polarization or refractory period, due to additional potassium currents and this mechanism prevents an action potential traveling back the way it just came.

In animal cells including humans, there are two primary types of action potentials:

One type is generated by voltage-gated sodium channels; sodium-based action potentials usually last for less than one millisecond. The second type is generated by voltage-gated calcium channels; calcium-based action potentials may last for 100

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milliseconds or longer. In some types of neurons, slow calcium spikes provide the driving force for a long burst of rapidly emitted sodium spikes. In cardiac muscle cells, on the other hand, an initial fast sodium spike provides a "primer" to provoke the rapid onset of a calcium spike, which then produces cardiac muscle contraction.

Almost all cells from animals, plants, and fungi function as batteries in the sense that they maintain a voltage difference between the interior and the exterior of the cell, with the interior being the negative pole of the battery. The voltage of a cell is measured in millivolts (mV), or thousandths of a volt. A typical voltage for an animal cell is –70 mV, approximately one-fifteenth of a volt. Because cells are so small, voltages of this magnitude give rise to very strong electric forces within the cell membrane.

A cell membrane consists of a layer of lipid molecules with larger protein molecules embedded in it. The lipid layer is highly resistant to movement of electrically charged ions, so it functions mainly as an insulator. The large membrane-embedded protein molecules, in contrast, provide channels through which ions can pass across the cell membrane, and some of the large molecules are capable of actively moving specific types of ions from one side of the membrane to the other. This is the basis of sodium and calcium pumps, which generate action potential to initiate cell activity and related function especially in the CNS neuronal complex as described in this invention.

As the membrane potential is increased, sodium ion channels on the cell membrane open, allowing the entry of sodium ions into the cell. This event is followed by the opening of potassium ion channels that permit the exit of potassium ions from the cell. The inward flow of sodium ions increases the concentration of positively charged cations in the cell and causes depolarization, where the potential of the cell is higher than the cell's resting potential. The sodium channels close at the peak of the action potential, while potassium continues to leave the cell. The efflux of potassium ions decreases the membrane potential or hyperpolarizes the cell. For small voltage increases from rest, the potassium current exceeds the sodium current and the voltage returns to its normal resting value, typically –70 mV. However, if the voltage increases past a critical threshold, typically 15 mV higher than the resting value, the sodium current dominates. This results in a runaway condition

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whereby the positive feedback from the sodium current activates even more sodium channels. Consequently, the cell "fires," producing an action potential propagated along the nerve fibers to the next relay and so on. Currents produced by the opening of voltage-gated channels in the course of an action potential are typically significantly larger than the initial stimulating current. Thus, the amplitude, duration, and shape of the action potential are determined largely by the properties of the excitable membrane and not the amplitude or duration of the stimulus.

The all-or-none property of the action potential sets it apart from graded potentials such as receptor potentials, electrotonic potentials, and synaptic potentials, which scale with the magnitude of the stimulus. A variety of action potential types exist in many cell types and cell compartments as determined by the types of voltage-gated channels, leak channels, channel distributions, ionic concentrations, membrane capacitance, temperature, and other factors.

The principal ions involved in an action potential are sodium and potassium cations; sodium ions enter the cell, and potassium ions leave, restoring equilibrium. Relatively few ions need to cross the membrane for the membrane voltage to change drastically. The ions exchanged during an action potential, therefore, make a negligible change in the interior and exterior ionic concentrations. The few ions that do cross are pumped out again by the continuous action of the sodium–potassium pump, which, with other ion transporters, maintains the normal ratio of ion concentrations across the membrane. Calcium cations and chloride anions are involved in a few types of action potentials, such as the cardiac action potential and the action potential in the single-cell alga Acetabularia, respectively.

Although action potentials are generated locally on patches of excitable membrane, the resulting currents can trigger action potentials on neighboring stretches of membrane, precipitating a domino-like propagation. In contrast to the passive spread of electric potentials (electrotonic potential), action potentials are generated anew along excitable stretches of membrane and propagate without decay. Myelinated sections of axons are not excitable and do not produce action potentials and the signal is propagated passively as electrotonic potential. Regularly spaced unmyelinated axons, called the nodes of Ranvier, generate action potentials to boost the signal. Known as saltatory conduction, this type of signal propagation provides a

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favorable exchange of a signal velocity and axon diameter. Depolarization of axon terminals, in general, triggers the release of neurotransmitters into the synaptic cleft. In addition, back propagating action potentials have been recorded in the dendrites of pyramidal neurons, which are ubiquitous - everywhere in the neocortex. These are thought to have a role in spike-timing-dependent plasticity.

Nevertheless, the main excitable cell is the neuron, which also has the simplest mechanism for the action potential. Neurons are electrically excitable cells composed, in general, of one or more dendrites, a single soma, a single axon and one or more axon terminals. The dendrite is one of the two types of synapses, the other being the axon terminal boutons. Dendrites form protrusions in response to the axon terminal boutons. These protrusions or spines are designed to capture the neurotransmitters released by the presynaptic neuron. They have a high concentration of ligand-activated channels. It is, therefore, here where synapses from two neurons communicate with one another. These spines have a thin neck connecting a bulbous protrusion to the main dendrite. This ensures that changes occurring inside the spine are less likely to affect the neighboring spines. The dendritic spine can, therefore, with rare exception, act as an independent unit. The dendrites then connect onto the body of the neurons. The neuron houses the nucleus, which acts as the regulator for the neuron. Unlike the spines, voltage activated ion channels populate the surface of the soma, these channels help transmit the signals generated by the dendrites. Emerging out from the soma is the axon hillock. This region is differentiated by having an incredibly high concentration of voltage-activated sodium channels. In general, it is considered a spike initiation zone for action potentials. Multiple signals generated at the spines and transmitted by the soma all converge here. The present inventive device will initiate and activate the electrical signal and conductivity in these neuronal components, which are silenced in the neurons of Alzheimer's.

An axon is a thin tubular protrusion traveling away from the soma of a neuron. The axons are insulated by a myelin sheath. Myelin is composed of Schwann cells that wrap themselves multiple times around the axonal segment in the peripheral nerves, and it is formed by the oligodendroglia in the CNS. This forms a thick fatty layer that prevents ions from entering or escaping the axoplasm and their

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coming in contact with adjacent axons. This insulation also prevents significant signal decay as well as ensuring faster signal speed. This insulation, however, has the restriction that no channels can be present on the surface of the axon. There are, therefore, regularly spaced patches of membrane, (nodes of Ranvier) which have no insulation. These nodes of Ranvier are considered to be 'mini axon hillocks', as their purpose is to boost the signal in order to prevent significant signal decay. At the furthest end, the axon loses its insulation and begins to branch into several axon terminals. These axon terminals then end in the second class of synapses, axon terminal buttons. These buttons have voltage-activated calcium channels, which come into play when signaling other neurons. Our invention of delivering the electrical impulses helps in activation of voltage activated ion channels.

The action potential generated at the axon hillock propagates as a wave along the axon. The currents flowing inwards at a point on the axon during an action potential spread out along the axon, and depolarize the adjacent sections of its membrane. If sufficiently strong, this depolarization provokes a similar action potential at the neighboring membrane patches. This basic mechanism was demonstrated by Alan Lloyd Hodgkin in 1937. This mechanism discovered by Hodgkin is one of the basis and foundation of our invention to treat Alzheimer's and other neurological - neurodegenerative diseases.

The Na and K ions play a major role in the production of electrical impulses in the neurons and nerve fibers. The concentration of potassium ions inside a cell is ten times greater than the extracellular K+ concentration, and vice versa for sodium ions. A special protein in the cell and nerve fiber membrane (the Na-K pump) actively transports K+ into the cell and Na+ out of the cell, using ATP as the source of energy in the resting axon membrane. There is a selective permeability to K+ ions, allowing the net efflux of a small number of K+ ions and leaving the axoplasm electrically negative (polarized) while making the outside electrically positive. This accounts, for the most part, for the cell's "resting potential" which typically equals -70 millivolts.

Inward currents, carried by Na+ ions, depolarize the cell whereas outward currents, carried by K+ ions repolarize the cell. Repolarization of the membrane to the negative resting value occurs because of three factors: 1. The force moving Na+

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into the cell diminishes as the axoplasmic potential becomes less negative; 2. the sodium channels ultimately close during a depolarization; 3. new potassium channels open and allow a large, outward K+ current that returns the axoplasmic potential toward its resting value. Sodium ions tend to flow in to the axon because it is now electrically negative inside and the Na+ ions are more concentrated outside. The selective permeability to Na^+ takes place when specific "sodium channels" in the axon membrane are opened. That means the impulses have a depolarization phase and a repolarization phase.

In order to initiate an impulse in the CNS, conditions must exist wherein a net inward current occurs. This requires that a sufficient number of sodium channels are opened in order to overcome the actions of the outward current pathways. A small depolarization of 15 to 20 mV is sufficient to initiate an impulse in a resting axon and neuron. However, a larger stimulating depolarization current is needed shortly after a preceding impulse. Our invention transmits both small and large depolarization electrical impulses without the use of ATP energy and the least or no active participation of sodium and potassium channels in the cell membrane for initiation of an electrical impulse, for example to bring back memory to silent Alzheimer's brain to resume activity.

Once an action potential has taken place at a patch of membrane, the membrane patch needs time to recover before it can fire again. At the molecular level, this absolute refractory period corresponds to the time required for the voltage-activated sodium channels to recover from inactivation, i.e., to return to their closed state. There are many types of voltage-activated potassium channels in neurons, some of them inactivate fast (A-type currents) and some of them inactivate slowly or do not inactivate at all; this variability guarantees that there will be always an available source of current for repolarization, even if some of the potassium channels are inactivated because of preceding depolarization. On the other hand, all neuronal voltage-activated sodium channels are inactivated within several milliseconds during strong depolarization, thus making following depolarization impossible until a substantial fraction of sodium channels have not returned to their closed state. Although it limits the frequency of firing, the absolute refractory period ensures that the action potential moves in only one direction along an axon. The

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currents flowing in due to an action potential spread out in both directions along the axon. However, only the unfired part of the axon can respond with an action potential; the part that has just fired is unresponsive until the action potential is safely out of range and cannot restimulate that part.

In the usual orthodromic conduction, the action potential propagates from the axon hillock towards the synaptic knobs (the axonal termini); propagation in the opposite direction—known as antidromic conduction—is very rare. However, if a laboratory axon is stimulated in its middle, both halves of the axon are "fresh", i.e., unfired; then two action potentials will be generated, one traveling towards the axon hillock and the other traveling towards the synaptic knobs. This can happen with our device described here to activate the Alzheimer's disease affected neuronal complex.

Our invention activates the generation and propagation of action potential as described above and below without much participation of sodium, potassium, and calcium ion pumps, thus helping the neuronal action through axons and dendrites into the synapses and nerve cell itself, which translates into various functions of the brain including memory, recall, and cognition with augmentation effect on the neurotransmitters.

In the nervous system, the generation of electrical impulses and propagation of these impulses is due to neurotransmitters' mediated electrical activity which must be in place in order to activate the nerve conduction, which is important for proper functioning of CNS and all the functions including motor, sensory, memory, cognition, and related functions. The electrical generation takes place due to changes in the ionic concentration in the sodium and potassium at the cell membrane. If there is no generation of electrical impulses within the neurons and their processes, transmitted through the synapses, and conduction of these electrical impulses generated due to the activity of neurotransmitters such as acetylcholine which brings changes in the neuronal body, synapses, nerve fibers and terminals, the function of the CNS decreases is not carried out. The part of the brain that lacks such electrical activity becomes silent as seen in Alzheimer's. This is what also happens in patients with many other degenerative diseases of the CNS. Our inventive device and method of use enhance the electrical activity of the CNS,

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augments the effect of remaining residual neurotransmitters, and thus restores function in Alzheimer's disease afflicted patients.

The life and functioning of the brain, whether a person is living, functioning normal or not functioning as expected (such as loss of memory seen in Alzheimer's) is evaluated based on the electrical activity of the brain. In modern medicine, the person is pronounced dead if there is no electrical activity of the brain-brain stem based on electroencephalogram (EEG). This tells us how important it is to maintain the electrical activity of the brain for proper functioning of all the neuron-related activities all the time including memory and cognition as well as various CNS initiated motor, sensory, and autonomic nerve functions. This electrical potential generation and its propagation is the lifeline of the brain functioning in totality. Because of low or no neurotransmitter acetylcholine in diseases such as Alzheimer's, the electrical activity is reduced, not generated, defective, or deficient. It is said to be both cause and effect due to synaptic and neuronal decline, associated with reduced acetylcholine neurotransmitter, which is needed to generate and transfer electrical activity of the CNS and make changes to store and retrieve the old and new memories. The present inventive method activates the electrical signals, augments and amplifies the effects without the help of the neurotransmitters, and/or helps it even when the neurotransmitters are very low in concentrations in the CNS, to restore the normal function to the neurons and their synapses. Thus, the invention elaborated in this application will curtail the diseases such as Alzheimer's, senile dementia and others neurodegenerative afflictions, thus restoring the memory and other functions of the CNS.

All cells in the body (tissues and organs) are electrically polarized; in other words, they maintain a voltage difference across the cell's plasma membrane, known as the membrane potential. This electrical polarization results from a complex interplay between protein structures embedded in the membrane, called ion pumps and ion channels. In neurons, the types of ion channels in the membrane usually vary across different parts of the cell, giving the dendrites, axon, and cell body different electrical properties. As a result, some parts of the membrane of a neuron may be excitable (capable of generating action potentials), whereas others are not. The most excitable part of a neuron is usually the axon hillock (the point where the

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axon leaves the cell body), but the axon and the rest of neuronal cell body are also excitable.

Each excitable piece of neuronal membrane has two important levels of membrane potential: the resting potential, which is the value the membrane potential maintains as long as nothing perturbs the cell, and a higher value called the threshold potential. At the axon hillock of a typical neuron, the resting potential is around -70 mV and the threshold potential is around -55 mV. Synaptic inputs to a neuron cause the membrane to depolarize or hyperpolarize; that is, they cause the membrane potential to rise or fall. Action potential is triggered when enough depolarization accumulates to bring the membrane potential up to threshold. When an action potential is triggered, the membrane potential abruptly shoots upward; often reaching as high as +100 mV, then equally abruptly shoots back downward, often ending below the resting level, where it remains for some period. The shape of the action potential is stereotyped; that is, the rise and fall usually have approximately the same amplitude and time course for all action potentials in a given cell. In most neurons, the entire process takes place in less than a thousandth of a second. Many types of neurons emit action potentials constantly at rates of up to 10-100 per second; some types, however, are much quieter, and may go for minutes or longer without emitting any action potentials. Our invention helps the neurons to emit action potential to improve the sensory and motor function of the CNS especially related to memory, recall, and cognition.

THE BLOOD BRAIN BARRIER (BBB) AND ITS IMPLICATIONS IN THE TREATMENT OF CNS DISEASES SUCH AS ALZHEIMER'S

The problem in the treatment of CNS diseases including Alzheimer's is that 98% of therapeutic agents are not transported to, delivered to, or reach the site of pathology in the brain. The BBB is responsible for creating such a barrier to the delivery of therapeutic agents to the brain and spinal cord. This is how the brain is protected from the extraneous assault from various substances and cells that travel all over the body in the blood. The BBB is located in 400 miles of capillaries within the brain and has a unique histological make up compared to the other capillaries in other regions of the body. The endothelial cells of the blood vessels (BV) of the

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CNS differ from the peripheral capillary endothelial cells due to many structural differences such as:

i. Lack of fenestration in the endothelial cells: The endothelial cells are joined by tight junctions, which block the protein molecule movement from within. In addition, they block the hydrophilic transfer of substances from the capillary to the CNS.

ii. These tight endothelium junctions in the BBB are 100 times tighter than similar junctions of other systematic capillary endothelium (Butte AM, Jones HC, Abbot NJ. Electrical resistance across the blood-brain barrier in anaesthetized rats; a development study. J Physiol 1990; 429:47-62.), thus creating a formidable barrier, which blocks almost 98% of the therapeutic agents delivered to the systemic circulation reaching the neuropile and neurons of the CNS. That is why the olfactory nerve mucosal delivery (ORE) of therapeutic agents is the most important method of bypassing these tight junctions of the BBB, delivering the therapeutic agents directly to the CNS for the treatment of Alzheimer's disease and other neurodegenerative diseases.

iii. The endothelial cells contain a specific receptor transport system for given molecules, such as insulin, glucose, glucagon etc. but not for most of the therapeutic agents used.

iv. They display a net negative charge inside the endothelial cell and basement membrane impeding anionic molecules to cross the membrane.

v. They show paucity of pericytes in the wall of these BV.

vi. There are hardly any pinocytotic vesicles in the cytoplasm of the endothelial cells compared to peripheral endothelial blood vessels cells that are involved in uptake and transport of various substances.

vii. Astrocytes foot process covers 95% of the endothelium outer surface.

viii. There is a thick basement membrane encasing these brain capillaries completely.

ix. The cerebral vascular endothelial cell possesses a transcellular lipophilic pathway, allowing diffusion of small lipophilic compounds such as insulin, transferrin, glucose, purines, and amino acids.

x. The BBB prevents passage of ionized water-soluble compounds with a molecular weight greater than 180 Daltons. Many new neuro therapeutic agents have been discovered, but because of a lack of suitable strategies for drug delivery across the

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BBB, these agents are fruitless and only effective if methods to break the BBB are discovered.

xi. The concentration gradients also play a role in transport of therapeutic agents across the systemic BV, but make hardly any such effect across BBB blood vessels of the CNS.

Due to the above-described histological differences in the histological features, the brain blood vessels form a formidable 400 miles of BBB capillaries within the brain. The brain capillaries prevent transport of most of the therapeutic agents (98%) from inside the BV; they also prevent and / or inhibit clearance of neurotoxin compounds such as beta amyloid and their precursor in Alzheimer's; reactive oxygen species, toxic metabolites and their derivatives from the CNS entering the systemic circulation for clearance and to provide homeostatic neuropil milieu functional. Hence, the brain keeps on accumulating toxins with no path or passage to exit from the brain contributing to the CNS afflictions such as beta amyloid in Alzheimer's.

Attempts have been made to break the BBB by shrinking or expanding for disrupting adhesions (mannitol, bradykinin), or by local application of ultrasound. These methods are difficult to adopt by a patient without going to a clinic or hospital. This invention of transmitting the electrical impulses does not have any such barrier. It helps to overcome some of these obstacles posed by the CNS for the treatment of Alzheimer's by generating electrical impulses and breaking the BBB by vascular dilatation to allow therapeutic agents to reach the site of pathology to curtail the disease.

Even today, there is no cure for Alzheimer's disease; the cause and progression of Alzheimer's disease is not well understood and the disease progresses unabated. So is also the case with senile brain atrophy. Symptoms can include confusion, irritability, and aggression, mood swings, trouble with language, and long-term memory loss. As the sufferer declines, they often withdraw from family and society. Gradually, bodily functions are lost, ultimately leading to death in about 7 years (Average lifespan after diagnosis). The disease is associated with plaques and tangles in the brain (Tiraboschi P, Hansen LA, Thal LJ, Corey-Bloom J. The

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importance of neuritic plaques and tangles to the development and evolution of AD. Neurology. 2004;62(11):1984.

Current treatments only help with the symptoms and there are no cures to stop or reverse the progression of the disease. As of 2008, more than 500 clinical trials have been conducted to find ways to treat the disease, but it is unknown if any of the tested treatments will work. At present, the treatment is to use Cholinesterase inhibitors to increase the level of acetylcholine in the CNS. The approved drugs for the management of Alzheimer's symptoms are donepezil (Aricept™), galantamine (Razadyne™), and rivastigmine (branded as Exelon and Exelon Patch™). Mental stimulation, exercise, statins to control cholesterol, and a balanced diet have been recommended as possible ways to delay symptoms in healthy older individuals, but they have not been proven as effective. It is one of the most costly diseases to society, becoming more burdensome with the increasing aged population.

The newest treatment for Alzheimer's is Bexarotene (Targretin®), a vitamin A derivative, used in skin for cutaneous T cell lymphomas, off label used for lung cancer, breast cancer, and Kaposi's sarcoma show promising results in mice studies. Bexarotene is a member of a subclass of compounds called retinoids. Certain retinoids are believed to selectively activate retinoid X receptors (RXRs). A chemical name for bexarotene is 4-[I-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl) ethenyl] benzoic acid. Mice studies showed that a single dose lowered the most toxic form of the amyloid beta peptide by 25 percent within six hours, an effect that lasted for up to three days in experimental mice according to Dr. Paige Cramer of Case Western Reserve University School of Medicine. Bexarotene quickly and dramatically improved brain function and social ability and restored the sense of smell in mice bred with a form of Alzheimer's disease. One example of the improved behaviors involved the typical nesting instinct of the mice. When Alzheimer's-diseased mice encountered tissue paper material suited for nesting, they did nothing to create a space to nest. This reaction demonstrated that they had lost the ability to associate the tissue paper with the opportunity to nest. Just 72 hours after the bexarotene treatment, however, the mice began to use the paper to make nests. Administration of the drug also improved the ability of the mice to sense and respond to odors.

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The plaques in the CNS of Alzheimer's are compacted aggregates of amyloid that form in the brain and are the pathological hallmark of Alzheimer's disease. It appears that the bexarotene reprogrammed the brain's immune cells to phagocytose the amyloid deposits they encountered. This observation demonstrated that the drug addresses the amount of both soluble and deposited forms of amyloid beta within the brain and reverses the pathological features of the disease.

Bexarotene does not act directly on the β amyloid; instead, it activates retinoid receptors on brain cells that increase production of a fat-protein complex, apolipoprotein E, that helps to clear excess β amyloid in the fluid-filled space (neuropile, subarachnoid space, cerebrospinal fluid, Virchow-Robin space) between neurons. Dr. Landreth and his colleagues at Case Western Reserve University at Cleveland, Ohio; chose to explore the effectiveness of bexarotene for increasing ApoE expression. The elevation of brain ApoE levels, in turn, speeds the clearance of amyloid beta from the brain. Bexarotene acts by stimulating retinoid X receptors (RXR), which control how much ApoE is produced in the CNS. The invention described here can activate retinoid receptors on brain cells that increase production of a fat-protein complex, apolipoprotein E that helps to clear excess β amyloid to curtail Alzheimer's disease. Bexarotene also appears to enhance another cleanup process called phagocytosis, in which the brain immune cells engulf amyloid and move it away from the neuropile (Cramer P E, et al. (9 February 2012). "ApoE-Directed Therapeutics Rapidly Clear β-Amyloid and Reverse Deficits in AD Mouse Models". doi:10.1126/science.1217697: Science Express.). Human trials are underway to determine whether the drug crosses the blood-brain barrier and clears amyloid, as it does in mice. These researchers were struck by the speed with which bexarotene improved memory deficits and behavior even as it also acted to reverse the pathology of Alzheimer's disease. The present view of the scientific community is that small soluble forms of amyloid beta cause the memory impairments seen in animal models and humans with the disease. Within six hours of administering bexarotene, however, soluble amyloid levels fell by 25 percent; even more impressive, the effect lasted as long as three days. Finally, this shift was correlated with rapid improvement in a broad range of behaviors in three different mouse models of Alzheimer's.

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It is important to note that insulin has been touted as a hormone in the treatment of Alzheimer's, because it is labeled as third diabetes of the brain (Steen E, Terry BM, Rivera EJ; et al. Impaired insulin and insulin-like growth factor expression and signaling mechanisms in Alzheimer's disease—is this type 3 diabetes? J Alzheimers Dis. 2005;7(1):63-80). The latest study by Craft et al. whose findings are incorporated herein in its entirety; showed that Insulin has a number of important functions in the central nervous system and plays a major role in Alzheimer's (Craft S. et al. Intranasal Insulin Therapy for Alzheimer Disease and Amnestic Mild Cognitive Impairment. Arch Neurol. published online September 12, 2011, Pages 1-13). Brain insulin receptors are heavily and thickly localized in the hippocampus, the entorhinal cortex (olfactory bulb connected), and the frontal cortex. They are found primarily in synapses, where insulin signaling contributes to synaptogenesis and synaptic remodeling (Chiu SL, Chen CM, Cline HT. Insulin receptor signaling regulates synapse number, dendritic plasticity, and circuit function in vivo. Neuron. 2008;58 (5):708-719. Zhao WQ, Townsend M. Insulin resistance, and myloidogenesis as common molecular foundation for type 2 diabetes and Alzheimer's disease. Biochim Biophys Acta. 2009;1792(5):482-496.). Insulin also modulates glucose utilization in the hippocampus and other brain regions and facilitates memory at optimal levels in normal metabolism. The importance of insulin in normal brain function is underscored by evidence that insulin dysregulation contributes to the pathophysiology of Alzheimer's disease (AD), a disorder characterized in its earliest stages by synaptic loss and memory impairment. Our study on people with memory and cognition showed that olfactory nerve delivery through olfactory mucosa resulted in rapid recovery of cognition, and many of the depressed patients became normal. Studies show that Insulin levels and insulin activity in the central nervous system are reduced in AD. Insulin has a close relationship with the β-amyloid peptide, a toxic peptide produced by endoproteolytic cleavage of the amyloid precursor protein. Insoluble Aβ deposits in the brain's parenchyma and vasculature in Alzheimer's is an important pathology found in Alzheimer's disease. Soluble Aβ species, particularly oligomers of the 42 amino acid species (Aβ42), also have synaptotoxic effects (Selkoe DJ. Soluble oligomers of the amyloid beta-protein impair synaptic plasticity and behavior. Behav Brain Res.

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2008;192 (1):106-113.). We believe that bexarotene acts by removing the soluble Aβ species, particularly oligomers of the 42 amino acid species (Aβ42), which has synaptotoxic effects and improves the memory almost within hours after the administration of bexarotene. Insulin will augment and amplify the effects of bexarotene and at the same time reduce the excitotoxic effects of glutamate, make easier to synthesize glutathione, which is neuroprotective, and facilitate to remove the effects of ROS. Its effects can be further augmented by insulin administered to olfactory mucosa and olfactory nerves. Insulin modulates the levels of Aβ and protects against the detrimental effects of Aβ oligomers on synapses. Thus, reduced levels of insulin and of insulin activity contribute to a number of pathological processes that characterize Alzheimer's disease. Restoring insulin to normal levels in the brain may therefore provide therapeutic benefit to adults with Alzheimer's disease and other degenerative brain afflictions.

Peripheral administration of insulin is not possible owing to the risk of hypoglycemia or induction and/or exacerbation of peripheral insulin resistance. In contrast, intranasal administration of insulin provides rapid delivery of insulin to the central nervous system via bulk flow along olfactory and trigeminal subperineural epithelial space, to the SAS of the CNS, CSF and is then distributed to the rest of the brain (Shantha T.R. and Yasuo Nakajima. Histological and Histochemical Studies on the Rhesus Monkey (Macaca Mulatta) Olfactory Mucosa. Yerkes Regional Primate Research Center, Emory University, Atlanta, Georgia: Z. Zellforsch. 103, 291—319 (1970). Shantha T.R.: Peri-vascular (Virchow - Robin) space in the peripheral nerves and its role in spread of local anesthetics, ASRA Congress at Tampa, Regional Anesthesia 17 (March-April, 1992). Shantha T.R. and Bourne G.H.: The "Perineural Epithelium": A new concept. Its role in the integrity of the peripheral nervous system. In Structure and Function of Nervous Tissues. Volume I. pp 379-458. (GH Bourne, Ed.). Academic Press, New York. 1969. U. S. Patent Application Publication Number: 201110020279 Al Rabies cure by T. R. Shantha, U. S. Patent Application Publication Number: US 2012/0323214 Al Pub. Date: Dec. 20, 2012; Alzheimer's Disease Treatment With Multiple Therapeutic Agents Delivered To The Olfactory Region Through a Special Delivery Catheter And Iontophoresis by Totada R. Shantha). The delivery of therapeutic agents including

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insulin is a slower delivery via olfactory bulb axonal transport. Olfactory nerve and olfactory mucosal delivery will not adversely affect blood insulin or glucose levels unless it is delivered to the respiratory mucosa of the nasal cavity. In rodent models, intranasally administered insulin binds to receptors in the hippocampus and the frontal cortex within 60 minutes.

In human studies, intranasal insulin increases insulin levels in cerebrospinal fluid (CSF) within a similar period and acutely enhances memory. Furthermore, a 3-week trial of daily administration of intranasal insulin improved delayed story recall and caregiver-rated functional status in a small sample of adults with AD and in adults with amnestic mild cognitive impairment (aMCI), a condition thought to represent prodromal AD in most cases. Insulin improves memory in normal adults and patients with Alzheimer's disease without altering blood glucose. Energy metabolism in the CNS is dependent upon glucose uptake and is regulated by insulin in key brain regions. It has long been known that glucose uptake and utilization are deficient in patients with Alzheimer's disease. Recently, the gene expression levels of insulin, IGF-1, and their receptors were shown to be noticeably reduced in the brains of patients with Alzheimer's disease. Consequently, ability to deliver insulin to the CNS without altering blood glucose could provide an effective means to improve glucose uptake and utilization, and reduce cognitive deficits in patients with memory disorders. The benefit of olfactory mucosal insulin treatment was seen primarily for Alzheimer's patients without the apolipoprotein E (APOE) g4 allele. Longer treatment with olfactory mucosal insulin (21 days) enhanced memory, attention, and functioning compared with placebo in patients with either early stage Alzheimer's disease or mild cognitive impairment. Our own study of olfactory spray of dilute insulin in healthy volunteers resulted in better performance in tests scores.

Alzheimer's is a neurodegenerative dementia related to aging. It is characterized by the accumulation of neurofibrillary tangles and neuritic plaques (tau –τ– protein) in the brain affecting especially the degeneration of neurons in the olfactory bulb and its connected brain structures - the hippocampal formation, amygdaloid nuclei, nucleus basalis of Meynert, locus ceruleus, and the brainstem raphe nuclei, all of which project to the olfactory bulb (Figs. 14, 15). These degenerative alterations result in the loss of memory and cognitive function. There

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is a major loss of cortical and hippocampal choline acetyltransferase activity and degeneration of basal forebrain cholinergic neurons. Loss of smell in Alzheimer's is due to necrosis and apoptosis of olfactory neurons, olfactory bulbs, olfactory tracts and the pre-pyriform cortex.

Alzheimer's is the most common form of dementia that demonstrates hardly any or no electrical pulse or action potential generation in the afflicted neurons due to low or the lack of neurotransmitter acetylcholine, which is associated with death and degeneration of neurons. Alzheimer's is a complex, slow evolving disease, and there is no cure. It worsens as it progresses with advancing age, and eventually leads to death in a vegetative state.

The incidences of Alzheimer's increase with age. In the United States, the prevalence of Alzheimer's was estimated to be 1.6% in 2000 both overall and in the 65–74 age group, with the rate increasing to 19% in the 75–84 group and to 42% in the greater than 84 age group (Hebert LE, Scherr PA, Bienias JL, Bennett DA, Evans DA (2003). "Alzheimer disease in the US population: prevalence estimates using the 2000 census". Arch. Neurol. 60 (8): 1119–22). Alzheimer's is found in about 10% of the population over the age of 65 and 47% of the population over the age of 85 affecting about 4 million people in the USA and 20 million people worldwide (Evans DA, Funkenstein HH, Albert MS, et al. Prevalence of Alzheimer's disease in a community population of older persons: higher than previously reported. JAMA. 1989;262:2551-2556). The World Health Organization estimated that in 2005, 0.379% of people worldwide had dementia, and that the prevalence would increase to 0.441% in 2015 and to 0.556% in 2030. Another study estimated that in 2006, 0.40% of the world population (range 0.17–0.89%; absolute number 26.6 million, range 11.4–59.4 million) were afflicted by Alzheimer's, and that the prevalence rate would triple and the absolute number would quadruple by 2050 and is expected to affect 1 in 85 people worldwide by then. The disease affects not only the person, but also the person's entire family, care givers and proves to be very burdensome financially and to the health care system.

The list of diseases treated using this inventive method described herein with or without insulin are endless but the most important ones include, among others, neurological conditions associated with memory loss, cognitive impairment and

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dementia, including Alzheimer's, Parkinson's-type dementia, Huntington's-type dementia, Pick's-type dementia, Lewy body disease, MS, ALS, pain, PTSD, cerebral palsy, autism and those listed and unlisted. This electrical activation of the neuropil in the brain due to neurotransmitter-mediated activity is intricately involved in memory, attention, learning, cognitive processes and including various autonomic, sensory and motor function of the CNS. Besides delivering the electrical impulses; this present invention augments, and amplifies, the effects on existing neurotransmitters and any therapeutic agents inside the CNS. Note, however, that methods of the invention can be therapeutic methods of delivering the electrical impulses without delivery of any therapeutic device (active agent) other than saline or non-metabolically active agent to a location of the nasal cavity. Embodiments of methods can involve delivery of electrical impulses that are therapeutic in themselves, without the need for metabolically active agents such as a pharmaceutical or other biologically active agent. Similarly, devices as described can be useful for delivery of the electrical impulses but need not be capable of delivering a therapeutic agent to a location of the nasal region such as the olfactory mucosa, the sphenoid sinus, both of these locations, or other locations of the sinus cavity, with the insertion end of the device being located in a trans-nasal location. An apparatus that need not deliver a therapeutic fluid does not require and may exclude one or more ejection ports such as an opening or orifice located at a surface of the device shaft at the insertion end at the insertion end, in fluid communication with the proximal end, and through which fluid can be delivered externally of the device shaft to a region of the nasal cavity such as at the olfactory mucosa or the sphenoid sinus, with the insertion end located at the trans-nasal location. Exemplary methods do not require and may exclude delivery of a therapeutic agent (e.g., any described herein for treatment of Alzheimer's Disease or another condition) to a region of a nasal cavity, e.g., olfactory mucosa or sphenoid sinus.

Alzheimer's is the most common form of senile and pre-senile dementia in the world. It is known clinically as the progressive loss of memory, intellectual function, and disturbances in speech (Merritt, 1979, A Textbook of Neurology, 6th edition, pp. 484-489, Lea & Febiger, Philadelphia). Alzheimer's disease starts with inappropriate behavior, gullible statements, irritability, and a tendency towards

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grandiosity, euphoria, and deteriorating performance at work. It progresses to deterioration in operational judgment, loss of insight, depression, loss of recent memory, and it ends in severe disorientation and confusion, apraxia of gait, generalized rigidity, and incontinence (Gilroy & Meyer, 1979, Medical Neurology, pp. 175-179, MacMillan Publishing Co.).

Pathological changes in Alzheimer's disease for example, involve degeneration of cholinergic neurons (nerves activated by acetylcholine or that release it) in the subcortical regions and of neuronal pathways that project from the basal forebrain, particularly Meynert's nucleus basalis to the cerebral cortex and hippocampus (Robert P H et al. 1999. "Cholinergic Hypothesis and Alzheimer's: The Place of Donepezil (Aricept), " Encephale 5:23-5 and 28-9). Alzheimer's is characterized by the accumulation of insoluble, 10 nm filaments containing β amyloid (Aβ) peptides, localized in the extracellular space of the cerebral cortex and vascular walls. There is dense accumulation of neuro fibrillary tangles of the tau (τ) protein observed intracellular in this dementia. The chief constituent of the cores is a peptide of 39 to 42 amino acids called the amyloid β protein, or Aβ. Although the Aβ protein is produced by the intracellular processing of its precursor (APP), the amyloid deposits forming the core of the plaques are extracellular. Both plaques and tangles are found in the same brain regions affected by nerve cell and synaptic loss. It is a known fact that the Alzheimer's is associated with degeneration of cholinergic neurons, in the basal forebrain, which play a primary role in memory and cognitive functions; decreased cholinergic function may be a fundamental cause of cognitive decline seen in Alzheimer's patients. This invention will activate the electrical activity and will restore the memory to functional level, acting at the basal forebrain, and at the same time restore the acetylcholine function.

Neuro fibrillary tangles are found within the cell bodies of dying neurons as well as some dystrophic neurites in the halo surrounding neuritic plaques of the Alzheimer's afflicted brain. The tangles are composed of paired-helical filaments whose biochemical analyses revealed that the main component is composed of hyper-phosphorylated form of the microtubule associated protein Tau (τ).

The factor that contributes to the occurrence or cause of the Alzheimer's is unknown. Familial incidence of the disease indicates genetic contribution.

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Alzheimer's disease is typified by the following neuro pathological features, which display the huge loss of neurons, and synapses in the brain regions involved in higher cognitive functions (association cortex, hippocampus, and amygdala). Cholinergic neurons are particularly affected. The Alzheimer's plaques in the neuropil of the brain are composed of a core of amyloid material surrounded by a halo of dystrophic neurites, reactive astrocytes, and microglial cells. Even more, diminished cholinergic function may be an underlying cause of cognitive decline seen in Alzheimer's patients. No acetylcholine means no electrical pulse generation, with the loss of neuronal function, and loss of memory. This invention will remedy this deficiency.

Dementia testing is made by early measurement of cognitive testing. Standardized testing in humans can be performed using the Reye Auditory Verbal Learning Test, the Mini-Mental State Exam (MMSE), the Schier Logical Memory Test, or the Selective Reminding Test, among others. The cognitive subscale is also a major indication in the Alzheimer's Assessment Scale (ADAS-cog), and simultaneously assesses short-term memory, orientation in place and time, attention span, verbal ability and praxis. ADAS-cog testing is done for diagnosis of the condition and is used to evaluate success in treatment. Testing higher scores indicates cognitive impairment. Reduced scores, following treatment with tacrine, donepezil and the longer-acting rivastigmine are noted.

Scanning of the brain is in order whenever the cognition problems are detected. Although the neuronal and synaptic loss are universally recognized as the primary cause of the decline of cognitive functions, the cellular, biochemical, and molecular events responsible for this neuronal and synaptic loss are contentious and debated. There is global shrinkage of the brain mass and the brain of Alzheimer's patients weighs less than the non-Alzheimer's brain.

The delivery of therapeutic molecules across the blood brain barrier (BBB) has proven to be a major obstacle in treating various brain disorders including Alzheimer's disease. This invention describes transmitting the electrical nerve impulses through nerves that can include one or more of the olfactory nerves, sphenopalatine ganglion (SPG) nerve complex, trigeminal nerves, five cranial nerves in the cavernous sinus, pituitary gland to the hypothalamo - hypophysial system

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complex, cerebral cortex, brain stem, and cerebellum. Therefore, it improves nerve conduction, restores lost cerebral function, delays, and curtails Alzheimer's and other neurological diseases by dilating the cerebral blood vessels to deliver the therapeutic agents to the neuropil.

This invention of electrical stimulation application can be adopted to deliver electrical current to create Iontophoresis and electroporation effect on the olfactory mucosa and lining of the sphenoid sinus. This enhances the permeability, uptake, and transport of therapeutic agents from the ORE and sphenoid sinus bypassing the BBB, by creating elecroporation and iontophoresis effects of olfactory mucosa and sphenoid sinus lining.

US 7,640,062 B2 (the entirety of which is incorporated herein by reference) describes the stimulation of the parasympathetic sphenopalatine ganglion to dilate the cerebral blood vessels to break the BBB and deliver therapeutic agents across the BBB. The '062 patent describes complex invasive surgical procedures to place a stimulator on the anatomical location of the sphenopalatine ganglion to archive the results. The '062 patent does not describe stimulation of various complex nerve structure and blood vessels of sphenoid sinus, pituitary gland or olfactory nerves that are easily accessible for widespread stimulation of the brain as described in the present inventive methods.

There are reported cases of cancer pain treated by removing the pituitary gland or destroying it with an alcohol injection. The subsequent autopsies demonstrate that the removal or destruction of the gland was not needed to obtain pain relief. Stimulation of the pituitary gland by alcohol injection or electrical stimulation has the same effect of relieving pain. See T.R. Shantha US patents 5,7 35,8 17, and 5,7 79,2,100, the entireties of which are incorporated herein by reference.

There are methods of application of electrical stimulation of nerves for treatment of epilepsy and depression by vagus nerve stimulation (VNS) described in U.S. Pat. No. 4,702,254; and U.S. Pat. No. 6,341,236. U.S. Pat. No. 5,299,569 entitled Treatment of neuropsychiatric disorders by left vagus nerve stimulation, at a location on the neck by first implanting an electrode there, then connecting the electrode to an electrical stimulator.

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U. S. Patent Application Publication Number: US 2011/10152967 A1 discloses method and devices for the non-invasive treatment of neurodegenerative diseases through delivery of energy to target nervous tissue, particularly the vagus nerve. The devices used is a magnetic stimulator having coils with toroidal windings, which are in contact with an electrically conducting medium that is adapted to conform to the contour of a target body surface of a patient. These coils induce an electric current and/or an electric field within the patient, thereby stimulating nerve fibers within the patient. The stimulation brings about reduction of neuroinflammation in patients suffering from conditions comprising Alzheimer's disease, Parkinson's disease, Multiple Sclerosis, postoperative cognitive dysfunction and postoperative delirium. This is also one of the mechanisms the inventive device described here in uses to curtail Alzheimer's bringing about the reduction of neuroinflammation in the afflicted brain. The present invention described here is more effective in bringing down the neuroinflammation, because the electrical impulses are transmitted directly to many centers of the brain by thousands of nerve fibers projecting to periphery. This reduction in inflammation is effected by enhancing the anti-inflammatory capability of cytokines such as TGF-beta, wherein a retinoid or component of the retinoic acid signaling system provide an anti-inflammatory predisposition, by enhancing anti-inflammatory activity of a neurotrophic factor such as NGF, GDNF, BDNF, or MANF, and/or by inhibiting the activity of pro-inflammatory cytokines such as TNF -alpha.

A more efficient approach to selecting stimulation parameters might be to select a stimulation waveform that mimics electrical activity in the region of the brain that one is attempting to stimulate, in an effort to entrain the naturally occurring electrical waveform, as suggested in U.S. Pat. No. 6,234,953, and US2009/0299435. The patient may be more psychologically prepared to experience a procedure that is non-invasive and may therefore be more cooperative, resulting in a better outcome. Non-invasive procedures avoid damage to tissues that can result in bleeding, infection, skin or internal organ injury, blood vessel injury, and vein or lung blood clotting and are mostly painless. Less training may be required for use of non-invasive procedures by medical professionals. The procedures may be suitable for use by the patient or family members or caregiver at home or by a medical clinic

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trained technician. The cost of non-invasive procedures is considerably less compared to invasive procedures.

Because the present inventive device can be inserted with ease, non-invasively, into the olfactory region (ORE), the sphenoid sinus and its actions controlled by delivering measured electrical pulses, this inventive device has application in the treatment of Alzheimer's disease. Other CNS affliction where it can be applied are as follows: Autism, cerebral palsy, chronic fatigue syndrome, PTSD, senility, hypo pituitary and hyper pituitary function, intractable pain including thalamic pain, various kinds of headaches, Lewy body dementia, Parkinson's disease, multiple sclerosis, ALS, spastic paraplegia, Down's Syndrome, psychological illnesses, addiction, phantom limb syndromes, reflex sympathetic dystrophy, Vascular dementias (or multi-infarct dementia), Frontal lobe dementias (such as Pick's disease) , Subcortical dementias (such as Huntington, or progressive supranuclear palsy), Focal cortical atrophy syndromes (such as primary aphasia), Metabolic-toxic dementias (such as chronic hypothyroidism or B12 deficiency), Infections (such as syphilis, neuro-AIDS or chronic meningitis), and such others.

A pharmaceutic agent or drugs administered along with neural stimulation as described herein can be selected based on the condition, e.g., disease, being treated. Examples include the following: the chemotherapeutics, insulin, IGF-1; levodopa (5-10% crosses BBB) combined with a dopa decarboxylase inhibitor or COMT inhibitor, dopamine agonists and MAO-B inhibitors (selegiline and rasagiline), dopamine agonists (include bromocriptine, pergolide, pramipexole, ropinirole, piribedil, cabergoline, apomorphine and lisuride), non-steroidal anti-inflammatory drugs, acetyl cholinesterase inhibitors such as tacrine, donepezil and the longer-acting rivastigmine; antibiotics, 2,4-dinitrophenol, glutamate receptor antagonist, glutathione, NMDA-receptor blocker such as ketamine, β amyloid inhibitor, Alzheimer's vaccine, non-steroidal anti-inflammatory drug including COX-2 inhibitor, deferoxamine, hormones, enzymes, erythropoietin, Intranasal fibroblast growth factor, epidermal growth factor, microglial activation modulator, cholinesterase inhibitor, stimulant of nerve regeneration, nerve growth factor, non-steroidal anti-inflammatory drugs, antioxidants, hormone, vitamin B_{12}, A, E, D_3, and

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B complexes, and inhibitor of protein tyrosine phosphatase and others as they evolve.

This invention described herein restores and facilitates to overcome a number of obstacles posed by the CNS for the treatment of Alzheimer's;

1. By generating electrical impulses and transmitting them to the brain, activating neurons, and neuronal transmission through the synapses. Thus, activating the inactive neurons and activating the acetylcholine and their function to conduct nerve impulses that have become silent due to loss of acetylcholine neurotransmitter with abnormal accumulation of neurofibrillary tangles (amyloid (Aβ) deposits) and neuritic plaques (tau -τ – protein) in the neurons of the CNS is the one of the fundamental principle of this invention. It is also intent of this invention of using bexarotene, acetylcholine esterase inhibitors and insulin to remove or reduce the amyloid plaques, increase acetyl cholin neurotransmitter activity in the brain; thus, treat the fundamental factors that contribute to the disease.
2. By making the olfactory mucosa and sphenoid sinus lining more permeable to therapeutic agents by Iontophoresis and electroporation and transport the therapeutic agents to CNS by passing the BBB to deliver them to the site of pathology. The therapeutic agents we have selected are bexarotene, insulin, acetyl-cholin-esterase inhibitors, and ketamine delivered through the olfactory mucosa.
3. By breaking the BBB to allow therapeutic agents to reach the site of pathology to curtail Alzheimer's disease at the same time remove the toxic metabolites from neuropile to systemic circulation away from the brain.

SUMMARY OF THE INVENTION

The present invention disclosure involves a medical device and medical procedures that stimulate nerves by transmitting energy to adjacent nerves to be transmitted to the central nervous system non-invasively to treat Alzheimer's and other neurodegenerative diseases. This medical procedure is defined as being non-invasive when no break in the skin (or other surface of the body, such as a wound bed) is created through use of the method, and when there is no contact with an internal body cavity beyond a body orifice (e.g., Mouth, anus, external auditory meatus of the ear, eyes, and the nose). On the other hand, the invasive procedures (including minimally invasive procedures) procedures do involve inserting a

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substance or device into, through the skin, or into an internal body cavity beyond a body orifice.

Advantages of our non-invasive medical methods and devices relative to comparable invasive procedures described in this invention are as follows. 1. The patient may be more psychologically complaint to use the procedure that is non-invasive and may therefore be more cooperative, ensuing in a better outcome. 2. Non-invasive procedures of inserting this device avoid damage to tissue it comes in contact such as bleeding, infection, skin or internal organ injury, blood vessel injury, and vein or lung blood clotting. 3. Non-invasive procedures of inserting this device are almost painless or minimally painful. 4. The inventive device described herein may be positioned without the need for local or general anesthesia. 5. Less training may be required for use of this non-invasive device by medical professionals. 6. This device may be continued to be used by the patient or family members at home with brief training. 7. The cost of non-invasive device and procedures is relatively less compared to invasive procedures. 8. This inventive device can be used as therapeutic, prophylactic, and diagnostic objectives in the management of Alzheimer's disease (Alzheimer's-AD) and other neurodegenerative diseases of the CNS. 9. This device can be easily mass-produced using non-reacting, non-allergic or hypo allergic synthetic, semi synthetic composite material.

The present invention discloses methods and devices for the non-invasive delivery of electrical impulses for the treatment of neurodegenerative conditions such as Alzheimer's disease. It makes use of an energy source that transmits energy non-invasively to nervous tissue. In particular, the devices can transmit energy to, or in close proximity to the CNS of the patient, in order to stimulate, block, and/or modulate electrophysiological signals in the CNS involved in Alzheimer's disease. The neurodegenerative diseases that can be treated with the present invention include Alzheimer's disease, Parkinson's disease, multiple sclerosis, AIDS dementia complex, Creutzfeldt-Jakob disease , Huntington disease, Tay- Sachs disease, toxic encephalopathy, transmissible spongiform encephalopathy, Vascular dementia, ALS, and many such neurodegenerative diseases. Though many of these above diseases differ from each other, but their pathogenesis share common features, which makes it possible to treat them with similar therapeutic agents and methods.

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One of the important common features of these diseases is the presence of inflammation [Sandra Amor, Fabiola Puentes, David Baker and Paul van der Valko, Inflammation in neuro-degenerative diseases. Immunology, 129 (2010), 154-169}. Excessive and prolonged inflammation ultimately destroys the nervous tissue that is associated with the neurodegenerative disease. The neuroinflammation modulated by cytokines that are small signaling proteins or peptide molecules that are secreted by glial cells of the CNS, by numerous types of immune system cells. It is known that electrical stimulation brings about the reduction of neuroinflammation by enhancing the anti-inflammatory neurotrophic factors such as : Nerve growth factors (NGF), fibroblast growth factor (bFGF), glial-derived neurotrophic factor (CNTF), pigment epithelium-derived factor (PEDF), glial-derived neurotrophic factor (GDNF), brain-derived neurotrophic factor (BDNF), erythropoietin's, insulin, IGF-1, platelet derived growth factor (PDGF), and/or by inhibiting the activity of pro-inflammatory cytokines such as TNF -alpha. Hence, in the treatment of these diseases be directed to reduce the cytokine effect and restore the brain function as we propose in this invention.

It is an object of the present invention to provide methods and apparatus for delivery of measured electrical impulses to the CNS neuropil, neurons and their connections which are involved in and affected by Alzheimer's disease.

It is an object of the present invention to develop a device to treat Alzheimer's and other neurodegenerative diseases.

It is an object of this invention to develop a device for stimulating the surface of the sphenoid sinus and its adjacent structures: pituitary gland, five cranial nerves and the internal carotid artery; olfactory mucosa; sphenopalatine ganglion (its afferents and efferent connection), using electrical impulses as described herein to activate the inactive neurons and their connections involved in Alzheimer's disease.

It is a further object of this invention to develop a device for stimulating the sphenopalatine ganglion located immediately below the sphenoid sinus on the lateral wall of the uppermost part of the nasal roof and send electrical impulses and signals to inactive neurons though its extensive CNS connections.

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It is a further object of this invention to develop a device for stimulating the olfactory mucosa with its connection of olfactory nerves connecting the olfactory bulb and its connection to the CNS involved in Alzheimer's disease.

It is a further object of this invention to develop a device for stimulating the anterior ethmoidal nerve, which emerges from the roof of the nose in front of the olfactory mucosa, branch of the ophthalmic division of the trigeminal nerve.

It is a further object of this invention to develop a device for stimulating the surface of the sphenoid sinus, which will transmit the electrical impulses (stimulus, pulse, signals) to neurological structures, BV, and pituitary gland, hypothalamus, thalamus, and thalamic radiation; which the patient uses while engaging in normal activities and being ambulatory, to treat Alzheimer's.

Applicant has invented a device for stimulating the interior surface of the sphenoid sinus, its walls, and surrounding neuronal structure. The apparatus consists of an insertion body having a flexible outer surface adapted for insertion into the sphenoid sinus. The insertion body is constructed of a flexible material, which contracts and conforms to the interior surface of the sphenoid sinus. The insertion body is an inflatable outer membrane or balloon. This balloon attached to flexible tubing through which air or fluid can be pumped to inflate the balloon to position the balloon against the surface of the sphenoid sinus.

The inflatable balloon is inserted in the uninflated state into the hollow sphenoid sinus through the sphenoid foramina, which communicates with the nose. The balloon is then inflated with liquid or air under slight pressure.

In some cases it may be desirable to cool the liquid depending on the purpose for which the device is being used (e.g., to lower the activity of the hyperactive pituitary gland).

The device is provided with an electrical impulse transmitter on the catheter as it passes to the sphenoid sinus to stimulate the olfactory bulb and its cortical and subcortical connections in treating Alzheimer's and other neurodegenerative diseases.

The device is provided with electrical impulse transmitter on the catheter as it passes to the sphenoid sinus to stimulate the sphenopalatine ganglion.

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Electrical stimulator wires are placed along the outer surface of the inflatable balloon for stimulating the pituitary gland and other nerve structures surrounding the sphenoid sinus in the cavernous sinus.

Temperature sensors are placed on the outer surface of the balloon to determine the temperature, which will approximate the temperature of the surface of the sphenoid sinus.

The interior shape of the balloon can be examined by using a fiber optic connection. By visual inspection through the fiber optic connection, the approximate size and shape of the sphenoid sinus can be determined and whether the balloon is filling that space or not to transmit the electrical impulses through the sidewalls and the roof of the sinus.

It is also an object of the present invention to provide methods and apparatus inserted to the anatomical sites explained below to deliver electrical impulses with a minimally invasive approach to treat CNS diseases such as Alzheimer's disease.

Means are provided for the quick detachment of the balloon from the rest of the apparatus. Under those circumstances, the balloon is left in the sphenoid sinus cavity and its activities controlled by a controller, outside the body through radio transmission, to a receiver located in the balloon. The battery-powered receiver, then directs that current to be provided to electrical stimulators on the outside of the balloon or to heating elements inside the balloon to heat the fluid to a desired temperature. This device will allow full mobility by the patient while being stimulated.

The apparatus and method of this invention is useful in the treatment of acute and chronic pain of headaches besides treating Alzheimer's and other neurological diseases. It also stimulates the structures surrounding the sphenoid sinus, and particularly the pituitary gland, which may be useful in treating various diseases that arise from the central and peripheral systems. A fluid able to be heated or cooled can be pumped into the balloon to enhance the output or decrease the output of pituitary hormones including growth hormone from the pituitary gland.

Thermocouples applied at the tip of the catheter inside the balloon are inserted into the sphenoid sinus. They are connected to the N-doped and P-doped legs of the semiconductor material which when connected to the direct current can

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heat or cool the thermocouples depending on the direction of current flow. This heating and cooling is called the Peltier effect and was discovered in 1831 by a Swiss Scientist. The same principle is used in the heat pump. Devices embodying the Peltier effect are currently being used to cool and heat the tissue and fluids in the body. Instead of using the heating or cooling circulating pump to heat or cool the fluid inside the inflated balloon as desired to treat various conditions and to increase or decrease the pituitary function. In some applications, it is desirable simply to use the inflated balloon with its pressure and stimulating the sphenoid sinus surrounding structures with electrical conductive wires.

A catheter in this invention can be attached to the balloon through which drugs may be infused into the sphenoid sinus for absorption by the central nervous system directly across the sphenoid bone and its perforating blood vessels around the cavernous sinus.

It is a further object of the present invention to provide such methods and apparatus to be able to facilitate delivery of electrical impulses to the CNS BBB. This is through the sphenopalatine ganglion and carotid artery -Circle of Willis parasympathetic nerves located close to sphenoid sinus to make them dilate and become leaky (breaking of BBB), thus improve the delivery of systemic administration of therapeutic agents to the CNS.

It is another object of this invention, by dilating the BBB BV to allow the toxic material to pass from the neuropil which has no passage to exit once formed adding to the causation of Alzheimer's and other neurological diseases.

It is yet a further object of the present invention to provide cost effective methods and apparatus for delivery of electrical pulses, which will help to deliver compounds through the BBB and improve the electrical activity in the neuropil to enhance the brain function.

It is still a further object of the present invention to provide improved methods and apparatus for remedying or modifying neuronal dysfunction and their synaptic activities through electrical impulse deliverance.

It is an additional object of the present invention to provide a superior method and apparatus for treating and preventing neurological diseases, whose prognosis and development of pathological symptoms are influenced by electrical

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impulses and neurotransmitters, which also improve with increased cerebral blood flow by activating the parasympathetic system.

It is still an additional object of some aspects of the present invention to provide improved methods and apparatus for treating and/or preventing Alzheimer's by improving the oxygen delivery to the brain by vasodilatation effect.

It is yet a further object of some aspects of the present invention to provide an insertable apparatus, which improves the function of the brain, without being implanted in the brain or in the nose.

These and other objects of the invention will become evident from the description of preferred embodiments thereof provided herein. In the preferred embodiments of the present invention, an electrical stimulator drives electrical pulses or current into the olfactory mucosal nerves, sphenopalatine ganglion, trigeminal nerves, cranial nerves III, IV, V, VI, pituitary gland with hypothalamo hypophysial tracts and into related neuro anatomical structures including neural tracts originating from these structures. Typically, the stimulator drives the current in order to control and/or modify these structures to induce changes in nerve conductivity within the neuropile and increase cerebral blood flow with more permeability for circulating therapeutic agents by modulating permeability of the BBB.

This invention is used in many medical applications by way of illustration and not with any limitation are as follows. The list of diseases that be treated by using this electrical simulator invention with or without adjuvant therapeutic agents , as well as other pharmaceutical, biochemical, nutraceuticals, and biological agents or compounds are many. They are: Alzheimer Disease, Arachnoiditis, Autism, Brain Ischemia, CNS Infections, Cerebral Palsy, senile dementias, ALS, Cerebrovascular Disorders, Corticobasal Ganglionic Degeneration (CBGD) (not on MeSH), Creutzfeldt-Jakob Syndrome, Dandy-Walker Syndrome, Dementia, Encephalitis, Encephalomyelitis, Epilepsy, Essential Tremor, Friedreich Ataxia, Huntington Disease, Hydrocephalus, Hypoxia Brain damage, Lewy Body Disease, Multiple sclerosis, Myelitis, Olivopontocerebellar Atrophies, PTSD, traumatic injury to the brain -blunt or otherwise, mental illnesses, Pantothenate Kinase Associated Neurodegeneration, Parkinson Disease, Parkinsonian Disorders,

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Postpoliomyelitis Syndrome, Prion Diseases, Pseudotumor Cerebri, Shy-Drager Syndrome, Spinal Cord Diseases, Stroke, Thalamic Diseases, Tic Disorders, Truett Syndrome, Uveomeningoencephalitic Syndrome, psychological disorders, addictions, in the treatment of cerebrovascular disorders such as stroke, PTSD, for the treatment of migraine, cluster and other types of headaches, and pain and other diseases listed below, most importantly in the treatment of neurodegenerative diseases such as Alzheimer's.

For the facilitation of drug, transport across the BBB by effective cerebral BV dilatation and by bypassing the BBB for delivery of therapeutic agents and large molecules across the olfactory and trigeminal nerve complexes by Iontophoresis and electroporation modality is incorporated into the device to treat the above listed diseases.

In the specification of the present patent application, unless indication to the contrary is stated, stimulation of the olfactory mucosal nerves, sphenopalatine ganglion, trigeminal nerves, pituitary gland with hypothalamo hypophysial region, thalamus complex, brain stem and cerebellum is used. It is to be understood to alternatively or additionally to include stimulation of the complex afferent and efferent nerve connections of the sphenopalatine ganglion, olfactory bulb, pituitary gland complex, five cranial nerves, and both afferent and efferent nerve tracts including autonomic nervous system components.

It is also to be understood that the electrical "stimulation," as provided by preferred embodiments of the present invention by electrical pulse catheter placement close to the region, is placed where it is going to stimulate conductive neural pathways. The parameters of stimulation is described herein by way of illustration and not limitation, and that the scope of the present invention includes other possibilities, which would be obvious to someone of ordinary skill in the art who has read the present patent application. Further, the parameters of stimulation include substantially any form of the current application to designated tissue, even when the current application is configured to block or inhibit the activity of hyperactive nerves.

It is to be appreciated that preferred embodiments of the present invention are described with respect to driving current into the neural structures, directly and

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to other sites in the brain, which upon stimulation modulate, enhance and restore the neuronal and synaptic function with improved conduction of nerve impulses; thus, restoring the brain function, especially in treating Alzheimer's and senile dementias.

It is yet further to be valued that while chosen embodiments of the invention are generally described herein with respect to electrical transmission of power and electrical stimulation of tissue, other modes of energy transport may be used as well. Such energy includes, but is not limited to, direct, or induced electromagnetic energy, RF transmission, ultrasonic transmission, optical power, and low power laser energy delivered through a fiber optic transmission cable.

The preferred embodiments of the present invention are described with regard to application of electrical currents to tissue, equivalent to applying an electrical field e.g., by creating a voltage drop between two electrodes.

With the neuronal center located, we send electrical impulses by this inventive device situated in the prefrontal, frontal cortex, hypothalamus, hippocampus, and amygdaloid nucleus, basal ganglion, cerebellum, and brain stem nuclei in the brain above and behind the nose. It is important to note the activation of these neuronal structures by electrical impulses causes restoration and improvement of their function. Circle Willis BV stimulation results in the opening of pores in the BBB vessel walls due to the dilatation effect of parasympathetic innervations, causing plasma proteins and therapeutic agents to extravasate which were unable to break the BBB thus allowing the large therapeutic molecules from within the blood vessels to the cerebral tissue to be substantially increased. Thus, this invention acts as a neurological drug delivery facilitator, without altering the molecular weight.

The added benefit of the use of this invention is due to the vasodilatation resultants improvement in oxygen supply to the CNS tissues.

It is also to be valued that electrical "stimulation," as provided by preferred embodiments of the present invention, is meant to include substantially any form of current application (galvanic) to designated tissue, even when the current configured to activate or to block or inhibit the activity of nerves. A voltage drop between two electrodes creates an electrical field.

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It is another object of the present invention, a method for treating Alzheimer's and other neurodegenerative diseases, to cause an increase in clearance of an Alzheimer's related constituent CNS of the subject. This helps to remove from the neuropil of the subject to a systemic blood circulation of the subject, so as to treat the Alzheimer's or other neurodegenerative disease by electrical stimulation of one or more of the olfactory mucosal nerves, cranial nerves, sphenopalatine ganglion, trigeminal nerves, pituitary gland with hypothalamo hypophysial system, resulting and due to dilatation of BBB blood vessels.

There is therefore provided, in accordance with a preferred embodiment of the present invention, apparatus for modifying a property of a brain of an afflicted patient using one or more electrodes adapted to be applied directly to one or more olfactory nerves, other cranial nerves, sphenopalatine ganglion, trigeminal nerves, pituitary gland with hypothalamo hypophysial site separately or in combination.

Embodiments of devices can include an electrical delivery control unit adapted to drive one or more electrodes to apply a current or other electrical signal to a site, e.g., one or more nerve as described herein, capable of stimulating the CNS of the patient. The electrical conduction wires and one or more (e.g., proximal and distal) electrodes are connected to the electrical output manipulator. As a preferred embodiment, the apparatus has a catheter with balloons, which includes conductive wires adapted to connect the control unit to the one or more electrodes, wherein the control unit is adapted to drive the one or more electrodes from a position at a proximal end of the device and external to the patient.

Applying an electrical signal, as described herein separately or in a combined device to treat Alzheimer's or another neurological condition, to the olfactory nerves results in transmission of electrical pulses from the olfactory nerves to the olfactory bulb. From the olfactory tract, the pulses are delivered to subarachnoid space (SAS) to the cerebrospinal fluid (CSF) then to various centers of the brain and cerebral cortex, especially temporal and frontal lobes.

Applying an electrical signal as described herein separately or in a combined device to the olfactory nerve, the electrical stimulus reaches the CNS through the olfactory bulb, and then to the olfactory tract to prefrontal cortex, medial olfactory

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area, to temporal lobe ,to lateral olfactory area, hippocampus, hypothalamus ,brain stem nuclei, and to cerebellum.

Transmitting electrical impulses as described to treat Alzheimer's or another neurological condition separately or in a combined device to the sphenopalatine ganglion results in transmission of electrical pulses to all its connecting branches. Electrical impulses from a device as described are transmitted to the CNS through the anterior, and posterior ethmoidal nerves, the communicating branch between them, the retro-orbital branch of an sphenopalatine ganglion of the subject, greater and lesser palatine nerve, sphenopalatine, communicating branch between a maxillary nerve and sphenopalatine ganglion, nasopalatine nerve, posterior nasal nerve, infraorbital nerve, otic ganglion of the subject, an afferent fiber going into the otic ganglion, Vidian nerve, greater and lesser superficial petrosal nerve, and deep petrosal nerve of the subject.

Transmitting the electrical impulses as described herein to treat Alzheimer's and other CNS diseases through the sphenoid sinus results in transmission of the electrical pulses to the pituitary gland. From this anatomical site, the electrical impulses are transmitted to one or more cranial nerve, e.g., I, III, IV, V, VI, to the brain stem nuclei, and other neurons in the brain stem, cerebellum; and parasympathetic plexus on the carotid artery in the cavernous sinus, basilar and posterior cerebral arteries on the brain stem (circle of Willis). The electrical impulses from the pituitary gland are relayed to the hypothalamo-hypophysial tract to the hypothalamus, the thalamus, thalamic radiation, basal ganglion, hippocampus, amygdala, Cingular gyrus, brain stem, and cerebral cortex, and cerebellum.

Yet another objective of described devices and methods to treat Alzheimer's is to deliver adjuvant therapeutic agents directly to olfactory mucosa and sphenoid sinus tissue in combination with electrical nerve stimulation as described, allowing the therapeutic agent to enter the brain due to iontophoresis, and electroporation electrical effects or otherwise on the olfactory mucosa and sphenoid sinus. Thus, this invention will facilitate the uptake and transport of these therapeutic agents from ORE to the CNS bypassing BBB through the olfactory nerves and other cranial nerves, enumerated. It is the intent of this invention to deliver the therapeutic agents

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we have selected such as bexarotene, insulin, acetyl-cholin-esterase inhibitors, monoclonal antibodies and ketamine delivered through the olfactory mucosa.

Yet another objective of this invention to treat Alzheimer's is to deliver adjuvant therapeutic agents directly delivered to ORE and sphenoid sinus, such as bexarotene, dissolved in DMSO at 65 mg/mL or in ethanol at 10 mg/mL, which is instilled, with insulin and acetyl cholinesterase inhibitors in Alzheimer's patient's olfactory mucosa.

Applying electrical signals to olfactory mucosal nerves, sphenopalatine ganglion, trigeminal nerves, pituitary gland with hypothalamo hypophysial tract causes an increase in molecular passage between cerebrospinal fluid of the subject and another body fluid of the subject, to facilitate a diagnosis of Alzheimer's.

The stimulation of the neuropil by using this device also brings about reduction of neuroinflammation in patients suffering from conditions comprising Alzheimer's disease, Parkinson's disease, Multiple Sclerosis, postoperative cognitive dysfunction, and postoperative delirium as such. This also one of the mechanisms by which the inventive device described herein curtails Alzheimer's disease bringing about the reduction of neuroinflammation in the afflicted brain.

This invention delivers electrical impulses to the olfactory nerves, sphenopalatine ganglion, trigeminal nerves, pituitary gland with hypothalamo hypophysial tract, five cranial nerves in the sphenoid sinus wall (in the cavernous sinus). This results in stimulation of circle of Willis BV with its parasympathetic autonomic nerve supply which causes an increase in passage of therapeutic agents from systemic circulation or from the olfactory mucosal area of the nose of the subject into a central nervous system. Therapeutic agents are delivered by passing the BBB, besides the electrical stimulation of Alzheimer's disease afflicted patient's brain.

Therapeutic agents can be administered orally, intravenously or intranasally along with this inventive device in operation.

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BRIEF DESCRIPTION OF THE DRAWINGS

The present invention will be completely implicit from the following detailed description of preferred embodiments thereof taken together with the drawings, in which:

FIG. 1 is the diagrammatic presentation 100 of the olfactory mucosa covering the medial and lateral walls of the nose, sphenopalatine ganglion, and anterior ethmoidal nerve.

FIG. 1a is the diagrammatic presentation of 100a showing head position and the olfactory mucosa when the device needs to be placed in the nose.

FIG. 2 is the diagrammatic presentation of the lateral wall 200 of the nerve structures in the nose.

FIG. 3 is the diagrammatic presentation of the medial wall 300 of the nerve structures in the nose.

FIG. 4 presents the views of diagram 400 showing structure stimulated by electrical impulses transported to the CNS.

FIG. 5 is the diagrammatic presentation 500 showing structure that may be stimulated by electrical impulses to be transmitted to the CNS.

FIG. 6 is the diagrammatic drawing 600 showing an embodiment of the inventive device used to stimulate olfactory mucosa.

FIG. 7 is the drawing 700 showing an embodiment of the inventive device with an insertion end located at a location to deliver electrical stimulation, a proximal electrode at olfactory mucosa and a distal electrode at the sphenoid sinus.

FIGS. 8 includes diagram 800 showing an embodiment of the inventive device with an insertion end located at a location to deliver electrical stimulation, a proximal electrode at olfactory mucosa and a distal electrode at a sphenoid sinus with anchoring balloon.

FIG. 9 is the diagrammatic presentation 900 of an embodiment of electrical simulator inventive device as described herein, incorporating olfactory mucosal, sphenoid sinus, pituitary gland, sphenopalatine ganglion stimulators in one device.

FIG. 10 is the diagrammatic presentation 1000 of an embodiment of a completely assembled electrical impulse delivering catheter as described, including

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balloon and inflating syringes, useful to treat Alzheimer's and other neurological diseases.

FIG. 11 is the diagrammatic presentation 1100 showing the longitudinal section of the olfactory bulb, which conducts electrical impulses to the cortical centers, e.g., to treat Alzheimer's and other diseases delivered through the olfactory nerves from the olfactory mucosa.

FIG. 12 is the diagrammatic presentation 1200 showing an embodiment of a sphenoid sinus balloon as described herein, located in the sphenoid sinus, and the surrounding structures to which electrical impulses can be transmitted.

FIG. 13 is the diagrammatic presentation 1300 showing the sagittal section of the sphenoid sinus with an embodiment of inventive device in the sphenoid sinus, and the surrounding cavernous sinus structures to which electrical impulses can be transmitted.

FIG. 14 is the diagrammatic presentation 1400 showing the spread of electrical impulses from the olfactory nerves to the olfactory bulb and to the rest of the centers in the brain involved in the Alzheimer's and other disease processes.

FIG. 15 is the diagrammatic presentation 1500 of the medial wall with an insertion end of an embodiment of an electrical impulse delivering device as described herein in place in electrically-stimulative contact with the olfactory mucosa, olfactory bulb, sphenopalatine ganglion, pituitary gland, other neurological structures, and BV in the cavernous sinus.

FIG.16 is the diagrammatic presentation of catheter device in the sinus and the nose.

FIG.17 is the diagrammatic presentation shows the electrical stimulator catheter device in place

FIG. 18 is the diagrammatic presentation shows an example of an assembled catheter in position with an insertion end located at a trans-nasal location.

FIG.19 is the diagrammatic presentation shows various embodiments of the electrical stimulation catheter that can be incorporated.

FIG.20 is the diagrammatic presentation shows another embodiment of the electrical stimulation catheter placed in a trans-nasal location.

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FIG. 21 is the diagrammatic presentation shows another embodiment of electrical stimulation with two balloon expanding syringes and electrical cell output monitor.

DETAILED DESCRIPTION

The term "Alzheimer's" means Alzheimer's disease, Alzheimer's afflicted brain. The term is used to allude to "neurodegenerative diseases" "neurological diseases" "CNS diseases" such as Parkinson's, senile brain atrophy, stroke, PTSD, Tumors, vascular disorders, and other such afflictions.

The terms "apparatus" "device" "inventive device" are used interchangeably.

The terms "therapeutic," "therapeutically effective doses," and their cognates refer to doses of a substance, e.g., of a protein, e.g., insulin, of an IGF-l, that result in prevention or delay of onset, or amelioration of one or more symptoms of a neurodegenerative disease such as Alzheimer's, Parkinson's, or another as described herein.

As used herein, the term "treating" or "treatment" and "example" refers to both therapeutic treatment, prophylactic or preventative measures and method of use.

A "subject," "individual" or "patient" used interchangeably herein, which refers to a vertebrate, preferably a mammal, more preferably a human.

The term "mammal (s)" include but are not limited to, humans, mice, rats, monkeys, farm animals, sport animals, and pets.

The term "neuropil" in the following description refers to an intricate, complex network of axons, dendrites, and glial branches that form the bulk of the central nervous system's grey matter with Microglial cells with BV endowed with BBB and in which nerve cell bodies are embedded.

The term "BBB" (blood brain barrier) refers to the 400 miles of blood vessels in the form of capillaries that supply the neuropil and form the bulk of the blood supply (20% of the cardiac output) of the central nervous system's gray matter in which the nerve cell bodies lay surrounded and embedded in the neuropil. Fortunately, the olfactory nerves provide a route bypassing the BBB, presenting the select therapeutic agents directly to the neuropil of the brain to the site of pathology to treat CNS diseases.

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The term "Circle of Willis," "Cerebral BV," or brain "BV" includes anterior cerebral arteries, anterior communicating arteries, internal carotid arteries, posterior cerebral arteries, the basilar artery and middle cerebral arteries supplying the brain and give branches to from the BBB capillaries inside the brain, brain stem, and spinal cord.

The term "olfactory region" (ORE) includes olfactory mucosa, sphenopalatine ganglion and its branches, branches from the trigeminal nerve, olfactory nerve fasciculi as they enter the olfactory bulb, and the communicating blood vessels of this region to the CNS. It is located in the upper third of the medial and lateral wall of the nose (figs. 1, 2, 3) and covers the entire roof of the nose (cribriform plate of the ethmoid bone).

The term "olfactory mucosa" (OM) refers to the olfactory area in the upper part of the nose, which contains olfactory receptor bipolar neurons, that forms about 20 bundles of olfactory nerve fasciculi (Figs. 1,2,3). Olfactory neuro-epithelium is the only area of the body in which an extension of CNS meets the external environment.

The terms "tumor necrosis factors," (TNF), or "cytokines" refers to a naturally occurring cytokines present in humans or mammals, which play a key role in the inflammatory immune response and in the response to infection.

The term "perineural epithelium" (PE) means a histological structure of continuous flat squamous cell layers completely surrounding the nerve fasciculi (axons bundles) and separating the axons from the tissue space around the nerve bundle and protecting them.

The term "sub perineural epithelial space" (sub PE) is used to describe the tissue space between the nerve bundles of axons (fasciculi) and below the perineural epithelium (Fig. 11).

The terms "antibodies" and "immunoglobulins" mean the proteins produced by one class of lymphocytes (B cells) in response to specific exogenous foreign molecules (antigens, infections). They can be also be synthesized.

The term "monoclonal antibodies" (mAB) means the identical immunoglobulins which recognize a single antigen that are derived from clones

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(identical copies) of a single line of B cell which can be a cytokine blocker, or a cytokine inhibitor, or as a cytokine antagonist.

The terms Alzheimer's and related diseases, and neurodegenerative disease, are interchangingly used.

The term electrical "pulse," "signal," and "impulse," are used interchangeably.

"Brain" and "CNS" signify the same structures and are used interchangeably.

The terms "treat," "treating," "treatment," "curtail" as used herein and unless otherwise specified, are used to mean that which reduces or retards or slows the progression or severity of a disease or condition.

The present invention disclosure relates to devices and medical procedures that stimulate nerves by transmitting electrical energy to nerves and tissue, preferably non-invasively. Described methods of treatment of Alzheimer's disease relate to stimulation of one or more cranial nerve, CN I (also referred to as the olfactory nerve), III, IV, V, and VI, (a total of 12 cranial nerves which include both sides of the sphenoid sinus and ORE). In accordance with particular embodiments of the invention, neural stimulation (multiple cranial nerves) may correspond to transcranial (through sphenoid sinus), cortical, subcortical, cerebellar, deep brain, spinal column, cranial or other peripheral nerve, and/or other types of stimulation.

Electrical stimulation impulses described herein are capable of various effects, as described, such as reducing neuroinflammation, wherein pathways involving anti-inflammatory cytokines, the retinoic acid signaling system, and/or neurotrophic factors enhanced, and/or pathways involving pro-inflammatory cytokines are inhibited with enhancement of neurotransmitters and memory related protein and amino acid output in the neurons.

ANATOMY OF THE SITES WHERE A DEVICE AS DESCRIBED CAN BE POSITIONED TO TREAT ALZHEIMER'S AND OTHER CNS DISEASES

Before we describe this invention, it is important to describe the anatomical regions we intend use this device to stimulate to treat or curtail Alzheimer's and other neurological diseases; and why these anatomical regions were selected to use this inventive device. Such knowledge also facilitates the insertion and placement of

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this inventive device (especially an "insertion end" thereof) at a useful and therapeutic anatomical site. For these reason, we consider in detail:

a) The anatomy of the sphenoid sinus and its relation to five cranial nerves, pituitary gland, and hypothalamic and thalamic radiation,

b) Anatomy of the olfactory mucosa with olfactory neurons, its connection to the olfactory bulb, and its relay of electrical impulses to the CNS and entorhinal cortex,

c) Anatomy of the sphenopalatine ganglion and its sensory, motor, and autonomic nerve system connections.

ANATOMY OF THE SPHENOID SINUS, PITUITARY GLAND, HYPOTHALAMUS, THALAMUS AND CAVERNOUS SINUS (FIGS. 1-5,12-15) INVOLVED IN THE TREATMENT OF ALZHEIMER'S AND OTHER NEUROLOGICAL CONDITIONS

The sphenoid sinus is located within the body of the sphenoid bone posterior to the upper point of the nasal cavity. The sphenoid sinus consists of two large irregular cavities separated by a bony septum. The middle of the anterior wall of the sphenoid bone forms a crest, which articulates with the perpendicular plate of the ethmoid bone, which forms part of the nasal septum (FIG.13). On each side of the sphenoid crest, a rounded opening called the sphenoid foramina (Fig. 13 arrows 524) about 4 mm in diameter opens into the sphenoid sinus from the posterosuperior part of the nasal cavity. The hypophyseal fossa commonly known as sella turcica (shape of Turkish saddle) is located in a depression in the body of the sphenoid bone. The sella turcica forms a bony caudal border for the pituitary gland. Completing the formation of the saddle posteriorly is the dorsum sellae, continuous with the clivus, inferoposteriorly. The pituitary gland is encased in this thin boney fossa (Figs. 3-5, 12, 13, 15) surrounded by the cavernous sinus 541 with five cranial nerves 503-507, internal carotid artery 510, and is easily accessible for electrical stimulation as described in our invention through the sphenoid sinus.

The sphenoid sinus is about 2 cm high, 2 cm wide and 2.1 cm antero-posteriorly. The sphenoid sinus communicates with the sphenoid-ethmoidal recess behind the olfactory mucosa (Fig. 3, 4, 13) in the upper part of the nose through this ostium. It is through this ostium that a distal portion of the device as described herein, i.e., a distal portion of the insertion end of the described device, can be

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inserted for treatment of various neurological diseases including Alzheimer's. If needed, the ostium diameter can be enlarged with a dilator without damage to any vital structures which are not in close proximity to the ostium, to facilitate the entry and placement of a distal portion of the inventive device. The posterior ethmoidal blood vessels supply the sphenoid sinus. The lymph is drained by retropharyngeal lymph nodes. The sphenoid sinus is innervated by the posterior ethmoidal nerve and orbital branch of the sphenopalatine ganglion. It is related to the pituitary gland and hypothalamus above and on each side of the sinus and is walled by the cavernous sinus containing carotid arteries, perforating blood vessels, internal carotid artery and the five cranial nerves.

The pituitary gland is located inside the sella turcica in a round bony cavity that is separated from the sphenoid sinuses by a thin plate of bone; the floor of the sella turcica forms part of the roof of the sphenoid sinuses (Figs. 2-5, 12, 13, and 15). On either side of the sphenoid sinus is located a pair of intercommunicating venous channels called the cavernous sinuses connected to the brain stem and orbital part of the brain around the infundibulum. Several important nerves and vascular structures pass through the cavernous sinus between the venous channels; these play an important role in conduction of electrical impulses from our inventive device from the sphenoid sinus to the brain and brain stem: They are:

i. The internal carotid artery (#510) which forms a major part of the Circle of Willis
ii. The ophthalmic division of the trigeminal nerve (V1-505)
iii. The maxillary division of the trigeminal nerve (V2-507)
iv. The occulomotor nerve (III 503)
v. The trochlear nerve (IV-504)
vi. The abducens nerve (VI-506)

Immediately below the sphenoid sinus embedded in the upper most part of lateral wall is the sphenopalatine ganglion with extensive connections (Figs. 2, 3). Above the sinus is the pituitary gland with infudibulum connected to the hypothalamus, thalamus, and the rest of the brain through the thalamic radiation, which transmit electrical impulses delivered through a device and method as described.

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The pituitary gland is connected to the hypothalamus, thalamus, central gray, reticular system, hippocampus, parahippocampal gyrus, cingulate gyrus, and cortical centers through the thalamic projections. The basal ganglion, red nucleus, and substantia nigra are in close proximity to the hypothalamus and are inter-linked. The electrical impulses imparted to the pituitary gland spread to the above brain structures and play an important role in the treatment of Alzheimer's, and other nervous system diseases.

The pituitary gland rests immediately above the thin sphenoid bone, which will allow the electrical impulses to be transmitted to the surrounding above described brain structures.

In recent years, a number of devices have been developed for insertion into the human body cavities, and hollow tubes (BV) to treat a particular problem including the dilation of coronary blood vessels and stimulation of the heart and spinal cord. The miniaturization of various devices has made this possible. This inventive device, once described as to its structure, utility, and details of use and operation, is of a type that can be manufactured using known methods and materials and as now described herein can be useful to treat Alzheimer's and other neurodegenerative diseases.

ANATOMY OF THE OLFACTORY MUCOSA, OLFACTORY NERVES AND OLFACTORY BULB AND ITS CONNECTION TO CNS CORTICAL CENTERS FOR THE TREATMENT OF ALZHEIMER'S AND OTHER NEURODEGENERATIVE DISEASES, USING THE DESCRIBED DEVICE

The olfactory epithelium is a specialized epithelial tissue inside the nasal cavity that is involved in perception of smell located in the dorsoposterior aspect of the nasal vault. Because the olfactory neural cells are the only surface neural cells in the body, olfactory mucosa is considered in this aspect, as a "window to the brain."

Interestingly, the human adult olfactory mucosa is a potential source of olfactory ensheathing cells and multipotent neural stem cells. They have been used in autologous transplantation therapies aimed at the treatment of degenerative or traumatic conditions of the central nervous system, spinal cord injury or Parkinson's disease (Mackay-Sim A et al (2008) Autologous olfactory ensheathing cell transplantation in human paraplegia: a 3-year clinical trial. Brain 131(Pt 9):2376–

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2386. Murrell W et al (2005) Multipotent stem cells from adult olfactory mucosa. Dev Dyn 233(2):496–515). It is demonstrated that the anatomical configuration of the nasal cavities affects the olfactory airflow, and the fraction of the air stream entering the naris that reaches the olfactory cleft is only between 10 and 15% (Hornung DE (2006) Nasal anatomy and the sense of smell. Adv Otorhinolaryngol 63:1–22. Hahn I, Scherer PW, Mozell MM (1993) Velocity profiles measured for airflow through a large-scale model of the human nasal cavity. J Appl Physiol 75(5):2273–2287). That is why to deliver most of the therapeutic agents to olfactory mucosa, a special delivery catheter and ordinary sprays result in depositing in respiratory mucosa, not in olfactory mucosa.

Humans have about 10 cm^2 (1.6 sq inch) of olfactory epithelium. Olfactory mucosa in humans lies on the roof of the nasal cavity about 7 cm above and behind the nostrils. The human olfactory mucosa consists of a pseudo-stratified columnar epithelium resting on a highly cellular lamina Propria. Olfactory epithelium consists of 4 distinct cell types:

1. Olfactory cells of the epithelium are bipolar neurons, which congregate to form the olfactory nerve (cranial nerve I). They are responsible for conducting the electrical impulses to the olfactory bulb and rest of the CNS. As they emerge to the lamina propria, they form up to 20 olfactory nerve fasciculi surrounded by Perineural epithelium and sub Perineural epithelial space, which conduct the therapeutic agents to the SAS and CSF surrounding the olfactory bulb. From there, the therapeutic agents are transported to the rest of the CNS (Shantha T.R. and Yasuo Nakajima. Histological and Histochemical Studies on the Rhesus Monkey (Macaca Mulatta) Olfactory Mucosa. Yerkes Regional Primate Research Center, Emory University, Atlanta, Georgia: Z. Zellforsch. 103, 291-319 (1970).
2. Supporting cells: Analogous to neural glial cells are the supporting cells (sustentacular cells) of the olfactory epithelium.
3. Microvillar cells: They were first described in 1982, and hypothesized as a second morphologically distinct class of chemoreceptor in the human olfactory mucosa. However, their putative role in the olfaction has not yet been definitely demonstrated.
4. Basal cells divided into two types.

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a. The horizontal basal cells line the olfactory epithelium and the slightly more superficial globose basal cells thought to be the primary stem cell.
b. Brush Cells resting on the basal lamina of the olfactory epithelium, are stem cells capable of division and differentiation into either supporting or olfactory cells. The constant divisions of the basal cells lead to the olfactory epithelium replaced every 2-4 weeks.

Bowman's (olfactory) Glands deliver a protenacious secretion via ducts onto the surface of the mucosa. The role of the secretions is to trap and dissolve odiferous as well as therapeutic agents to transport to the bipolar neuronal pathways, Perineural epithelium, sub Perineural epithelial space to the olfactory bulb, SAS and CSF.

Stimulation of the olfactory nerves in the olfactory mucosa (see FIGS. 2-5, 13-15) results in transmission of electrical impulses to the olfactory neurons, olfactory nerve fasciculi, olfactory bulb, and olfactory tract to various nuclei in the CNS as shown in the figure 14. Examples of devices capable of delivering therapeutic agents to treat Alzheimer's and other neurological diseases with adjuvant therapeutic agents and insulin delivered to the olfactory mucosa, is described in U. S. Patent Application Publication Number: 2012/0323214 AD by Dr. Shantha, the entirety of which is incorporated herein by reference. The combination of olfactory nerve stimulation and delivery of therapeutic agents through the olfactory mucosa is the most important method of treatment for Alzheimer's, senile dementia and other CNS diseases.

Hundreds of studies have shown that the olfactory mucosa with olfactory nerves transports many therapeutic agents directly to the brain by passing the BBB. Hence, it is a useful anatomical site besides electrical impulses delivery to the CNS, and for the delivery therapeutic agents with or without producing Iontophoresis and electroporation described in U. S. Patent Application Publication Number: 2012/0323214. The device described herein can optionally incorporate Iontophoresis and electroporation stimulation applied to olfactory mucosa to cause the olfactory mucosa open up (leaky) to deliver large molecules to the CNS by bypassing BBB.

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ANATOMY OF SPHENOPALATINE GANGLION AND ITS CONNECTION TO THE CNS CORTICAL, AND BRAIN STEM CENTERS FOR THE TREATMENT OF ALZHEIMER DISEASE USING THIS INVETIVE DEVICE (FIGS. 1-5, 13, 15)

The sphenopalatine ganglion (synonym: SPG, Meckler's ganglion, ganglion pterygopalatinum, nasal ganglion, pterygopalatine ganglion,) is the largest parasympathetic ganglion in the body found in the pterygopalatine fossa associated with the branches of the maxillary nerve (Fig. 2). The sphenopalatine ganglion supplies the lacrimal gland, paranasal sinuses, glands of the mucosa of the nasal cavity and pharynx, the gums, and the mucous membrane and glands of the hard palate and cerebral blood vessels, which form the Circle of Willis and its branches. It gets many nerve connections from CNS to ganglion and back, which transmit electrical impulses to the CNS. When we say the stimulation of sphenopalatine ganglion, it includes any and all of these communicating branches of the ganglion described herein. Sphenopalatine ganglion receives a sensory, a motor, parasympathetic, and sympathetic roots. Activation of the ganglion is believed to cause vasodilatation of these blood vessels as described in US 7,640,062 B2. Such stimulation opens the pores in the vessel walls of the cerebral BBB blood vessels due to the dilatory effect, causing plasma proteins and therapeutic agents to extravasate to neuropil. This effect allows easy transport of molecules from within these blood vessels to surrounding tissue and from the neuropile back to the circulation, thus facilitating the removal of neurotoxin compounds, which are involved in Alzheimer's disease.

The stimulation of olfactory mucosal nerves, sphenopalatine ganglion, trigeminal nerves, pituitary gland with hypothalamo hypophysial tract, cause an increased clearance of the substance from cerebrospinal fluid such cytokine, and RNA fragments, neurotoxins and others which act as marker of neuronal pathology resulting in Alzheimer's and other neurodegenerative diseases.

The main object of the present invention is to deliver the electrical impulses to activate the Alzheimer's afflicted brain and reset the function of the CNS at neuronal and synaptic level (by increasing the electrical conductivity and reducing the inflammation). The present invention also provides a method and apparatus for

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delivery of electrical impulses by stimulation of the olfactory nerves, sphenopalatine ganglion, trigeminal nerves, pituitary gland with hypothalamo hypophysial tract, five cranial nerves on each side, and their outgoing parasympathetic connection to cerebral BV. Methods and devices as described can also be optionally used to deliver therapeutic agents directly to the CNS through the olfactory mucosa by passing the BBB.

Stimulation as described herein of one or more of olfactory mucosal nerves, sphenopalatine ganglion, trigeminal nerves, pituitary gland with hypothalamo hypophysial tract, may lead to increased clearance of the substance from cerebrospinal fluid for example amyloid, tau, cytokine, and RNA fragments, which act as a marker of neuronal death resulting in Alzheimer's and other neurodegenerative diseases.

The middle and anterior cerebral arteries provide the blood supply to the cerebral hemispheres, including the frontal and parietal lobes in their entirety, the insula, the limbic system, and most of the temporal lobes, internal capsule, basal ganglia, and thalamus. These structures are involved in many of the neurological and psychiatric diseases of the brain. Hence, certain embodiments of methods and devices as described herein can involve providing improved blood supply and drug delivery to these structures. There is a presence of parasympathetic innervations in the posterior cerebral and basilar arteries from the sphenopalatine ganglion resulting in the above described therapeutic agents' delivery and effects due to BV dilatation and leakage development in the BBB.

A function of the present invention is to deliver the electrical impulses to activate the silent Alzheimer's afflicted brain, their neurons, and synapses. According to certain embodiments described methods and apparatus also deliver therapeutic molecules bypassing the BBB. It is accomplished by this inventive device due to stimulation of the olfactory mucosal nerves, sphenopalatine ganglion, trigeminal nerves, pituitary gland with hypothalamo hypophysial tract, five cranial nerves on each side, and their outgoing parasympathetic connection to cerebral BV to make them more permeable to large molecules from within the cerebral BV.

The afferent fibers innervate from the cranial nerves that are stimulated by our method include several midbrain, pons and medullary structures; and their

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nucleus including the tractus solitarius (NTS). They receive most of the afferents and bilateral inputs of all cranial afferents. The cranial nerve nuclei stimulated has widespread projections, including direct or multiple synaptic projections to the parabrachial nucleus, vermis, inferior cerebellar hemispheres, raphe nuclei, periaquaductal gray, locus coeruleus, thalamus, hypothalamus, amygdala, nucleus accumbens, anterior insula, infralimbic cortex, and lateral prefrontal and temporal cortex. Brain functional imaging studies show that stimulation of these cranial nerves bring about changes in several areas of the brain, including the thalamus, cerebellum, orbitofrontal cortex, limbic system, hypothalamus, basal ganglion and medulla.

The stimulation of particular areas of the brain has been suggested as a mechanism for the effects of vagus nerve stimulation, but such localized stimulation of the brain may depend upon the parameters of the stimulation (current, frequency, pulse width, duty cycle, etc.). These parameters may determine which neurotransmitters are modulated including norepinephrine, seratonin, and GABA (Mark S. George, Ziad Nahas, Daryl E. Bohning, Qiwen Mu, F. Andrew Kozel, Jeffrey Borckhardt, Stewart. Mechanisms of action of vagus nerve stimulation (VNS). Clinical Neuroscience Research 4 (2004) 71-79; Jeong-Ho Chae, ZiadNahas, Mikhail Lomarev, Stewart Denslow, Jeffrey P. Lorberbaum, Daryl E. Bohning, Mark S. George. A review of functional neuroimaging studies of vagus nerve stimulation (VNS). Journal of Psychiatric Research 37 (2003) 443-455; G. C.Albert, C. M. Cook, F. S. Prato, A. W. Thomas. Deep brain stimulation, vagal nerve stimulation and transcranial stimulation: An overview of stimulation parameters and neurotransmitter release. Neuroscience and Biobehavioral Reviews 33 (2009) 1042-1060; Groves D A, Brown V J. Vagal nerve stimulation: a review of its applications and potential mechanisms that mediate its clinical effects. Neurosci Biobehav Rev (2005) 29:493-500; Reese TERRY, Jr. Vagus nerve stimulation: a proven therapy for treatment of epilepsy strives to improve efficacy and expand applications. Conf Proc IEEE Eng Med Biol Soc. 2009; 2009:4631-4). The most important effects of electrical stimulation are to inhibit inflammation by inhibiting the cytokines, increase acetylcholine in the brain content and other neurotransmitters including epinephrine, facilitate the removal of the Aβ from the neuropile, prevent further

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apoptosis of neurons, improve the mitochondrial, endoplasmic reticulum and nuclear function by increasing the production of proteins, and amino acids involved in memory and cognition.

This invention is used to deliver electrical impulses directly to the CNS through the ORE by passing the BBB by making the CNS blood vessels leaky.

Optional therapeutic agents that may be delivered in combination with the described electrical stimulation of nerve fibers, using an electrical stimulator-catheter system as described to treat Alzheimer's disease are numerous. Some of them are:

I. glutamate receptor antagonist, and
II. an NMDA-receptor blocker for example ketamine and others;
III. β- amyloid inhibitor,
IV. bexarotene which increases the production of a fat-protein complex, apolipoprotein E, that helps to clear excess β amyloid form the brain,
V. an Alzheimer's vaccine;
VI. anti-inflammatory drugs;
VII. a microglial activation modulator;
VIII. a cholinesterase inhibitor, acetylcholine enhancer;
IX. various nerve growth factor, brain-derived neurotrophic factor,
X. gangliosides,
XI. phosphatidylserine (PS),
XII. fibroblast growth factor,
XIII. insulin,
XIV. insulin like growth factors (IGF-1),
XV. ciliary neurotrophic factor and glial derived nexin;
XVI. antioxidant; hormones; Vitamin B_{12} and B Vitamins,
XVII. an inhibitor of protein tyrosine phosphatases;
XVIII. endogenous protein for instance albumin and memory enhancing nerve growth factors to protect the brain from neurodegenerative diseases,
XIX. anti tumor necrosis factors, (TNF), anti cytokines therapeutic agents-monoclonal antibodies, chemotherapeutic agents, and

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XX. A range of known therapeutic agents, as well as other pharmaceutical, biochemical, nurticeuticals, and biological agents or compounds including stem cells which have curative or curtailing effect on Alzheimer's and other neurodegenerative CNS diseases.

THE ADVANTAGES OF OLFACTORY REGION, SPHENOID SINUS, POTUITARY GLAND, AND CRANIAL NERVES I, III, IV, V, AND VI, INTERNAL CAROTID ARTERY, SPHENOPALATINE GANGLION AND TRIGEMINAL NERVE DELIVERY OF ELECTRICAL IMPULSES AND ADJUVANT THERAPEUTIC AGENTS FOR THE TREATMENT OF ALZHEIMER'S AND RELATED DISEASES BY THIS INVENTION DESCRIBED BELOW.

This present invention describes a method of use of electrical impulses through the above described anatomical regions transmitted and transported to the CNS to curtail Alzheimer's disease and other related diseases. These regions can also be used for administration of insulin, IGF-1 (7.65kDa) protein neurotrophic factor, vitamin A related compound bexarotene, to remove B amyloid, acetylcholine esterase inhibitors, and various adjuvant pharmaceutical, biochemical, nurticeuticals, and biological agents or compounds developed or being developed to treat Alzheimer's and neurodegenerative diseases in conjunction. The advantages of this invention are as follows:

a) Due to the close proximity of the olfactory nerves, sphenopalatine ganglion and its branches, and trigeminal nerves, pituitary gland, hypothalamus, it is easy to stimulate the central nervous system by transmitting electrical impulses (Figs. 1-5, 11-15) through these neural pathways;

b) Ease and convenience: This method is easy to use, painless, does not require strict sterile technique, intravenous catheters or other invasive devices; methods can be performed without the use of general anesthetic on a patient, and on an outpatient basis;

c) It is immediately and readily available to all patients at all times;

d) High therapeutic efficacy: Due to the achievement of higher local concentration of electrical impulses in the CNS through the rich nerve plexus delivered to disease afflicted areas of the CNS;

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e) Increased efficacy of its use along with optional adjuvant therapeutic agents: Due to the ability of the administered therapeutic molecule to reach the target tissue without degradation caused by digestive enzymes, hepatic or systemic circulation (first phase metabolism); and the ability of the insulin to augment and amplify the effects of other therapeutic agents used to treat CNS disease;

f) Fast onset of action: Due to their proximity to the CNS, the site where they are needed and most of the therapeutic modality reach the CNS within seconds to minutes;

g) The inventive devise can be used for long duration;

h) It has fewer side effects, if any;

i) Due to improved delivery of the therapeutic electrical pulses or signals to the CNS, the site of the disease, benefits are felt without delay; and has anti inflammatory effect thus reducing the subtle brain inflammation that contributes to the disease conditions.

j) The advantage of using this invention of electrical impulse delivery in the above-described regions is that it does not require any modification of the device or the use of therapeutic agents;

k) It is low cost, patient and healthcare provider friendly, hardly invasive, non injected, and is a safe method when used appropriately; and,

l) Electrical impulses can also act as iontophoresis, and electroporation of the olfactory mucosa, sphenopalatine ganglion and sphenoid sinus lining, thus augmenting the uptake of therapeutic agents from these regions to be delivered to the CNS by passing the BBB in the treatment of Alzheimer's and other neurological diseases.

Caution: Exercise cautions when using the device in epileptics, they should be under control to use this device. On the other hand, it can be of use to send counter pulses to treat status epilepticus, to counter the brain electrical activity. Its use may have effect on smell (anosmia). Nasal congestion due to cold or allergies, sinus pathology, tumors, and nasal septal diseases may interfere with the introduction of device, but are not contraindications to use this inventive device to treat Alzheimer's disease.

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DETAILED DESCRIPTION OF THE DIGRAMS EXPLAINING THE INVENTON TO TREAT ALZHEIMER'S AND HOW THE THERAPEUTIC AGENTS REACH THE CNS TO CURTAIL THE DISEASE

With reference now to the various figures in which identical embodiments are numbered alike throughout the description of the preferred devices and techniques of the present invention presented below. These diagrams represent examples of the present invention and describe how electrical impulses are delivered to CNS to treat CNS diseases including Alzheimer's and deliver the impulses to reach the site of pathology in the CNS to curtail the affliction. While preferred embodiments of the present invention have been described, it should be understood that various changes, adaptations, and modifications may be made thereto. It should be understood, therefore, that the invention is not limited to details of the illustrated invention.

FIG. 1 is the diagram of the lateral and medial wall of the nasal cavity 100 reflected back at cribriform plate of the ethmoid bone 8. It shows ORE (olfactory nerves) with various nerve structures (shown in black surface with white lines) with which electrical impulses come in contact, then are conducted to the CNS to the brainstem, hippocampus, entorhinal cortex, thalamic, hypothalamic, cerebral cortical centers, cerebellum and other cortical neuropil (see FIG. 14). The olfactory tracts are connected to the entorhinal cortex (EC) located in the medial temporal lobe (area 28, and 34 of the brain). The entorhinal cortex is one of the first areas affected in Alzheimer's disease. It functions as a hub in a widespread network for memory and navigation-routing of impulses. The EC is the main interface between the hippocampus and neocortex. The EC-hippocampus system plays an important role in autobiographical/declarative/episodic memories and in particular spatial memories including memory formation, memory consolidation, and memory optimization. Electrical impulses transmitted to this area from an inventive device as described have a remarkable therapeutic effect on Alzheimer's patients and senile brain atrophy, as well as other neurodegenerative diseases.

Note the olfactory mucosa (OM) with olfactory receptor and its nerve fasciculi 2, 5, cover extensive areas of the medial 3 and lateral 4 wall of the upper part of the nasal cavity, which is separate from the respiratory part of the nose, and

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pass through the cribriform plate of the ethmoid bone 8 to the olfactory bulb. This region also contains the sphenopalatine ganglion (Pterygopalatine) 6 with its extensive central and peripheral connecting branches (see Fig. 2 below). This ORE 2, 5 is also surrounded by anterior ethmoidal nerves 7 connected to the ophthalmic branch of the trigeminal nerves. The therapeutic agents and electrical impulses delivered through this invention pass on to the CNS through the olfactory nerves, trigeminal nerve branches 7 (CN V), III, IV, V (V1-2), VI th Cranial nerves 359, and sphenopalatine ganglion 6 that supply the upper third of the nasal cavity close to the olfactory mucosa, pituitary gland 362 and sphenoid sinus 361 with 10 cranial nerves in its wall located in the cavernous sinus. The therapeutic delivery of electrical impulses delivered through this invention is passed on to the CNS through the olfactory nerves, trigeminal nerve branches, III, IV, V, VIth Cranial nerves, and sphenopalatine ganglion that supply the upper third of nasal cavity close to the olfactory mucosa. The CSF (cerebrospinal fluid) in the SAS (subarachnoid space) surrounding the olfactory bulb also conduct the electrical impulses and therapeutic agents to the brain surface from short olfactory nerves in the treatment of Alzheimer's and other neurodegenerative diseases.

FIG. 1a is the diagrammatic presentation 100a showing vestibule 375, respiratory nasal mucosa 376 with olfactory nerve and olfactory mucosa 377 of the lateral and medial walls of the olfactory mucosal nerve area of the nose (ORE). The arrows point to the spread of electrical impulses and therapeutic agents from the ORE 377 to the CNS. Note to get the maximum delivery of therapeutic agents to the ORE, the head should be extended as shown in the diagram and electrical impulses delivered to the ORE 377 using the special delivery catheter described herein. Just passing electrical impulses through the vestibule 375 and the respiratory mucosa 376 is not effective for the treatment of Alzheimer's disease. The therapeutic dose of electrical impulses and therapeutic agents' delivery catheter and Iontophoresis device are placed on the ORE 377 to treat Alzheimer's disease.

FIG. 2 is the diagram of the lateral wall of the nasal cavity 200 showing how various nerve structures that the therapeutic electrical current (and optional therapeutic agents) delivered by a device as described come in contact with and are transported to the CNS through nerve fasciculi of the nerve structures located in the

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ORE, and sphenoid sinus (525) through the sphenoid ostium 524. The subarachnoid space (SAS) and the cerebrospinal fluid (CSF) surrounding the nerve fasciculi and olfactory bulb also conduct the electrical impulses to the surface of the brain. The therapeutic delivery of electrical impulses passes through the olfactory bulb 35 transported by the olfactory mucosa and olfactory nerves 105 passing through the cribriform plate of the ethmoid bone 8. The electrical pulse and stimulus are passed on to the CNS through the trigeminal nerve 118, external nasal nerve 116, the anterior ethmoidal nerve 117; and from the sphenopalatine ganglion 110 to the greater petrosal nerve 119, nerve of the pterygoid canal 111, pterygopalatine and pharyngeal nerve 112, lesser palatine nerve 114, greater palatine nerve 115, nasopalatine nerves 109, parasympathetics to the internal carotid artery 510 many cranial nerves immediately adjacent to the lateral wall of the sphenoid sinus 525. The sphenopalatine ganglion 112 neuronal center is located in the brain behind the nose (see Fig. 13). Besides the above branches, it consists of parasympathetic neurons innervating the Circle of Willis (middle cerebral, anterior cerebral, vertebral, basilar, posterior cerebral arteries and their lumen). Activation of this ganglion causes the vasodilatation of these vessels in the Circle of Willis including the basilar and posterior cerebral arteries. A second effect of such stimulation is the opening of pores in the vessel walls, breaking of the BBB causing plasma proteins and therapeutic agent's extravasations to neuropil. This effect allows better transport of molecules from within these blood vessels to surrounding nerve structures in the treatment of Alzheimer's.

The olfactory mucosa and olfactory nerves 105 and 10 cranial nerves adjacent to the sphenoid sinus (see Fig. 13) play a major role in delivering electrical impulses and therapeutic agents in the treatment of Alzheimer's in this invention by bypassing or overcoming the BBB (diagram modified after Grays Anatomy).

FIG. 3 is the diagram of the medial wall of the nasal cavity 300 and nerve structures located in the olfactory anatomical region. Various nerve structures on the medial wall of the nose conduct the electrical impulses to treat Alzheimer's as this invention comes in contact, and are transmitted to the CNS from the upper part of the nose from the ORE 106 and the 10 cranial nerves adjacent to the two outer walls of the sphenoid sinus 524. The electrical impulses of this invention are

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conducted through the olfactory nerves, through the cribriform plate of the ethmoid bone 8 to the olfactory bulb 35. The nerve impulses pass from the olfactory mucosa 106 and the 10 cranial nerves adjacent to the wall of the sphenoid sinus 525 to the various centers of the brain and cortex, especially the temporal and prefrontal and orbital cortex, the front part of the brain stem through the olfactory tracts 36, 38 as well as to the cerebellum (see FIG. 14). Olfactory nerves are the shortest of the cranial nerves, hence it is easy for them to carry the electrical impulses to the olfactory bulb, and the impulses connect to the CNS without decay.

The axons and dendrites of the olfactory tract transport the therapeutic delivery of electrical impulses to the brain centers involved in Alzheimer's disease. The electrical impulses also pass through the trigeminal nerve branches and sphenopalatine ganglion 110 that supply the nasal cavity through the anterior ethmoidal nerve 107, nasoplatine nerve 109, medial, posterior and superior nasal branches 108 and the sphenopalatine ganglion 110 and its branches to reach the circle of Willis to reach the brain stem cranial nerve nuclei. The electrical impulses also pass from the sphenoid sinus to pituitary gland 509, a rich vascular network surrounding the gland 511and pituitary stalk 512; pituitary hypothalamo-hypophysal tract 512, hypothalamic nuclei 513, and thalamic centers 514 and then to the cortical radiation of the entire brain. Note how easy it is to get into the sphenoid sinus 525 through sphenoid ostium 524 located behind the olfactory mucosa (diagram modified from Grays Anatomy).

FIG. 4 is the drawing of the nasal cavity diagram 400 showing the nerve structure locations involved in the transmission of electrical impulses to the brain using this invention. The electrical impulses are conducted to the CNS from the olfactory mucosa 45, olfactory mucosal nerves 44, olfactory nerve fasciculi 105, olfactory bulb 35, and medial and lateral olfactory tracts 516. The electrical impulses transmitted through the trigeminal nerve branches including anterior ethmoidal nerve 107, from the sphenopalatine ganglion and its branches 110, parasympathetic supply from the sphenopalatine ganglion to Circle of Willis 510, pituitary gland 509, rich portal blood system of the pituitary gland 511, hypothalamo-hypophysal tract 512, hypothalamic nuclei 513, and thalamic radiation 514 (insert 4A). Note the presence of five cranial nerves 515 (CN III, IV, V, and

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VI) on each side of the sphenoid sinus that conduct the electrical impulses to the CNS in the treatment of Alzheimer's and other neurodegenerative diseases.

FIG. 5 is the diagrammatic presentation 500 of the ORE with similar explanation of the regions as FIG. 4. It is showing the pituitary gland 509 (see insert 5A), sphenopalatine ganglion 110, olfactory mucosa with olfactory nerves, olfactory mucosal nerves 44, olfactory bulb 35 being electrically stimulated by electrical output manipulator control box 517. The power source is contained within this pulse generator box, and generates a battery powered current delivered through the conducting wires 518 which will send electrical impulses to the CNS for the treatment of Alzheimer's and other neurodegenerative diseases.

According to methods as described, electrical impulses are transmitted to the CNS from the trigeminal nerve branches including anterior ethmoidal nerve107 sphenopalatine ganglion and its branches 110, parasympathetic supply from the sphenopalatine ganglion to Circle of Willis 510, pituitary gland 509, rich portal blood system of the pituitary gland 511, hypothalamo-hypophysal tract 512, hypothalamic nuclei 513, and thalamic radiation 514 (insert 4A). Note the presence of five cranial nerves 515 (CN III, IV, V, and VI) on each side of the sphenoid sinus that conduct the electrical impulses to the CNS in the treatment of Alzheimer's and other neurodegenerative diseases.

FIG. 6 is the diagrammatic presentation 600 of this inventive device 220 designed to stimulate the ORE and deliver therapeutic agents. It has electrical output manipulator 517 attached to the olfactory stimulator part 520 passing the conductive wires through the main body of the device 518. It has balloon 519, capable of being inflated while the device is positioned in the ORE with the insertion end at a trans-nasal location. This balloon will prevent the trauma to the delicate nasal mucosa as the device is advanced to the ORE through the external nasal opening. The balloon is connected to the inflating syringe 522. The balloon is inflated with air or sterile liquid or gel and the size of the balloon can be adjusted according to the size of the patient's nose. The device connected to the therapeutic agents delivery syringe 521 which delivers them through the electrical current delivery part of the device 520 pores if needed in the treatment of Alzheimer's and other diseases. This catheter acts as iontophoresis and electroporation with simple

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modification to facilitate the delivery of therapeutic agents to the CNS by passing the BBB. The tip of the inventive device is provided with radio opaque marker 540 to identify the position of the catheter in the sphenoid sinus and/or on the olfactory mucosa after insertion and during insertion with radiographic examination. The device embodiment of figure 6 does not include a opening or injection orifice at the insertion end of the device that would allow for a fluid such as a fluid containing a therapeutic agent, to be dispensed from the device at the insertion end, such as to tissue of the olfactory mucosa, sphenoid sinus, or both.

FIG. 7 is the drawing of the medial wall of the nose 700, showing various structures of the described device (e.g., catheter) 220, that may be stimulated by the nasal stimulator device to transmit electrical pulses to the CNS. The insertion end of the device is placed at a trans-nasal location. The tip of the electrical impulses delivery device is positioned in the sphenoid sinus through the ostium of the sphenoid sinus 524. This positioning between the sphenoid sinus and the nasal balloon 519 will keep the proximal stimulating part of the device 520 located firmly in the desired location i.e. on the olfactory mucosa close to the cribriform plate of the ethmoid bone immediately below the olfactory bulb 35. The electrical impulses also pass (spillover effect) from this device to sphenopalatine ganglion 110 and to the anterior ethmoidal nerve 107. Optional injection port 522 is used to pass guide wire 523 to facilitate placement of this device with ease. Syringe with three way stop cock 521 can be used to deliver therapeutic agents to the olfactory mucosa through the catheter. The device insertion is facilitated by the use of flexible fiber optic nasal scope and guide wire 523. The desired current is delivered through the electrical output manipulator 517. The power source is contained within this pulse generator box and generates a battery powered current delivered through conducting wires 518, which send electrical impulses to the CNS for the treatment of Alzheimer's and other neurodegenerative diseases. The electrical current passes to the CNS through the pituitary gland 509.

FIG. 8 is the view of diagram 800 showing catheter 220 with two balloons holding the electrical impulses delivering part of the device 520 in position between the sphenoid sinus with a balloon 525 and nasal balloon 519 without movement at the olfactory region, i.e., in the insertion end is in a trans-nasal location. The syringe

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526 inflates the balloon in the sphenoid sinus 525 and the balloon in the nose 519 is inflated by the inflator 522 to hold the electrical impulses delivery on the olfactory mucosa (ORE) to the CNS in position especially in patients who are difficult to control. It is also provided with a guide wire port with a guide wire 523 to facilitate the insertion of this device and place it in the desired position. The device is connected to optional therapeutic agents delivery syringe 521, which is capable of delivering therapeutic agent to the interior of the nasal cavity through one or more external openings or apertures present along the shaft at the electrical current delivery part of the device 520 in the treatment of Alzheimer's and other diseases. The diagram also shows the proximity of portions of device 520 to the anterior ethmoidal nerve 107, olfactory mucosa 44, olfactory bulb 35, pituitary gland 509, and the sphenopalatine ganglion 110. The electrical impulses' spillover stimulates these structures. The rest of the explanation is the same as FIGS. 5 and 6. The olfactory mucosa is being electrically stimulated by electrical output manipulator control box 517. The power source is contained within this pulse generator box and generates a battery powered current delivered through the conducting wires 518 which will send electrical impulses to the CNS for the treatment of Alzheimer's and other neurodegenerative diseases.

FIG. 9 is the diagrammatic presentation 900 of the electrical impulse delivery device (catheter) 220. This diagram shows three separate electrical impulses delivery methods to the nerve structure as described here. This device incorporates olfactory nerve stimulator 520, and sphenoid sinus stimulator 527 which can be placed in a patient to stimulate the five cranial nerves and the internal carotid artery (part of the Circle of Willis) in the wall of the cavernous plexus located on the lateral wall of the sphenoid sinus. Sphenoid sinus stimulator 527 also sends electrical impulses to the pituitary gland to distribute the electric signals to the thalamic radiation and wake up the brain in those suffering from the Alzheimer's and other CNS diseases. Sphenoid sinus stimulator 527 can also be provided with a sphenopalatine ganglion stimulator in the form of an extension electrode that extends or that can be extended at the distal part of the catheter to be placed adjacent to and deliver electrical impulses to stimulate this ganglion in the treatment of Alzheimer's and other neurological diseases. Including an extension electrode, three

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separate electrical impulses delivery terminals can be activated through the electrical output manipulator 517 and connecting wires 518, at the same time, one at a time or two at a time as needed and depending on the tolerability and need of the patients. The balloons 519 and 520 can be expanded by using air or liquid by a tube in the interior connected through inflation stopcocks 521, 522 and 526 connected by a tube to the inflation syringe located outside the nose. The tip of the inventive device may be provided with radio opaque marker 540 to identify the position of the catheter in the sphenoid sinus and/or on olfactory mucosa after insertion and during insertion with radiographic examination. Injection port 522 is used to pass the guide wire 523 to facilitate placement of this device with ease.

FIG. 10 is the diagrammatic presentation 1000 of and embodiment of catheter device 220, which incorporates many features in the device. It has many of the features already described in FIGS. 7, 8, and 9. It shows the complete assembly of this inventive device to treat Alzheimer's disease. It has two balloons 519 and 527. The balloon 527 part has the insertion body or insertion end that may be is inserted in the human nose through the sphenoid foramina and then into the hollow sphenoid sinus optionally with the aid of a fiber optic nasal scope. The insertion body consists of two parts. One part is an inflatable outer membrane or balloon 527, which is adapted in size and flexibility to fit inside the sphenoid sinus cavity as illustrated in FIGS. 12, 3, and 15. The interior of this balloon 527 is connected to an inflation tube or inflation lumen, which in turn is connected through an inflation stopcock and a tube to the inflation syringe 521, 522, and 526. The inflation syringe 522 is used to pump air or fluid through the inflation tube to the interior of the balloon 527 so the balloon inflates to at least partially fill the sphenoid sinus cavity during the use of the apparatus. This embodiment includes additional syringe 529 (which is optional) with stopcock to deliver additional therapeutic agents. An infusion tube may also be connected to the interior of the balloon 527 and used to pump fluid at ambient, elevated, or low temperatures through the infusion tube and to the interior of the balloon during the operation of the apparatus. A device for heating or cooling the fluid to be pumped into the interior of the balloon 527 may also be included in the apparatus 530. The balloon 527 is provided with multiple electrical leads on the expandable exterior of the balloon as shown. The leads may

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be attached to or part of an expandable structure that is for example in the form of a polymeric mesh or fabric or a wire mesh that is placed at a surface of balloon 527, and that is capable of expanding as the surface of balloon 527 is expanded, e.g., within a sphenoid sinus. These leads are connected by electrical connectors 517 to an electrical output manipulator 517. This electrical output device 517 is connected to a source of electricity. Electrical stimulus is provided through the electrical leads to stimulate the pituitary gland, pituitary hypophysal track and surrounding five cranial nerve structures and the internal carotid artery encased in autonomic nerves. It is accomplished by stimulating the interior surface of the sphenoid sinus cavity and its walls through the balloon surrounded by electrical conductor wires, including electrodes, which will in turn transmit electrical impulses to the above mentioned tissue structures for treatment of Alzheimer's and other diseases of the nervous system including pain. It also has electrodes 531 which come in contact with the sphenopalatine ganglion and transmit electrical impulses to it for treatment of Alzheimer's.

An optional catheter and liquid dispensing port or aperture can be located at on the surface or the center of the balloon (527) with a suitable tube to allow a administer drugs or other therapeutic agent or other fluid to be directly dispensed to the sphenoid sinus cavity, besides delivering the electrical impulses. The therapeutic agents are infused so that they are absorbed by the central nervous system directly across the sphenoid sinus walls into the perforating vessels, which empty into the cavernous sinus plexus and circulate in the BV of the CNS. This method allows us to use a small dosage of drugs instead of using large dosages systematically. The antibiotics and anticoagulants may be impregnated onto the surface of the balloon of the sphenoid sinus cavity to prevent clotting and infection. The tip of the inventive device is provided with radio opaque marker 540 to identify the position of the catheter in the sphenoid sinus after insertion and during use with radiographic examination. Injection port 522 is utilized to pass the guide wire 523 to facilitate placement of this device with ease.

All of the tubes and connectors to the balloon 527 can be assembled together in a connector assembly. The inner portion of this connector assembly constitutes

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part of the insertion body. This assembly needs to be small in diameter and flexible for easy insertion through the nose and into the sphenoid sinus cavity ostium.

An optional temperature sensor wire can be connected to a temperature sensor and indicator. The temperature sensor wire is connected to sensors (not shown) in the balloon 527 to determine the temperature of the balloon surface and the structures in the immediate vicinity of it. This fluid within the balloon may be heated around 42°-44° C. or higher or cooled if so desired to stimulate or decrease the output of pituitary hormones, including growth hormone from the pituitary gland. Other means, for instance, a device embodying the Peltier 530 effect, can be used to heat or cool the outer surface of the balloon. Heating will enhance the conduction of electrical impulse and facilitate the stimulation of pituitary gland and other surrounding nerve structure.

FIG. 11 is the diagrammatic presentation 1100 of the longitudinal section of the olfactory bulb 1100 and the olfactory mucosa showing the route of electrical impulses transmission (and of transport of the insulin and other therapeutic agents) by the direct stimulation (application) of the olfactory mucosa in the treatment of Alzheimer's and other neurological diseases including autism. Electrical impulses and optional therapeutic agents pass through the olfactory nerves from the olfactory mucosa 45 transported through the subperineural epithelial space and olfactory axons to the olfactory bulb 35. The electrical impulses are also transmitted to the CNS to subarachnoid space (SAS) 36 after passing through the olfactory nerve fasciculi surrounded by perineural epithelium with CSF surrounding them. The SAS surrounding the olfactory bulb with its CSF is directly connected to the sub perineural epithelial space surrounding the olfactory nerve fasciculi 25 and other cranial nerves on the lateral wall of the sphenoid sinus which transmits the electrical impulses [Shantha et al: Z. Zellforsch. 103, 291—319 (1970). J National Cancer Inst 35(1):153-165 (1965). Expt Cell Res 40:292-300 (1965). Science 154:1464-1467 (1966). Nature 199, 4893:577-579 (1963). Nature, 209:1260 (1966). Histochemie 10:224-229 (1967).Structure and Function of Nervous Tissues. Volume I. pp 379-458]. The electrical impulses pass from receptor cells 44 and are transported through the axons, olfactory nerve fasciculi, retrograde through the cribriform plate of the ethmoid bone 43 to stimulate the olfactory bulb 35. From the

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olfactory receptor cell axons 45, the electrical impulses travel through the olfactory glomeruli 40 to periglomerular cells 39, mitral cells 41, and granule cells 42, to olfactory tract 37, and reach the CNS 38 then to the entorihinal cortex. The electrical impulses then exert their effect on the entorhinal cortical neurons, synapses between the neurons; oligodendroglia, astroglia and microglia in the neuropil involved in the disease process of Alzheimer's and other neurodegenerative diseases.

This diagram shows that the inventive device 220 may be placed on the olfactory mucosa to stimulate the olfactory nerves to allow the stimulation to be transmitted to the central nervous system. The entorhinal part of the olfactory system is very much involved in the genesis of Alzheimer's and other neurodegenerative diseases and the electrical impulses from this inventive device reach this area through the olfactory bulb with ease.

The above described nerve structures can be electrically stimulated by electrical output manipulator control 517. The power source is contained within this pulse generator box, and generates a battery powered current delivered through the conducting wires which will send electrical impulses to the CNS for the treatment of Alzheimer's and other neurodegenerative diseases.

FIG. 12 is the view of diagram 1200 showing the anatomy of the sphenoid sinus 525 and its relation to the surrounding structures in the cavernous sinus 541, and possible route of electrical impulses passing to the CNS. The inventive device is passed through the sphenoid ostium 524 into the sphenoid sinus 525 and the balloon 527 is inflated. Note that the balloon has fine electrical conducting wires (including electrodes) surrounding that are capable stimulating the pituitary gland, five cranial nerves, autonomic nerves and internal carotid artery. In the illustrated embodiment there is Peltier device 530 within the balloon to heat or cool the fluid within the balloon if desired. It also has a temperature sensor connected to the monitor outside the nose (not shown). The electrical impulses are transmitted to cranial nerves III, IV, V, VI and nerves 503, 504, 505, 506, 507 in the cavernous sinus that carry the electrical impulses to the brain stem and basal ganglion. The parasympathetic (autonomic) nerves supplying the internal carotid arteries 510 (and the Circle of Willis) within the wall of the cavernous sinus are stimulated by this

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inventive device, which makes them dilate within the BBB of the brain. This effect facilitates the transport of therapeutic agents within the BBB capillary plexus of the CNS and helps to remove the accumulated toxic substances within the neuropile. The tip of the inventive device is provided with radio opaque marker 540 to identify the position of the catheter in the sphenoid sinus after insertion and during use with radiographic examination.

The pituitary gland in the sella turcica also are exposed to electrical impulses transmitted to the pituitary gland 509, which also transmits impulses to arterio venous plexus 511, pituitary stalk 512, and hypothalamic nuclei 513 and to thalamic radiation 514 to the rest of the brain. The stimulation of the pituitary gland will have a profound effect on transmitting the electrical impulses and release of many trophic hormones from this master endocrine gland and hypothalamic nuclei. The pituitary gland is heated or cooled with the Peltier device within the balloon 530 to the desired temperature for the treatment of CNS disease.

FIG. 13 is the diagrammatic presentation 1300 of the coronal section of the sphenoid sinus with inflated balloon 527 inside the sinus and its anatomical relationship to five cranial nerves within the cavernous sinus 541 on both sides, pituitary gland in the sella turcica, hypothalamus, thalamic radiation, and internal carotid artery. In the diagram, the inventive device is positioned in one of the sphenoid sinus 525 passed through sphenoid sinus ostium 524, and the balloon 527 is inflated. The electrical impulses from the balloon are transmitted to cranial nerve III 503, CN VI 504, CN V_1 and V_2- 505, 507, and CN VI 506 and internal carotid artery 510, pituitary gland 509 with its portal system 511, pituitary stalk 512, with its connection to hypothalamus 513, and thalamus 514 (Insert 13A-511, 512, 513, 514). The insert 13A shows the detail of the structure, which gets stimulation from the electrical impulses from the sphenoid sinus. This inventive device delivers electrical stimulating impulses to these structures in the treatment of Alzheimer's and other neurological disease. Further, saline can optionally be infused from the catheter from pores at the end of the device, e.g., at or adjacent to balloon 527, and into the interior space of the sphenoid sinus; the saline can improve the strength of the electrical current, allowing improved transmission to the pituitary gland and its connection to cranial nerves and CNS.

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It is important to note that when the hypertonic saline fills the sphenoid sinus; the process must wait for 30-60 minutes so that the saline saturates the mucosal and boney wall of the sphenoid sinus absorbing the salt solutions. By this method, the walls of the sphenoid sinus become more conductive to electrical pulses conducted to the surrounding structures including the cranial nerves in the cavernous sinus 541 pituitary gland 509. The tip of the inventive device can be provided with radio opaque marker to identify the position of the catheter in the sphenoid sinus or on the olfactory mucosa after insertion and during use with radiographic examination. It is important to note that the sphenopalatine ganglion 508 is located immediately close to the sphenoid sinus ostium which can also be directly stimulated with additional electrical circuitry as shown in the diagram.

FIG. 14 is the diagrammatic presentation 1400 and the catheter device 220 whose tip is placed at the olfactory mucosa 45 lining of the nose close to the cribriform plate of the ethmoid bone and the olfactory bulb 35 within the cranium situated immediately above cribriform plate of the ethmoid bone. The diagram shows the transmission of electrical impulses and route taken by the therapeutic agents deposited at the olfactory region of the nose (ORE) in this invention to treat Alzheimer's and other neurological ailments. The electrical signals (therapeutic agents as well) from the olfactory mucosa 45 are transmitted to the olfactory bulb 35 to subarachnoid space (SAS) to the cerebrospinal fluid (CSF) then to various centers of the CNS. The electrical impulses spread to the olfactory tract 46, to prefrontal cortex 47, medial olfactory area 48, to temporal lobes 50 (Entorhinal cortex), to lateral olfactory area 51 and its associated adjacent nuclei 49, hippocampus 52, hypothalamus 53, brain stem nuclei 54, to cerebellum 55. The arrows show the extensive area where the electrical impulses and adjuvant therapeutic agents spread from the ORE to the CNS. From the subarachnoid space, the therapeutic agents can be transported to the eyes 56 through the optic nerve subarachnoid space, and the electrical impulses can also be transmitted to the eyes' optic nerve and cranial nerve III, IV, V, and VI nerves.

FIG. 15 is the diagrammatic presentation of the medial wall 1500 of the sagittal section of the nose with this inventive device in place. The electrical impulse transmitter comes in contact with the olfactory mucosa 44, olfactory bulb

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35, sphenopalatine ganglion 110, anterior ethmoidal nerve 107, pituitary gland 509 with its connection to the hypothalamus and thalamus, and its surrounding structures in the cavernous sinus with five cranial nerves 515 on each side and internal carotid artery 510.

The electrical impulses from the balloon are transmitted to cranial nerve on the adjacent wall of the sphenoid sinus and internal carotid artery 510, pituitary gland 509 with its portal system 511, pituitary stalk 512, with its connection to hypothalamus 513, and thalamus 514 (Insert 13A-511, 512, 513, 514). The insert 15B shows the detail of the structure, which gets stimulation from the electrical impulses from the sphenoid sinus. This inventive device delivers electrical stimulating impulses to these structures in the treatment of Alzheimer's and other neurological disease. Further, saline is infused from the catheter within the balloon 527 device and makes the electrical current more conductive and easier to be transmitted to the pituitary gland, and its connection to cranial nerves and CNS. The tip of the inventive device is provided with radio opaque marker 540 to identify the position of the catheter in the sphenoid sinus and /or on the olfactory mucosa after insertion and during insertion with radiographic examination. It has balloon 519, inflated while inserting and positioning the device in the ORE. A device for heating or cooling the fluid to be pumped into the interior of the balloon 527 may also be included in the apparatus 530.

Figure 16 shows the catheter (device) in sinus and the nose with the insertion end located in a trans-nasal location. Explanations of the dimension of the number given are as follows:

1. It indicates the dimension of the sphenoid sinus, which varies per patient and becomes bigger with advancing age. The height, breadth, and length of the sinus are around 2.2cm. That means it is about 1¼ to 1½ inches in all directions. So the catheter that enters the sphenoid sinus should be shorter, and may be a inch long (e.g., from 0.75 to 1.25 inch).
2. The ostium or the opening for the sphenoid sinus and diameter is not found in the literature. I do believe it is bout 2 to 4millimeter in diameter. It may be enlarged with a boogie or angocath dilator like catheter. It is mostly made of thin sphenoid bone. Even if it cracks, while dilating, had no consequence.

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So the diameter of the catheter distal end with the balloon should be no more than 3 to 5 mm, e.g., from 2 to 6 millimeters.

3. This part of the catheter represents the distance of the roof of the nose which forms the olfactory mucosa and olfactory nerve. It is about 2.5 (e.g., 2.2 to 2.7) inches long and the catheter lodged at this part can be bit bigger in diameter than the part that enters the sphenoid sinus.
4. This part represents the anterior descending part of the nose. It is about ½ -¾ inches' long. No special features are needed.
5. This represents the length of the catheter that occupies the external nose as it emerges from the roof of the nose. The size of the nose varies. This portion of the device may be from about 2-3 inches long. Note there is a balloon at the junction of the # 4 and #5. It holds the catheter in place without moving downwards. It abuts against the middle concha of the nose.
6. Represents as the catheter emerges through the external nasal opening.
7. This is external part of the catheter. It can be any length. It can be between ± 9-12 inches to be placed in the pocket and connected to electrical output monitor.

Preferred devices may include a nasal fiber optic scope to position the insertion end of the catheter device.

Figure 17 shows the electrical stimulator catheter device in place with the insertion end located at a trans-nasal location, connected to expanding balloon and/or injections port. The device includes only a single injection port at the proximal (external) end, and no fluid delivery port at a location to deliver therapeutic fluid to olfactory mucosa.

Figure 18 shows an example of an assembled catheter in position with an insertion end located at a trans-nasal location. It has three syringes. One each to expand the balloon and third one (which is optional) to instill therapeutic agents into sphenoid sinus or olfactory mucosa surface. It can be used to inject antibiotics to prevent any sphenoid sinus infection also or other anti Alzheimer's disease therapeutic agents.

Figure 19 shows various embodiments of the electrical stimulation catheter that can be incorporated. As an optional feature, the electrodes of the distal end are

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located on the expandable surface (e.g., balloon) and may be placed on an expandable mesh, such as an expandable wire, polymeric, or other type of natural or synthetic fabric or expandable sheet.

Figure 20 shows another embodiment of the electrical stimulation catheter placed in a trans-nasal location.

Figure 21 shows another embodiment of electrical stimulation with two balloon expanding syringes and electrical cell output monitor. The device does not include any port at the insertion end that will allow for delivery of a fluid, e.g., a therapeutic fluid, to the nasal cavity such as to the olfactory mucosa or sphenoid sinus; methods of using this device also do require delivery of therapeutic fluid to the nasal cavity.

The device (catheter) system described herein can be miniaturized and designed with a small diameter for insertion in the nose of children and teens to treat autism, cerebral palsy, Down syndrome and such related central nervous system diseases other than Alzheimer's disease.

It is a purpose and an intention of this invention to use the electrode stimulator system that is capable of conducting electricity with the least resistance and that the electrodes be made up of suitable conductive physiologically acceptable material, for example, silver, iridium, platinum, iridium alloy, titanium, nickel-chrome alloy or other suitable combination of conducting metal alloys. Each electrode can be insulated with a physiologically acceptable material such as polyethylene, polyurethane, or a co-polymer, which is a non-conductive, non-allergic, non-reacting synthetic or semi synthetic material. Each one of the electrodes can exhibit a smooth surface, except for the distal end of each such electrode. The ends can be optionally constructed to have a large surface area #110 to encounter the largest surface area of the olfactory mucosal nerves, sphenopalatine ganglion (SPG), trigeminal nerves, sphenoid sinus, and pituitary gland with hypothalamo hypophysial area. The amount of electrical current used for stimulation of the neurological structures described herein is conducted through these electrodes is controlled by a control pane in electrical output manipulator 517 as shown in other figure11 in order to keep the procedure within the desired parameters.

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In addition, embodiments of described methods can also result in improving the oxygen supply to neurons and surrounding nerve structures due to parasympathetically mediated Circle of Willis blood vessels stimulation, which results in dilatation of the BBB BV of the brain and their supply to the neuropil. This will be a therapeutic agent in the treatment of Alzheimer's and other CNS diseases. The dilatation of BV also results in the breaking of the BBB and allows the therapeutic agents to enter the brain substance. This method facilitates the drug delivery to the neuropil without the sacrifice of change in the molecular weight and its configuration. It is important to note that the permeability does not remain for a long time and closes very rapidly after the electroporation and Iontophoresis effects, indicating that this method of therapeutic window is open for a short time to deliver therapeutic agents circulating in the blood after intravascular administration. Hence, the longer we continue electrical stimulation, the longer the leaking of the therapeutic agents to the brain substance and the better the therapeutic effect. Before the electrical impulses stimulation, it is best to administer parenteral, oral or ORE therapeutic agents in advance, so that they will reach the effective therapeutic dose circulating in the BV and delivered by the BBB broken BV within the brain.

As appropriate, an optional therapeutic agent such as a pharmaceutical agent or other biologically active agent may be delivered to a patient in combination with electrical impulses stimulation as described. One or more of the following therapeutic active agents may be given systemically or if available through the olfactory mucosa. Examples of therapeutic agents that may be delivered to a patient for treating Alzheimer's and other CNS degenerative diseases delivered directly to ORE include:

I. Intranasal Insulin, and IGF-1

II. a glutamate receptor antagonist; and NMDA-receptor blockers and antagonists, including ketamine, memantine

III. a β amyloid inhibitor; and a microglial activation modulator for example bexarotene

IV. a combination of an Alzheimer's vaccine

V. anti-inflammatory non-steroidal anti-inflammatory drugs, COX-2 inhibitor (NSAIDS), glutathione antioxidant

VI. monoclonal antibodies (mAB) for instance Etanercept

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VII. a cholinesterase inhibitor which is already in use in the treatment of Alzheimer's such as tacrine, donepezil (Aricept®) Rivastigmine (Exelon®), Galantamine, and similar therapeutic agents

VIII. a stimulant of nerve regeneration and nerve growth factor using this method and adding neuro generative therapeutic agents

IX. Acetylcholine esterase inhibitor so as to enhance the acetylcholine in CNS

X. L-DOPA (L-3,4-dihydroxyphenylalanine), monoamine oxidase-B (MAO-B) inhibitors, apomorhine, and dopamine agonists (include bromocriptine, pergolide, pramipexole, ropinirole, piribedil, cabergoline, apomorphine and lisuride) to increase dopamine levels in basal ganglia of the CNS for treating Parkinson's

XI. an antioxidant; vitamins for example vitamin A, B_{12} B complex, D_3 and others

XII. hormone such as progesterone; an inhibitor of protein tyrosine phosphatases; an endogenous protein

XIII. Neurotrophic factors for example Nerve growth factors (NGF), fibroblast growth factor (bFGF), glial-derived neurotrophic factor (CNTF), pigment epithelium-derived factor (PEDF), glial-derived neurotrophic factor (GDNF), brain-derived neurotrophic factor (BDNF), erythropoietin's, insulin, IGF-1, platelet derived growth factor (PDGF) and as such

XIV. Gene and stem cell therapy; and therapeutic agents therapy through the ORE after electrical impulses stimulation, or after electroporation or Iontophoresis.

METHOD OF USE OF INTRANASAL INSERTION OF THE ELECTRICAL IMPULSES DELIVERY DEVICE

Before insertion of the electrical impulses stimulator through the nasal cavity, a thorough examination of the nasal cavity by an ENT specialist is in order. The patient should not be taking any blood thinning medications, free of nasal tumors, and without the history of epilepsy. It is also important for the attending physician to examine both sides of the nose with a fiber optic nasal scope and inspect the nasal passage, turbinates, roof of the nose, and ostium of the sphenoid sinus as well as the olfactory region (ORE). These scopes are flexible, easy to use and to clean. If the patient is sensitive for instrumentation, local anesthetic spray and KY jelly or similar lubricant will facilitate the examination and insertion of this device. It is important to have an intravenous infusion line open during the first

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insertion -stimulation, and it is not needed afterwards when one experiences the safety and simplicity of its use. For experimental reasons, the patient may also be connected to an EEG or EKG and record before, during, and after the insertion and turning on the electrical impulses delivery system of invention. If the EEG shows the epileptic type of brain waves, the amperes of electrical impulses delivered is reduced, so that no epileptic episode will occur during use of this inventive device. It may be important to have a brain scan and anterior-lateral view of X rays of the nose with sphenoid sinus and nasal sinuses. Have emergency first aid supplies available in case they are needed.

Once the diagnosis of Alzheimer's is established, and if there are no contraindication for the procedure, start the electrical impulses delivery procedure after carefully positioning the device in the sphenoid sinus, on the olfactory mucosa, and sphenopalatine ganglion. Use the nasal fiber optic scope to place the device anatomically in the correct position to deliver the electrical impulses to the desired anatomical site to stimulate the appropriate neurological structures.

Once the device is positioned at the desired anatomical position in the nose, with the insertion end at a trans-nasal location, start switching on the electoral output manipulator (Figs. 6-11, #517) slowly rising the mAP output. Only deliver the milliamps of electrical current the patient tolerates. The threshold amplitude for neuronal and neuropil activation will vary from one patient to the next. To ensure an adequate response, the stimulation parameters may be adjusted to stimulate at amplitude of about 5-10% below the patient's neuronal activation threshold to about 15-20% over the patient's neuronal activation threshold. The amplitude of the electrical stimulation typically is about 200 micro amps (uA) to about 400-500 milliamps (mA). Other suitable combinations of stimulation amplitude and frequency are provided on a per patient dependent basis. For example, the electrical stimulation can be provided by pulse trains of an intermittent duration or continuously, at a frequency of about 10 Hertz (Hz) to about 30 Hertz (Hz), with a pulse width of about 50 microseconds (μs). Put together an EEG recording during the procedure and set the desire milliamps of electrical current delivered to get the desired therapeutic effect.

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During the insertion, hold the device directed towards the external canthus of the eye abutting against the outer edge of the nose, directing it upwards and backwards. Do not pass the device horizontally where the tip will end at the respiratory mucosa. The device is inserted with the patient lying down with the neck extended and a small support under the patient's shoulders. The nose is sprayed with a local anesthetic and neosynephrine or Afrin to shrink the mucus membranes. A cotton wad soaked in local anesthetics and vaso-constrictors is packed with angled nasal forceps. Antiseptic solutions are sprayed inside the nasal cavity. As the local anesthetic takes effect, a fiber optic naso scope is introduced through the external naris, all the way up to the sphenoethmoidal recesses located at the posterior upper angle of the nose. Then the body of the device is guided gently into the sphenoid sinus through the sphenoid foramina. If the opening (ostium) of the sphenoid sinus is narrow, it can be enlarged by dilators or inflatable balloons. The balloon is inflated with a liquid and the stimulation started. It may be necessary in some cases to insert the apparatus into both right and left sphenoid sinuses to achieve the desired therapeutic effect. Make sure the patients and caregivers participate during the treatment so that they may carry out the treatment at home.

Position the electrical impulses delivering system as shown in the diagrams 5-15. Pull the electrical impulses delivery device out, slowly at the end of the procedure.

This invention is based on electrical impulses delivery to the afflicted area, as the memory recall is related to electrical activity. The device also give positive results during the stimulation processes by increasing the memory, recall of the past and remembrance of the events as they are happening due to the enhancing of the memory protein generation and activation of the ones that are already inside the neurons and providing electrical impulses needed to transmit the messages.

The electrical impulses are delivered continuously or intermittently depending upon the comfort of the patient and diagnosis of the condition. It may need to switched off as needed and the improvement in the signs and symptoms. The device can be left in place for hours and days or more at a time. The device can be removed to clean, treat with antiseptics, sterilize, reuse or replace. The patient can be put on antibiotics if the infection of the nose and sinus are suspected. The

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catheter and the balloon can be impregnated with antibiotics, antiseptics such as silver nitrate, antifungal agents to prevent the growth of the microbes on the device.

Therapeutic agents are administered orally, intravenously or intra nasally to olfactory mucosa depending on their formulation to the patient once it is determined the electrical impulse have caused dilatation CNS BV and broken the BBB to a certain extent. The drugs administered are specific to the disease. They are selected from described list herein for Alzheimer's disease.

EXAMPLES OF OLFACTORY MUCOSAL DELIVERY OF THERAPEUTIC AGENTS TO TREAT ALZHEIMER'S DISEASE

Once the nerve stimulation has been established using the inventive device described herein which incorporates Iontophoresis, any one or more of the following therapeutic agents may optionally be administered to the site of the olfactory mucosa to treat Alzheimer's disease through the delivery syringe attached to the catheter as shown in the diagrams Figs. 6-10 as an example. Optionally, a device and method may be used that do not involve delivery of therapeutic agent.

Preparation of stock solutions and method of olfactory mucosal administration:

a) Take 300 mg of bexarotene; dissolve it in a solvent alcohol, or dimethyl sulfoxide (DMSO), with suitable carriers, which include physiological saline or phosphate buffered saline (PBS). This solution can contain thickening and solubilizing agents, for example glucose, polyethylene glycol, and polypropylene glycol and mixtures thereof. The final formulation contains 30 mg of bexarotene per ml of solution.

b) Then take 100 IU of rapid acting insulin and dilute it in 5ml of normal saline, in which each ml contains 20 units of insulin.

c) Take 2.5 mg of Ketamine, and dilute it in 5ml of saline, resulting in 0.5 mg per ml or 500 mcg of active ingredient per ml.

d) Place the patient in a supine position with head extended, and the inventive device inserted and operating,

e) Instill through the syringe 0.5ml of bexarotene into delivery catheter to each olfactory mucosal surface as shown in figures 5-7. Wait for 10 minutes, then instill 0.25 to 0.5 ml insulin to each olfactory mucosal surface, wait for 10 minutes, then follow with olfactory mucosal delivery of ketamin, 0.5 ml to each

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side. During this procedure, olfactory mucosal stimulation is discontinued and resumed after the delivery of therapeutic agents to the olfactory mucosa. Electrical stimulation is continuing which will facilitate the uptake of these therapeutic agents. This procedure is repeated twice a day for the first week and then three times a week and then once a week depending on the response. The concentration of therapeutic agents is increased or decreased depending upon of the reaction and response of the patient.

It is important to note also that there are no adverse reactions due to use of bexarotene, which is entirely dose dependent. High dose usage in the treatment of cutaneous T-cell lymphoma can be associated with hypertriglyceridemia, hypercholesterolemia and decreased high-density lipoprotein levels, as well as hypothyroidism (SI Sherman, Gopal J, Haugen BR, et al et al, Central hypothyroidism with retinoid X receptors -selective ligands. N Engl J Med, 1999, 340:1075-1079.7), headache, asthenia, leucopenia, anemia, infection, rash, alopecia and photosensitivity. This is due to use of mega doses of bexarotene for weeks. The dose we use to treat Alzheimer's through the olfactory mucosal delivery is infinitesimally small compared to those seen to treat cancer, hence no such reaction is seen with this mode of delivery of bexarotene.

The manufacturer cautions that bexarotene given to diabetic patients concurrently with insulin, sulfonylureas, metformin (Glucophage), repaglinide (Prandin) or the thiazolidinediones ("glitazones") might cause hypoglycemia. Hence, in diabetics with Alzheimer's, the insulin should be used with caution. One should be prepared with glucose tablets and should be familiar with episodes of hypoglycemia, and how to treat if the complication develops. It is important to note that if it is deposited on the olfactory mucosa, chances of developing hypoglycemia will be avoided. It can occur if the insulin is deposited in the respiratory part of nasal mucosa instead of olfactory mucosa; which will be absorbed systemically which may contribute to the hypoglycemic effect. Since bexarotene is a vitamin A derivative, co administration with vitamin A may add to the drug's toxicity. The dose we use is so small; we do not believe that one need to be concerned with such toxic effects including hypoglycemia.

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We have used insulin delivered to the olfactory mucosa for the treatment of many neurodegenerative diseases including the cases of reduced mental cognition with declining memory in the aged, Parkinson's with glutathione, as well as for depression due to any number of reasons including Posttraumatic Stress Disorder (PTSD) which is a mental health problem that can occur after someone goes through a traumatic event like war, assault, or disaster. The treatment reduced the depression, improved the memory, and increased cognition. Further, the insulin augments and amplifies the effect of many therapeutic agents such as bexarotene and ketamine many fold as described in the ingenious experiments by Alabastor et al (Oliver Alabaster' et al. Metabolic Modification by Insulin Enhances Methotrexate Cytotoxicity in MCF-7 Human Breast Cancer Cells, Eur J Cancer Clinic; 1981, Vol 17, pp 1223-1228). It has a trophic effect on the neurons, and it is a mitogenic, thus it prevents or delays further decay of the neurons afflicted by this disease and reduces the ROS damage to the nerve tissue. Besides its effect on cognition, and improving the psychological status of the Alzheimer's patients, it is used in conjunction with the bexarotene to enhance its uptake and delivery to the CNS, as well as to augment and amplify the effects (paracrine and intracrine effect) on the neuropil to reduce the β amyloid, and its soluble precursors so as to curtail the disease.

Ketamine is a GABA receptors antagonist. It acts by blocking the N-methyl-D-aspartic acid (NMDA) receptor, which receives signals from glutamate. There are many examples of antagonists of the NMDA receptor, but ketamine is most suitable in the treatment of Alzheimer's. Besides protecting the neurons from the excitotoxicity of Glutamate, Ketamine is also a dissociative anesthetic (no such effect due to the very small doses we use here), an excellent sedative, it is an anti arrhythmic, and reduces the pain perception due to its local anesthetic like effects. We have used ketamine for wound dressing changing in burn patients since 1969 and postpartum after delivery to ally the anxiety under regional anesthesia. The micro doses of ketamine we use in the olfactory mucosal instillation in this invention have no hallucinogenic or other ill effects. The present inventor has used these therapeutic agents in hundreds of cases such as dissociative anesthesia, neuropathic pain, depression, hiccup (Shantha, T. R. Ketamine For the Treatment of

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Hiccups During and Following Anesthesia: A Preliminary Report in Anesthesia And Analgesia. Current Researches VOL. 52, No.5, September-October, 1973), ALS with Insulin -like growth factor-I (IGF-1), insulin, and experiment show that it inhibits the rabies virus multiplication (U. S. Patent Application Publication Number: 201110020279 AD-Rabies cure)

The invention described herein can incorporate ketamine delivered to olfactory mucosa with bexarotene and insulin. The intranasal use of ketamine delivery to the olfactory mucosa reduced or relieved the depression associated with many neurodegenerative diseases. In the early cases, it completely ameliorated the depressive condition especially in dementia. These patients felt a sense of well being. Because of the small dose used to treat the above described neurodegenerative diseases, it has no hallucinogenic effect. Along with the bexarotene, insulin, and ketamine, the adjuvant therapeutic agent such as acetyl cholinesterase inhibitors are added to increase the CNS levels of acetylcholine to enhance the memory and cognition in Alzheimer's disease patients.

The electrical stimulation of the brain described in this invention through the peripheral nervous system projections, and pituitary gland; which in turn stimulates the malfunctioning nerve tissue (neuropil) of the CNS holds significant promise for the treatment of Alzheimer's, and other neurodegenerative diseases. Such stimulation is reversible, non-destructive, easy to use, non invasive, and least expensive. Nerve stimulation is accomplished directly or indirectly by depolarizing a nerve membrane, causing the discharge of an action potential; or by hyperpolarization of a nerve membrane, preventing the discharge of an action potential. Such stimulation occur after electrical energy, transmitted to the vicinity of a nerve or directly in contact with the nerve itself as it happens in olfactory region stimulation to be transmitted to the afflicted brain of Alzheimer's disease. The nerve stimulation is also anti-neuroinflammatory. Neuroinflammation is the primary denominator in all these conditions including Alzheimer's disease.

Numerous modifications; adjuvants, alternative arrangements of steps explained and examples given herein may be devised by those skilled in the art without departing from the spirit and scope of the present invention and the appended claims are intended to cover such modifications and arrangements. Thus,

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the present invention has been described above in detail in connection with what is presently deemed to be the most practical and preferred embodiments of the invention. It will be apparent to those of ordinary skill in the art that numerous modifications, including, but not limited to, variations in size, materials, shape, form, function and manner of procedure, assembly, and use may be made. While the preferred embodiment of the present invention has been described, it should be understood that various changes, adaptations, and modifications may be made thereto. It should be understood, therefore, that the invention is not limited to details of the illustrated invention. Therefore, the present invention shall include embodiments falling within the scope of the appended claims. Different embodiments of the described methods and devices can include one or a combination of features as indicated by the following examples.

Example 1. A method for treating Alzheimer's diseases, with this said device and method applying to a subject a specific low frequency pulsed electrical impulses (signals, pulses) through this inventive device located at adjacent nerves whose stimulation is transmitted to the central nervous system to excite the central nervous system through the olfactory nerves, sphenopalatine ganglion, sphenoid sinus, cranial nerves III, IV,V, and VI, pituitary gland, hypothalamic - hypophysis tract, thalamic radiation, brainstem, cerebellum, parasympathetic nerves of the human body. This method and device is comprising of:

a. an insertion body having a balloon with a flexible outer surface adapted to contact and conform to the interior surface of the sphenoid sinus, the balloon having an interior;
b. means connected to the interior of the balloon for inflating the balloon while in the sphenoid sinus;
c. a (optional) thermocouple connected to and residing within the interior of the balloon for locally heating and cooling fluid present within the balloon and for locally heating and cooling the interior surface of the sphenoid sinus immediately adjacent to the outer surface of the balloon;

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d. a (optional) temperature sensor being connected to the interior of the balloon and to a temperature indicator external to the balloon for monitoring the temperature of the outer surface of the balloon;

e. multiple electrical stimulator electrodes incorporated onto the outer surface of the balloon which come in direct contact with the interior lining of the sphenoid sinus;

f. connection means for connecting the electrical stimulators electrodes to a power source and control device outside of the sphenoid sinus for stimulating the sphenoid sinus and proximate structures with controlled electric current output;

g. an open catheter at the end of the balloon to deliver saline to increase the electrical conductivity and for delivering adjuvant therapeutic agents.

Ex. 2. A method for delivering the electrical impulses according to example 1, for stimulating the brain of a Alzheimer's disease patients through olfactory nerves via olfactory mucosa comprising of:

a. Electrodes, applied to the olfactory nerves through olfactory mucosal area which conducts the electrical pulses to the neural tracts connecting these structures to the CNS through the olfactory bulb, and

b. a control unit, located outside the nasal cavity adapted to drive the one or more electrodes to apply a electrical current to the site capable of stimulating olfactory nerves, which will transmit the electrical impulses to the regions of the brain through their connection in the CNS conducted to the CNS affected by the Alzheimer's, and

c. the olfactory region (ORE) part of the inventive device is provided with therapeutic agents' delivery pores to deliver adjuvant therapeutic agents specific to Alzheimer's and neurodegenerative diseases to the olfactory epithelium to be transported to the CNS bypassing the blood brain barrier through the olfactory bulb.

d. The stimulator device for the olfactory mucosa is provided with Iontophoresis electrodes to enhance the uptake of therapeutic agents by the receptor cells to be transported to the CNS by passing the BBB.

Ex. 3. A method for applying the electrical impulses according to example 1, for stimulating the brain of Alzheimer's patients using electrical impulses through sphenopalatine ganglion nerves, comprising of:

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a. Electrodes, applied to the sphenopalatine ganglion area on the medial wall of the nasal cavity located immediately below the sphenoid sinus and to the neural tracts connecting these structures to the CNS through sphenopalatine ganglion, and

b. a control unit, located outside the nasal cavity adapted to drive the one or more electrodes to apply a electrical current to the site capable of stimulating sphenopalatine ganglion nerves, which will transmit the electrical impulses to the regions of the brain through their extensive connection in the CNS and to the blood vessels (BV) affected by the Alzheimer's.

Ex. 4 The method according to example 1, in which a tube is connected to the balloon for infusing fluid into the interior of the balloon which heats or cools the balloon. The apparatus is further comprising of a device external to the balloon and connected to the balloon for heating and cooling fluid prior to infusion into the interior of the balloon while the balloon is in the sphenoid sinus.

Ex. 5. The method according to example 1, in which the means for inflating the balloon is at least one tube connected to an inflator syringe.

Ex. 6. The method according to example 1 is comprised to configure the electrical impulses to cause an increase in the electrical activity in these diseases afflicted neurons and synapses of the brain and brain stem.

Example 7. According to the method of treating Alzheimer's and other neurodegenerative diseases using this device involves applying the electrical stimulation continuously or intermittently to olfactory nerves, sphenopalatine ganglion, trigeminal nerves, five cranial nerves, pituitary gland with hypothalamo hypophysial region, entorihinal and other cortical cognition centers.

Ex. 8. This present inventive method of treating Alzheimer's disease involves applying the electrical impulses through the transmitting device connected to the generator housing stimulator outside the nose by connecting electricity conduction wires.

Ex. 9. This present inventive method of treating Alzheimer's disease involves applying the electrical impulses through fine electrical wires made of suitable conductive physiologically acceptable material such as silver, iridium, platinum, iridium alloy, titanium, nickel-chrome alloy and other suitable combination of conducting metal alloys. Each electrode is insulated with a physiologically

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acceptable material such as polyethylene, polyurethane, or a co-polymer, which is non-conductive, non-allergic, non-reacting synthetic or semi synthetic materiel.

Ex. 10. The apparatus according to example 1 is comprised of flexible insulated electrodes adapted for insertion through a nostril of the patient to the desired anatomical and histological areas.

Ex. 11. The apparatus according to example 1 is comprised of three wires, connected to the control unit separately so that they may be individually turned on and off to stimulate olfactory nerve, sphenopalatine ganglion, or structures around the sphenoid sinus individually or combination, as needed from the electrical output manipulator, from the external position to get the maximum therapeutic effect.

Ex. 12. The apparatus according to example 1 is configured such that each one of the wires connected to these individual anatomical sites has an Ampere (mAP) adjuster and a time setter to deliver the desired amperage of stimulating electricity at a set time, located outside the nose from the electrical output manipulator.

Ex. 13. The apparatus according to example 1 is configured such that the electrical control delivery unit is introduced to both sides of the nose.

Ex. 14. The apparatus according to example 1 is configured such that the catheter with electrical wired embodiment is provided with the temperature and location sensor located at the tip of the stimulator device.

Ex. 15. The apparatus according to example 1 is configured such that one or more electrodes are adapted for use for hours, weeks, and months at a time, based on the patient's compliance and the stage of the disease afflicting the patient.

Ex. 16. The apparatus according to example 1 is configured such that the electrical amplitude and milliamps delivered are adapted to set the amplitude of the current, to induce the increase therapeutic effect and induce permeability in the BBB blood vessels.

Ex. 17. The apparatus according to example 1 is configured such that the shape of the electrical impulse waveform is selected and delivered from the catalog, consisting of an exponential decay, a ramp up and down, square wave, a monophasic shape, a biphasic shape, a sinusoid, a saw tooth, and with a direct current (DC) component. The control unit is set to deliver the selected waveform of the current,

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so as induce the desired therapeutic effect on the brain in the treatment of Alzheimer's, and other neurodegenerative diseases.

Ex. 18. The apparatus according to example 1 is configured such that the electrical amplitude and milliamps delivered are adapted to set the amplitude of the current, to induce the desired therapeutic effects. At the same time, it enhances the permeability (Iontophoresis), for the uptake and transport of therapeutic agents from the olfactory mucosa, and sphenoid sinus sites, bypassing the BBB, by creating elecroporation and iontophoresis effects of olfactory mucosa and sphenoid sinus lining, which allows large molecules of therapeutic agents' transportation to the CNS, the site of pathology bypassing blood-brain barrier.

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Claims:

1. An apparatus for electrically stimulating nerves in a region of olfactory mucosa of the nasal cavity, the apparatus comprising

an elongate shaft having a proximal end and an insertion end, the insertion end adapted for placement at a trans-nasal location within the nasal cavity extending from an exterior nasal opening, along the nasal cavity adjacent to olfactory mucosa, and to an interior of a sphenoid sinus,

the insertion end comprising

a distal electrode adapted to be located within the sphenoid sinus with the insertion end located at the trans-nasal location, and

a proximal electrode adapted to be located adjacent olfactory mucosa with the insertion end located at the trans-nasal location,

wherein the apparatus exhibits one or more of:

the distal electrode is located on expendable mesh, or

the apparatus does not include an ejection port at the insertion end in fluid communication with the proximal end through which fluid can be delivered to the olfactory mucosa with the insertion end located at the trans-nasal location, or

the apparatus does not include an ejection port at the insertion end in fluid communication with the proximal end through which fluid can be delivered to the sphenoid sinus with the insertion end located at the trans-nasal location.

2. An apparatus as recited at claim 1 comprising

an expandable surface at the insertion end adapted for placement and expansion within a sphenoid sinus with the insertion end located at the trans-nasal olfactory region location,

wherein

the distal electrode is located at the expandable surface and is adapted to contact an interior surface of the sphenoid sinus with the expandable surface expanded within the sphenoid sinus, and

the proximal electrode is located on a proximal side of the expandable surface to be located adjacent olfactory mucosa with the insertion end located at the trans-nasal location.

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3. An apparatus as recited at Claims 1 or 2 wherein the distal electrode is an electrode of a set or array of bipolar distal electrodes located at the expandable surface.

4. An apparatus as recited at Claim 3 wherein the bipolar distal electrodes are at the expandable surface and adapted to contact an interior lining of the sphenoid sinus with the expandable surface expanded within the sphenoid sinus.

5. An apparatus as recited at any of Claims 1 through 4 wherein the distal electrode or electrodes are capable of being activated to stimulate a nerve selected from cranial nerve I (also known as the Olfactory nerve), cranial nerve III, cranial nerve IV, cranial nerve V, cranial nerve VI, a pituitary gland, hypothalamic-hypophysis tract, thalamic radiation, brainstem, cerebellum, parasympathetic nerves on the internal carotid artery and circle of Willis in the brain, and combinations thereof, with the distal electrode or electrodes placed within the sphenoid sinus.

6. An apparatus as recited at any of Claims 1 through 5 wherein the proximal electrode is an electrode of a set or array of bipolar proximal electrodes located along a length of the insertion end on a proximal side of the expandable surface.

7. An apparatus as recited at any of Claims 1 through 6 wherein, with placement of the proximal electrode or electrodes adjacent olfactory mucosa with the insertion end located at the trans-nasal location, the proximal electrodes can be activated to stimulate olfactory nerves (also known as Cranial nerve I).

8. An apparatus as recited at any of Claims 1 through 7 wherein with the insertion end located at the trans-nasal location, the proximal and distal electrodes are adapted to stimulate one or more nerve capable of exciting the central nervous system and selected from the group consisting of an olfactory nerve, sphenopalatine ganglion, sphenoid sinus, cranial nerves III, IV,V, and VI, a pituitary gland, hypothalamic-hypophysis tract, thalamic radiation, brainstem, cerebellum, parasympathetic nerves on the internal carotid artery and circle of Willis in the brain, and combinations thereof.

9. An apparatus as recited at any of Claims 1 through 8 comprising a second expandable surface on a proximal side of the proximal electrode, wherein the expandable surface adapted for placement within a sphenoid sinus can be expanded to secure the insertion end at the trans-nasal location.

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10. An apparatus as recited at any of Claims 1 through 9 wherein the expandable surface adapted for placement within a sphenoid sinus can be alternately expanded and retracted, and in the retracted state can be passed through the sphenoid ostium to place the expandable surface within the sphenoid sinus.

11. An apparatus as recited at any of Claims 1 through 10 wherein the proximal end comprises:

a proximal electrode connector in electrical communication with the proximal electrode, and

a distal electrode connector in electrical communication with the distal electrode.

12. An apparatus as recited at Claim 11 in combination with an electric stimulator adapted to be located exterior to the exterior nasal opening with the insertion end located at the trans-nasal location, the stimulator comprising a power source, a control device, a first connector adapted to electronically engage the proximal electrode connector to deliver an electronic stimulation signal to the proximal electrode or electrodes, and a second connector adapted to electronically engage the distal electrode connector to deliver an electronic stimulation signal to the distal electrode or electrodes.

13. An apparatus as recited at any of Claims 1 through 12 wherein the shaft comprises a fluid delivery lumen extending between the proximal end and the insertion end, wherein the fluid delivery lumen allows delivery of a liquid fluid to the sphenoid sinus, olfactory mucosa, or both, with the insertion end located at the trans-nasal location.

14. An apparatus as recited at any of Claims 1 through 13 wherein the expandable surface adapted for placement within a sphenoid sinus comprises an inflatable balloon.

15. An apparatus as recited at Claim 9 or 12 wherein the second expandable surface comprises an inflatable balloon.

16. An apparatus as recited at any of Claims 1 through 15 comprising a thermocouple useful to measure temperature at the expandable surface.

17. A method of nerve stimulation, the method comprising

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providing an apparatus comprising an elongate shaft having a proximal end and an insertion end, the insertion end adapted for placement at a trans-nasal location within the nasal cavity extending from an exterior nasal opening, along the nasal cavity adjacent to olfactory mucosa located in the roof of the nose, and to an interior of a sphenoid sinus, the insertion end comprising

a distal electrode adapted to be located within the sphenoid sinus with the insertion end located at the trans-nasal location, and

a proximal electrode adapted to be located adjacent olfactory mucosa at the upper part of the nose with the insertion end located at the trans-nasal location,

inserting the insertion end into the exterior nasal opening and nasal cavity to place the insertion end at the trans-nasal location with the distal electrode at an interior of the sphenoid sinus and the proximal electrode adjacent to olfactory mucosa,

delivering an distal electrical signal to the distal electrode, and

delivering a proximal electrical signal to the proximal electrode, wherein the method does not include delivery of therapeutic fluid to the nasal region.

18. A method as recited at Claim 17 wherein the distal electrical signal is different from the proximal electrical signal.

19. A method as recited at Claim 16 or 17 wherein the distal electrical signal stimulates a nerve selected from cranial nerve III, cranial nerve IV, cranial nerve V, cranial nerve VI, and combinations thereof.

20. A method as recited at any of Claims 17 through 19 wherein the proximal electrical signal stimulates an olfactory nerve.

21. A method as recited at any of Claims 17 through 20 wherein the insertion end comprises an expandable surface capable of being placed within a sphenoid sinus and expanded within the sphenoid sinus to contact an interior surface of the sphenoid sinus, and the distal electrode is located on the expandable surface, the method comprising

passing the expandable surface through the sphenoid ostium to locate the distal electrode at an interior of the sphenoid sinus and expanding the expandable

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surface within the sphenoid sinus to place the electrode in contact with an inner surface of the sphenoid sinus.

22. A method as recited at Claim 21 wherein the distal electrode is an electrode of a set or array of bipolar distal electrodes located on the expandable surface, and the electrical signal is delivered to the distal electrodes with the distal electrodes in contact with an interior surface of the sphenoid sinus.

23. A method as recited at any of Claims 17 through 22 wherein the proximal electrode is an electrode of a set or array of bipolar proximal electrodes located along a length of the insertion end on a proximal side of the expandable surface and the electrical signal is delivered to the proximal electrodes with the proximal electrodes being located adjacent to or in contact with the olfactory mucosa on medial and lateral walls of the olfactory mucosal surface.

24. A method as recited at any of Claims 17 through 23 wherein the insertion end comprises a second expandable surface on a proximal side of the proximal electrode, and the method comprises

passing the second expandable surface through at least a portion of the nasal cavity with the second expandable surface in an expanded state.

25. A method as recited at any of Claims 17 through 24 wherein the shaft comprises a fluid delivery lumen extending between the proximal end and insertion end, and the method comprises delivering a liquid fluid to the sphenoid sinus, olfactory mucosa, or both.

26. A method as recited at any of Claims 17 through 25 comprising delivering a liquid fluid with or without therapeutic agent to the olfactory mucosa to be delivered to the brain by passing the blood brain barrier.

27. A method as recited at Claims 25 or 26 wherein the fluid is selected from saline and a fluid comprising a therapeutic agent.

28. A method as recited at Claim 25, 26, or 27 wherein the fluid comprises a neurostimulator.

29. A method as recited at any of Claims 25 through 28 wherein the fluid comprises acetylcholine, insulin, or a combination of these.

30. A method as recited at any of Claims 17 through 29 comprising removing the insertion end from the nasal cavity after delivery of the electrical signals.

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31. A method as recited at any of Claims 17 through 30 performed on an out-patient basis.

32. A method as recited at Claim 30 or 31 wherein the method, from the step of inserting the insertion end into the exterior nasal opening, to the step of removing the insertion end from the nasal cavity, takes not more than 30 minutes, not more than 60 minutes, or not more than 120 minutes.

33. A method as recited at any of Claims 17 through 32 performed without administering general anesthesia to the patient.

34. A method as recited at any of Claims 17 through 33 comprising administering the method to a patient diagnosed with a condition selected from the group consisting of: Alzheimer's Disease, Parkinson's Disease, Post-Traumatic Stress Syndrome, Senile brain atrophy, Cerebral Palsy, and stroke.

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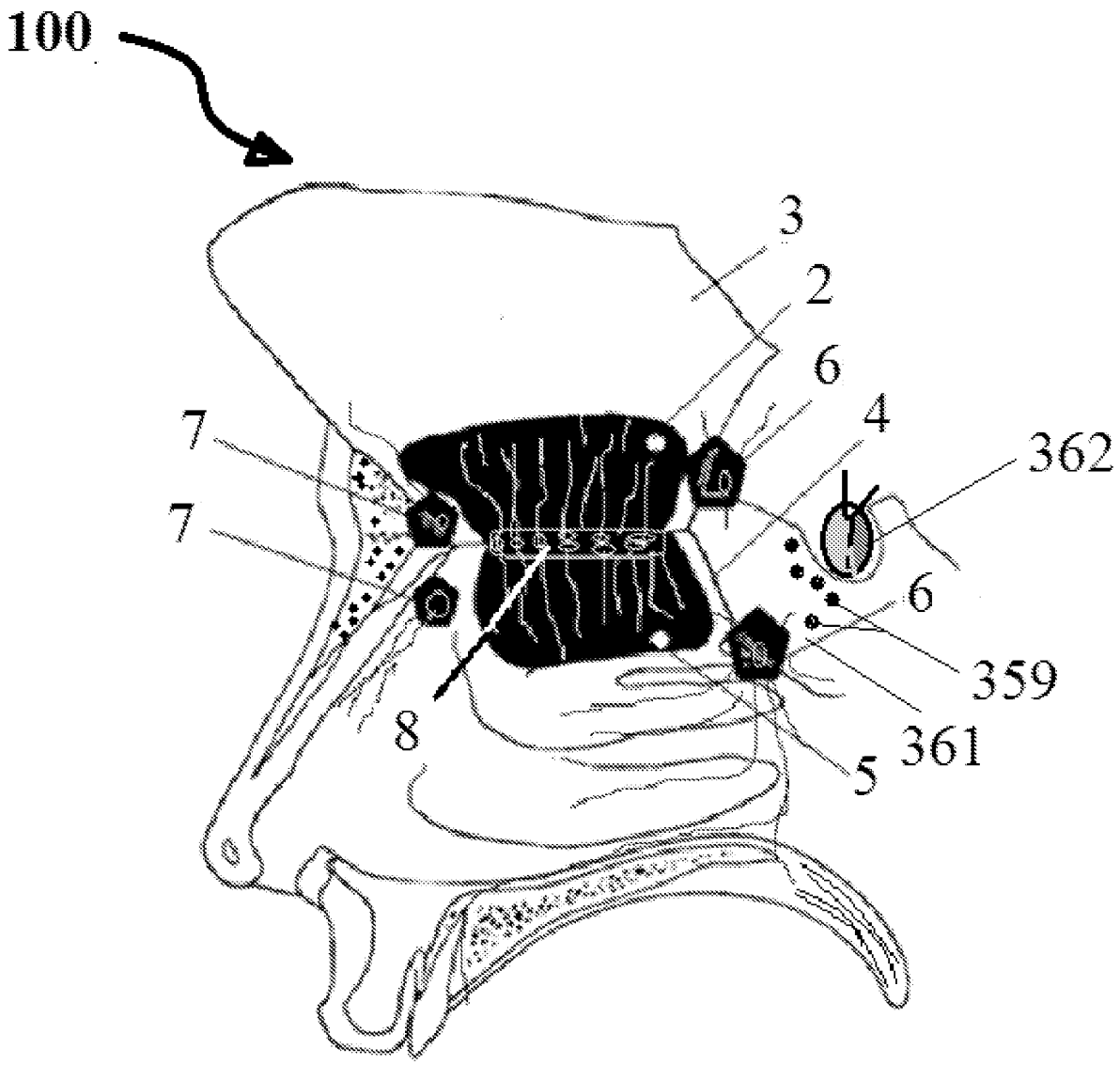


FIG. 1

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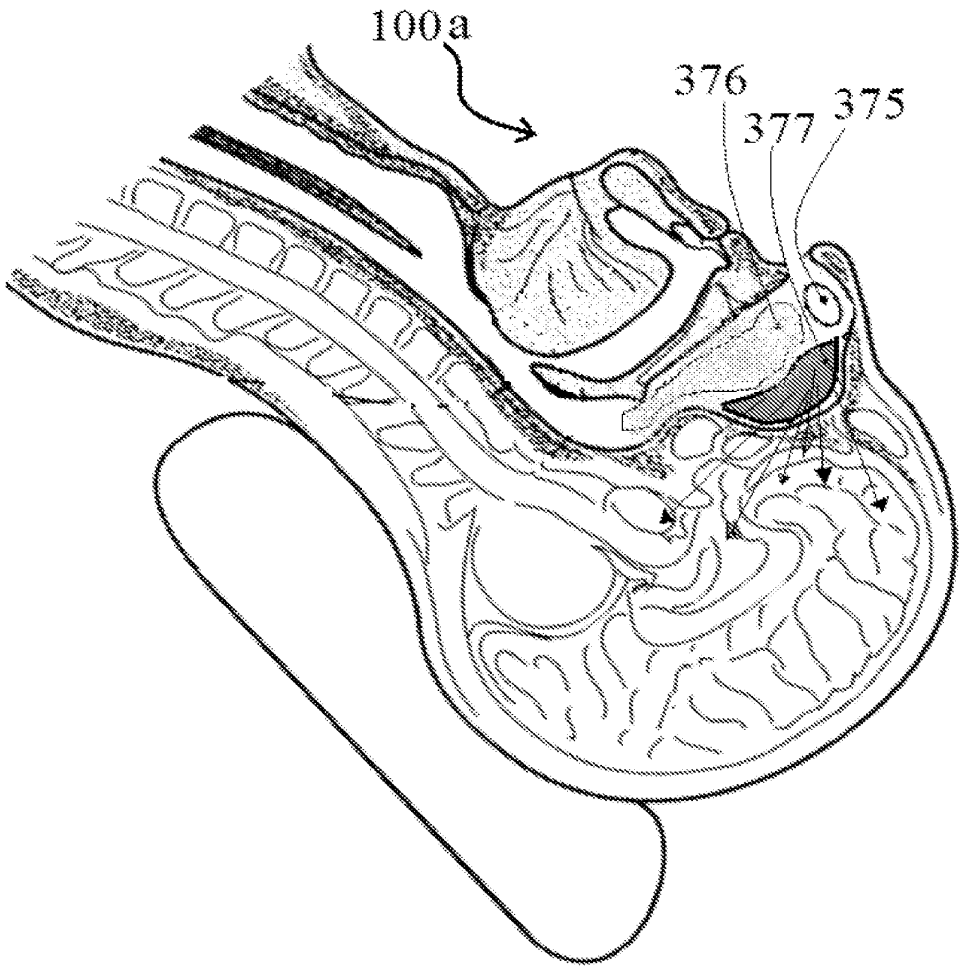


FIG. 1a

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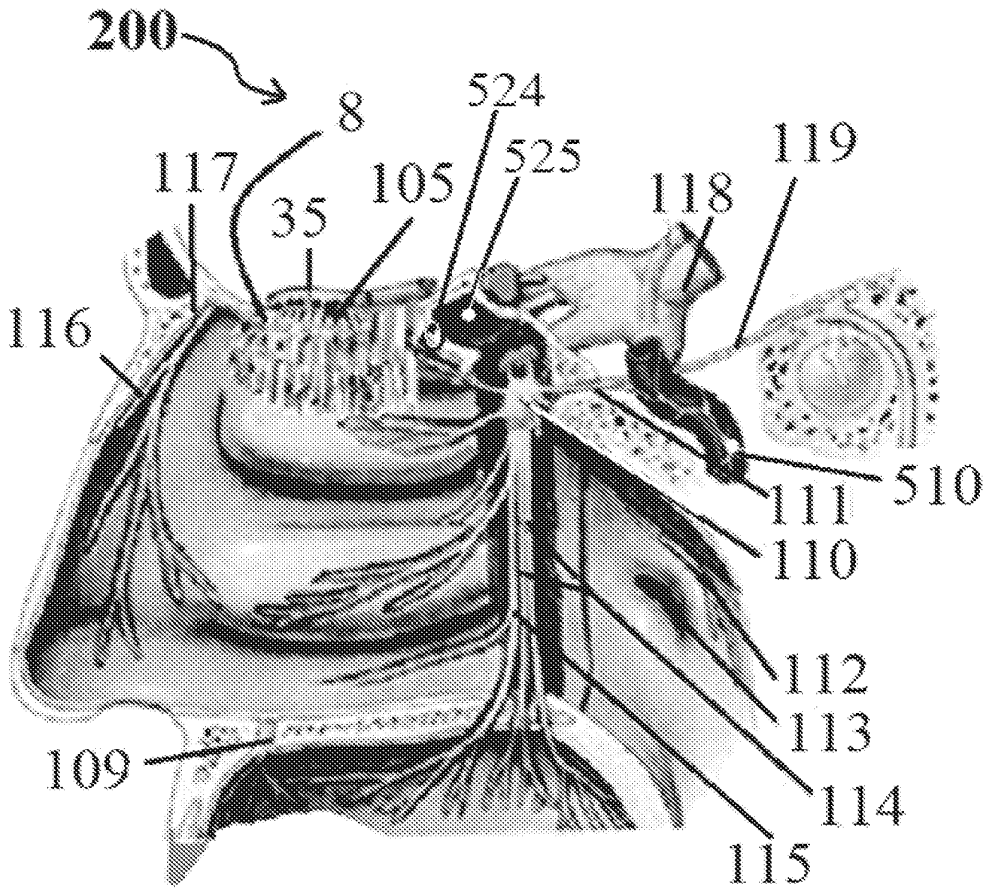


FIG. 2

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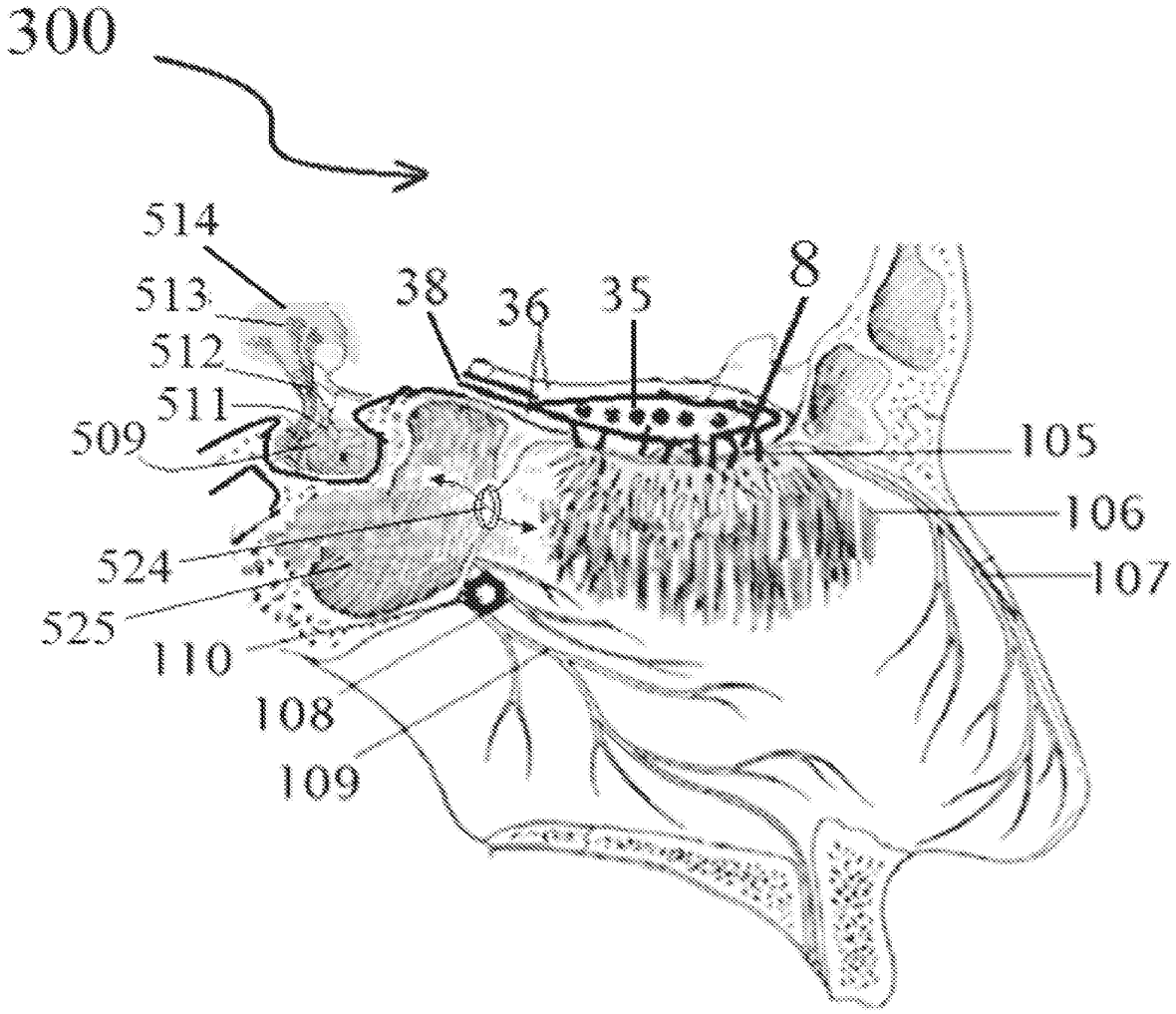


FIG. 3

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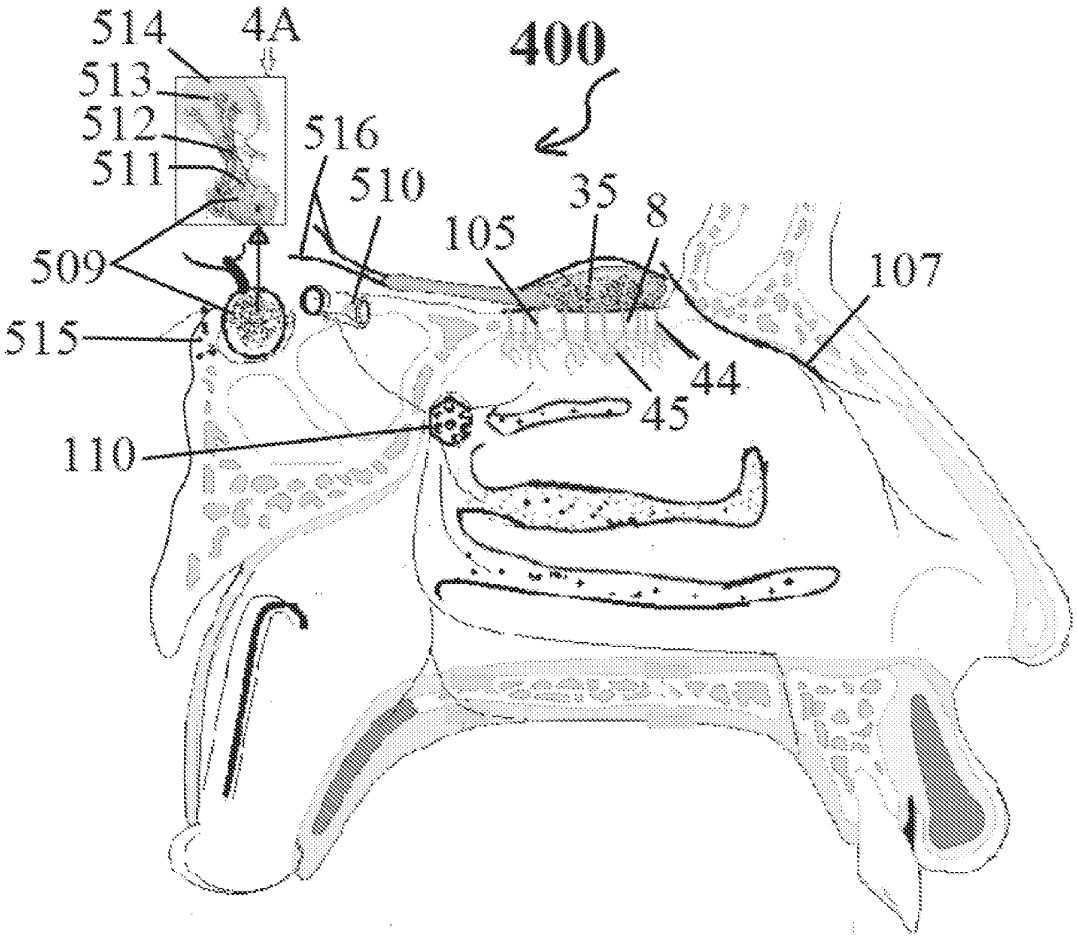


FIG. 4

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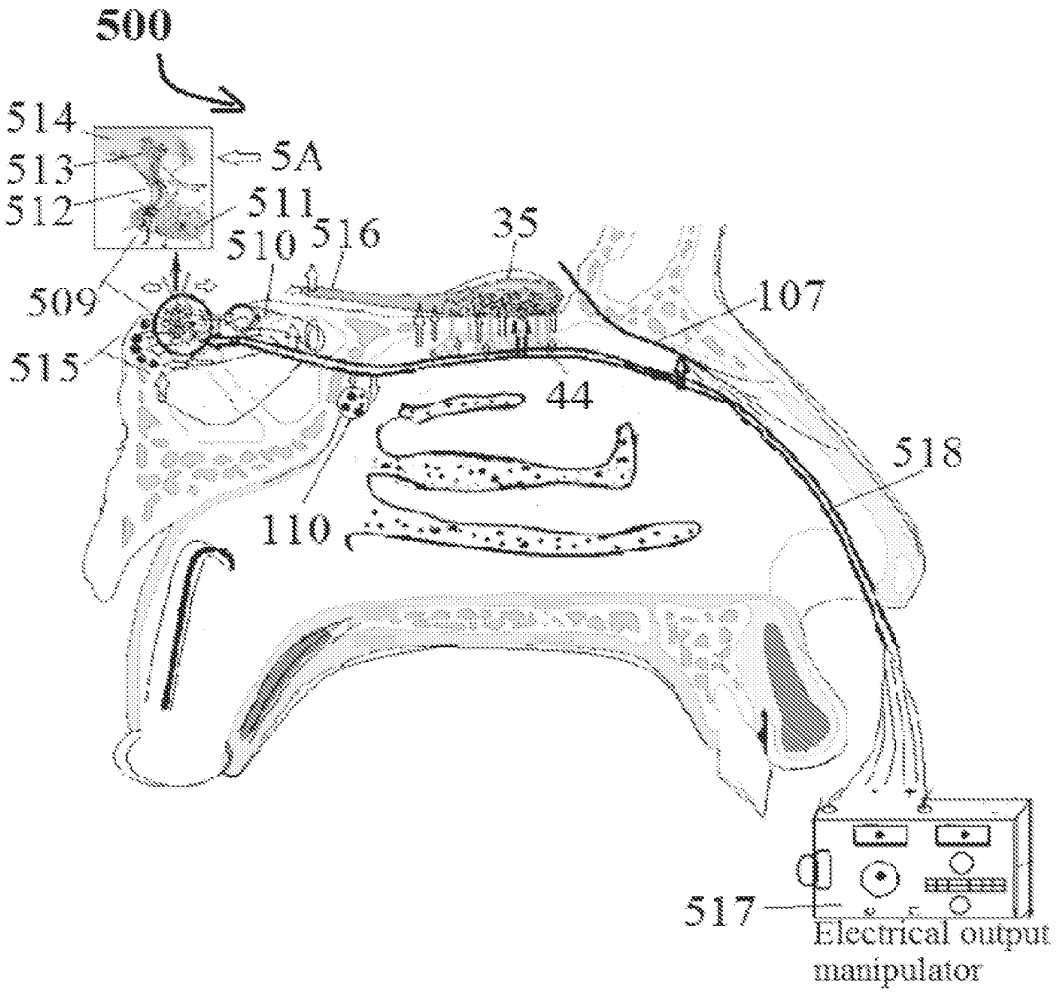


FIG. 5

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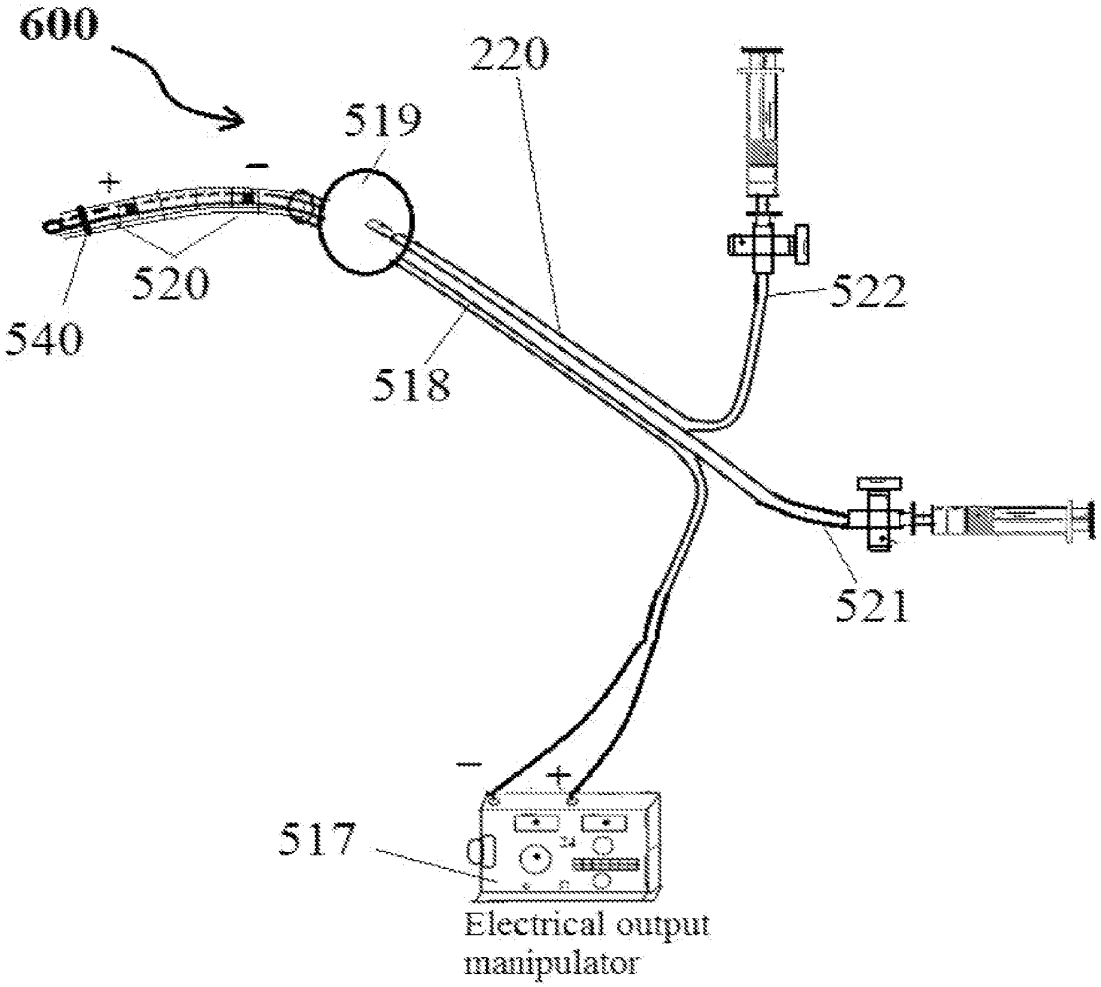


FIG.6

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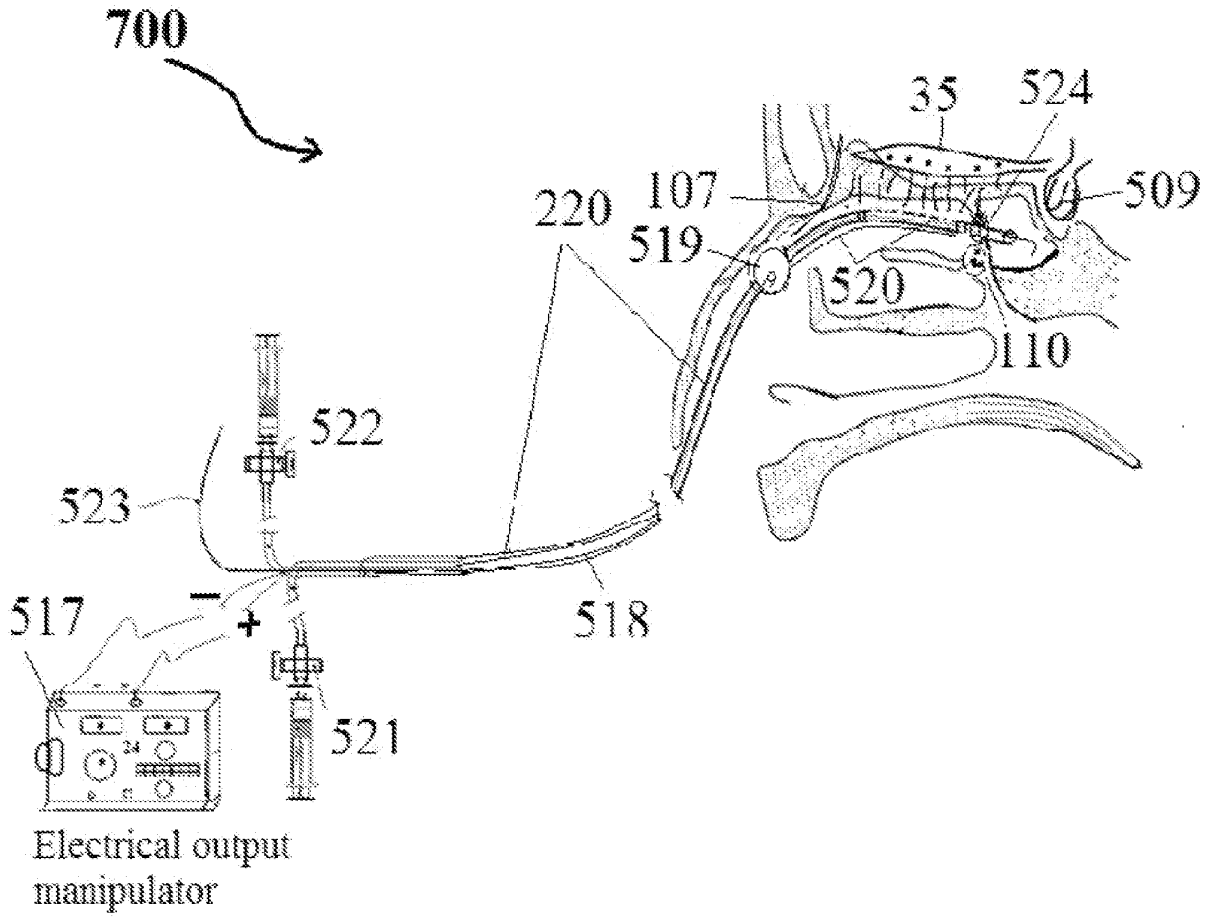


FIG.7

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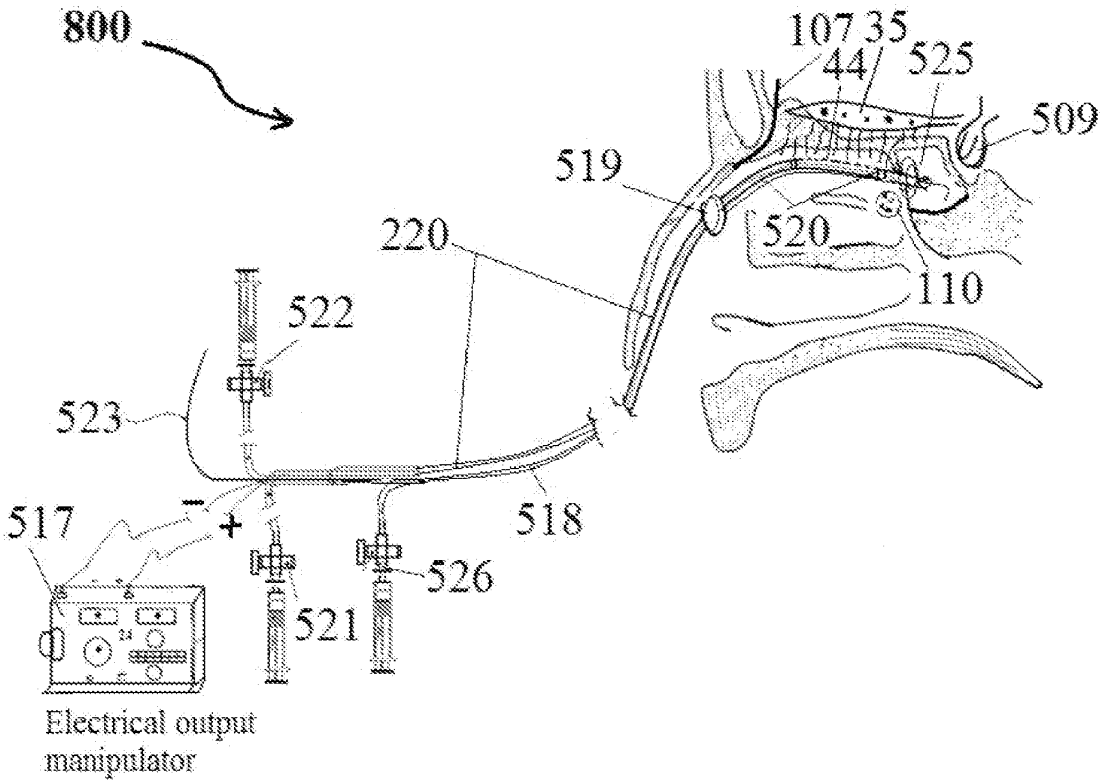


FIG. 8

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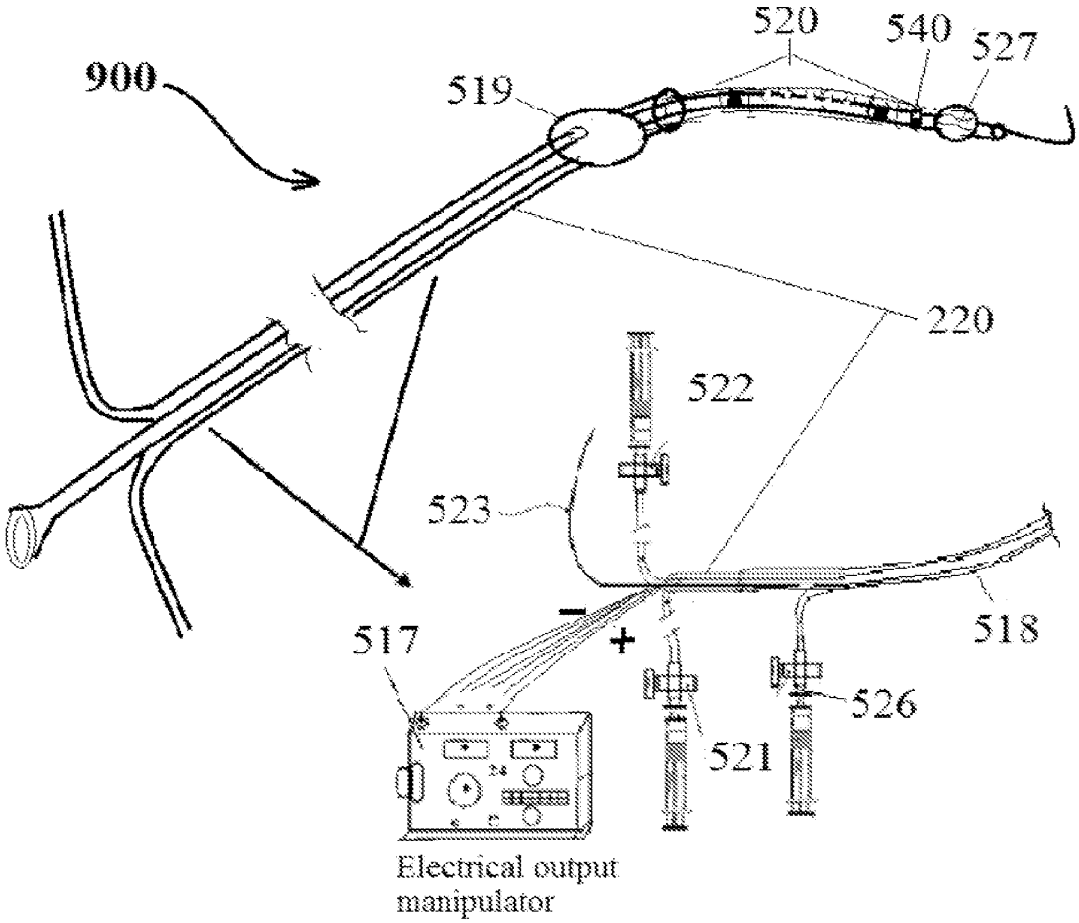


FIG. 9

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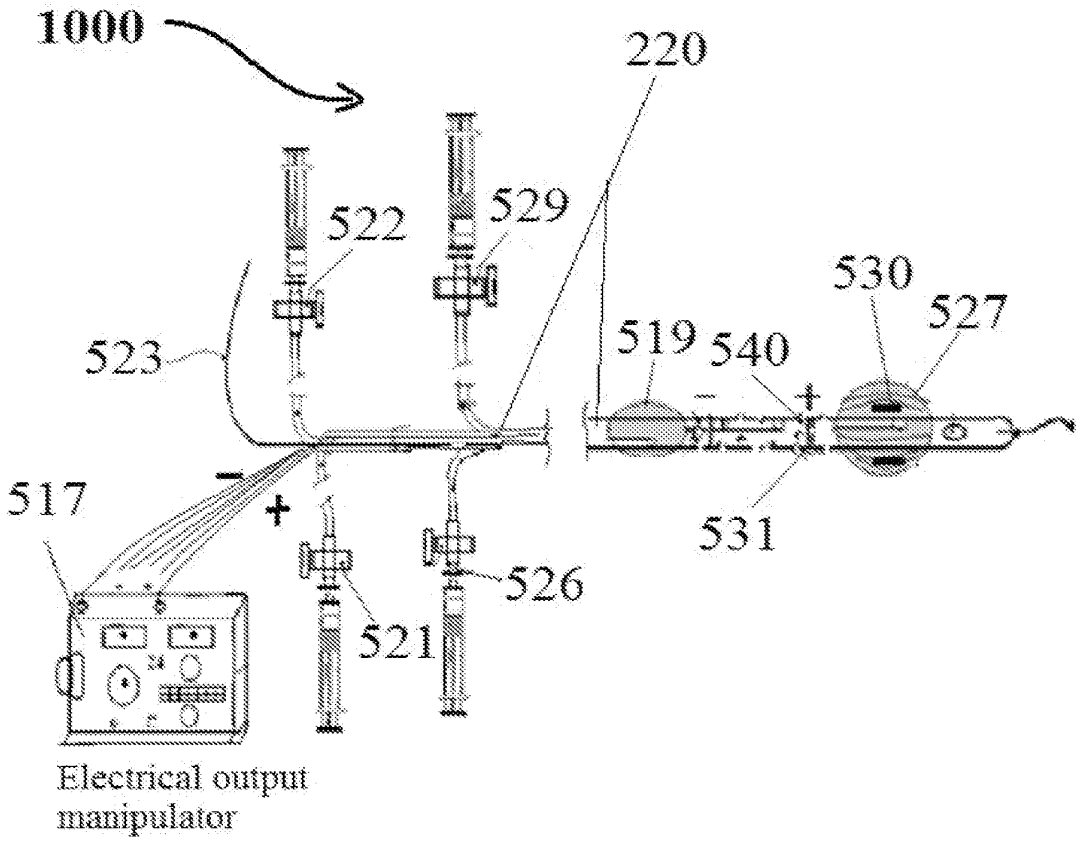


FIG. 10

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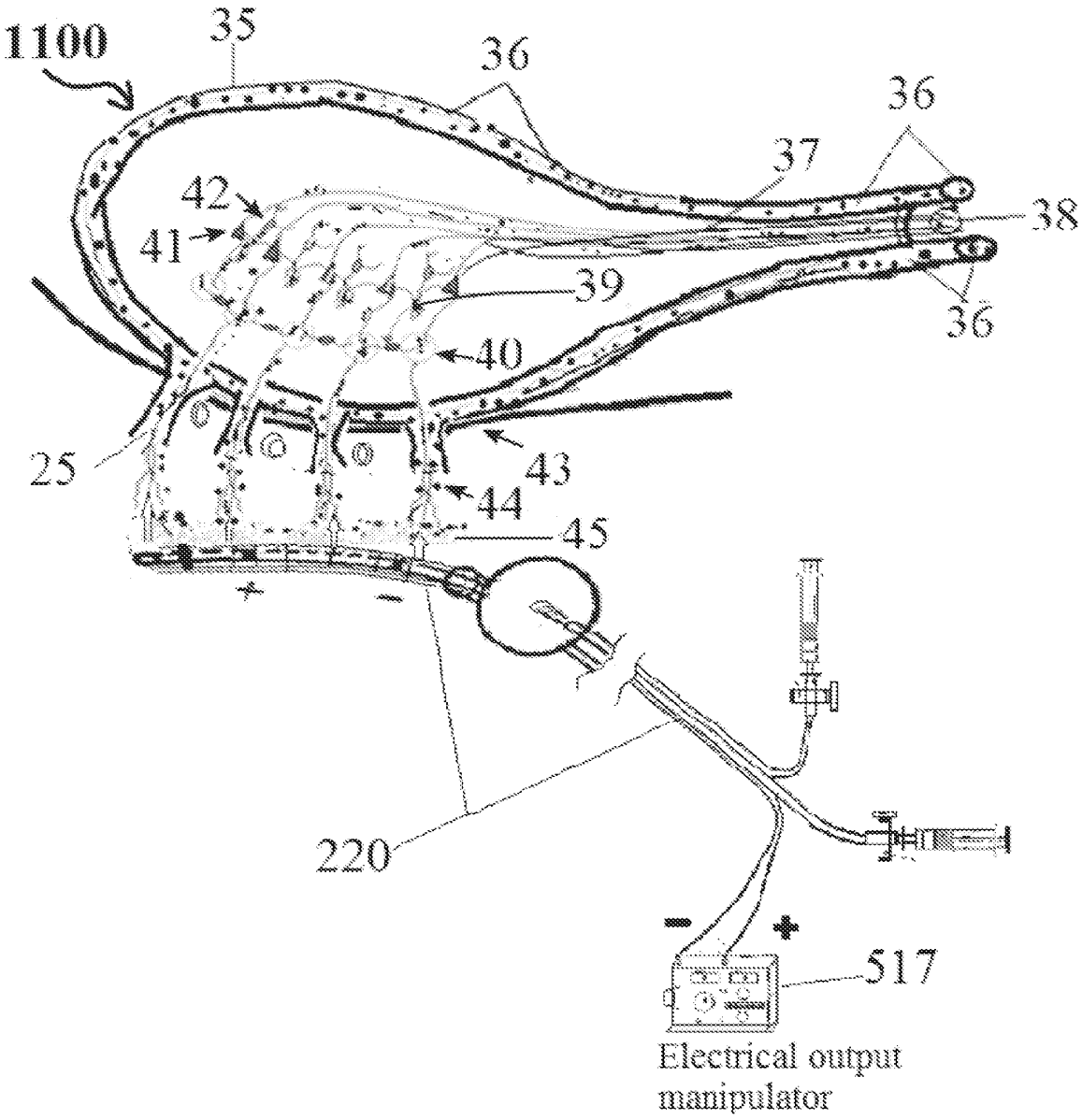


FIG. 11

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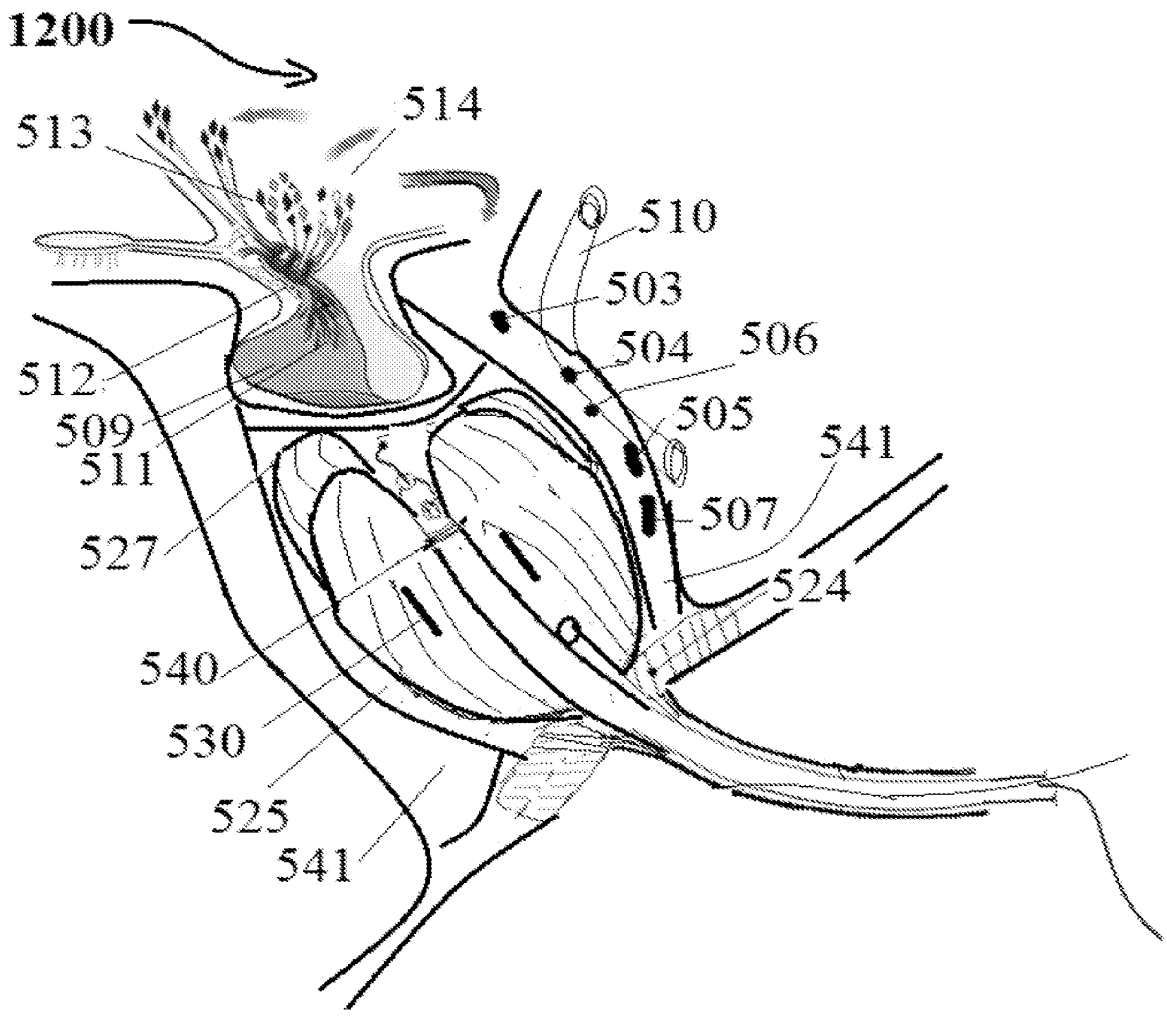


FIG. 12

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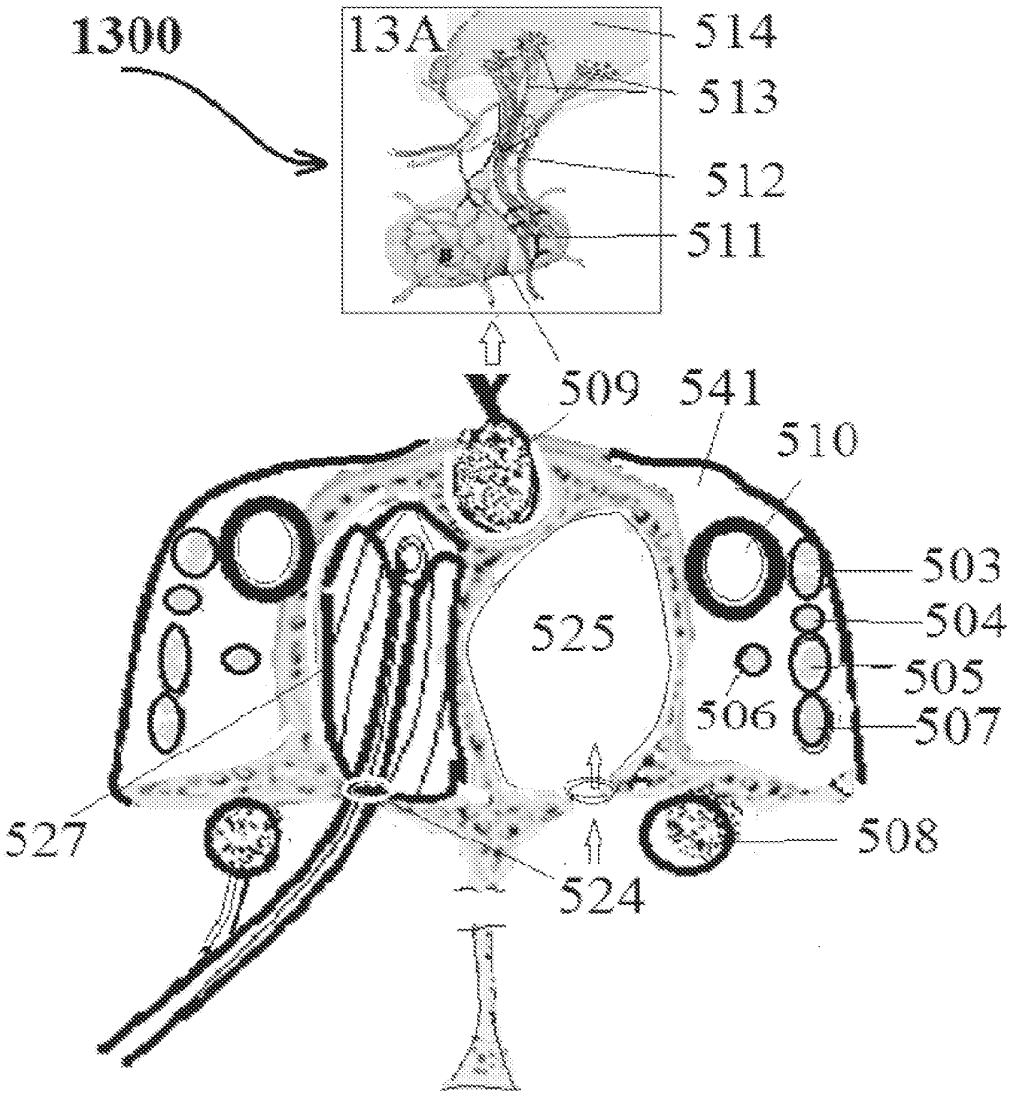


FIG. 13

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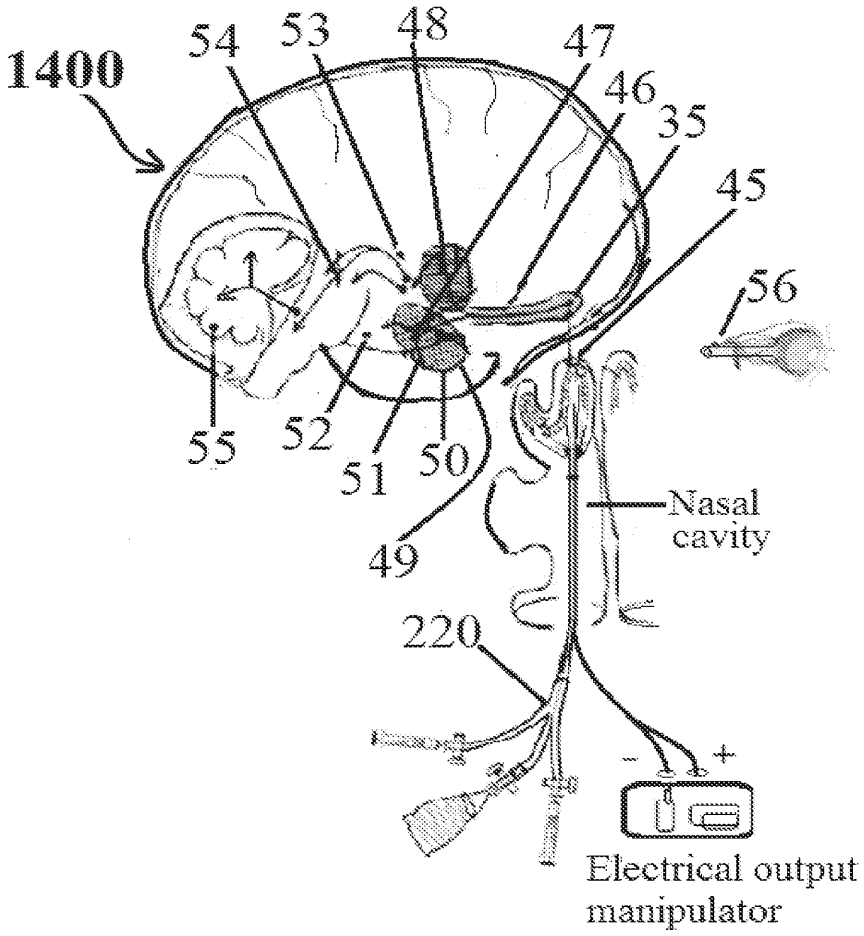


FIG. 14

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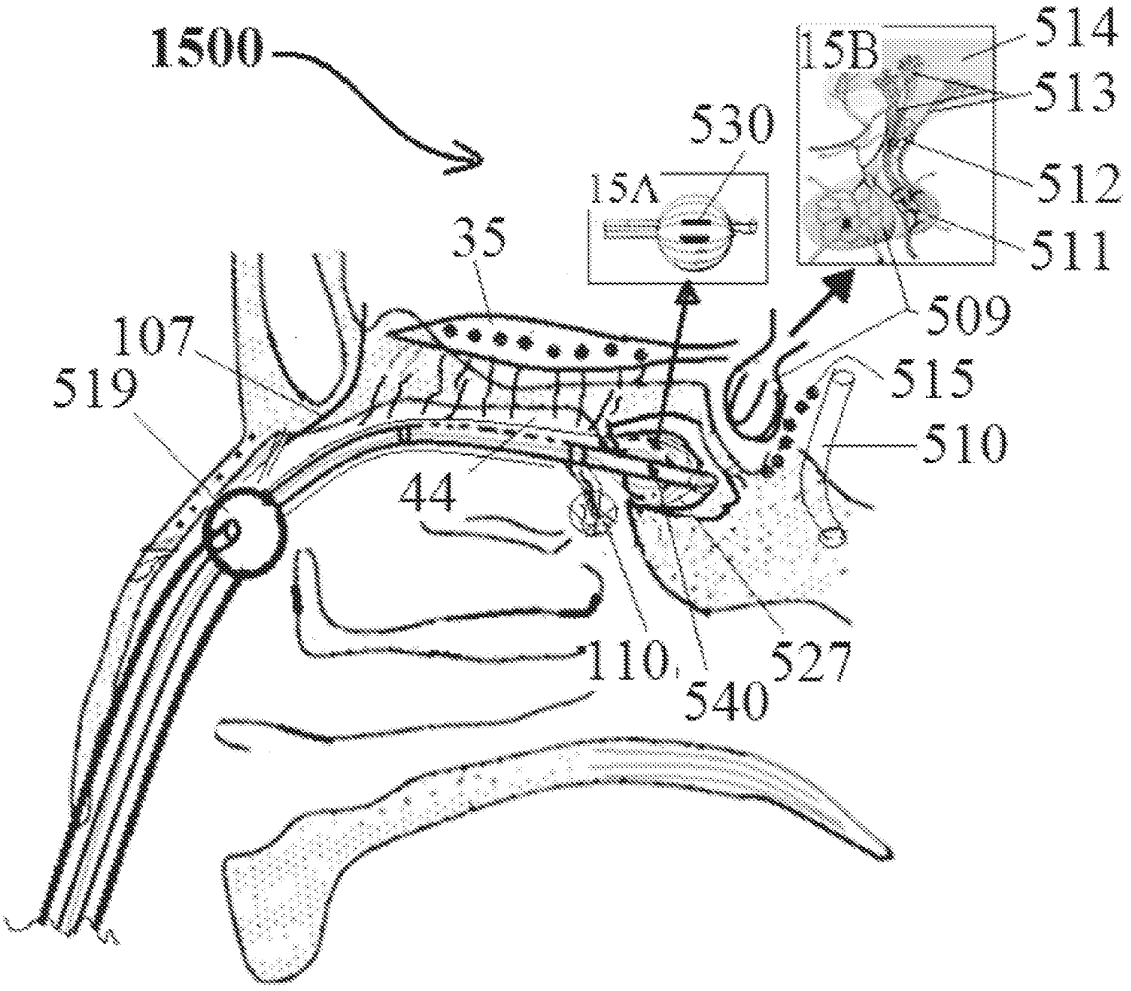


FIG. 15

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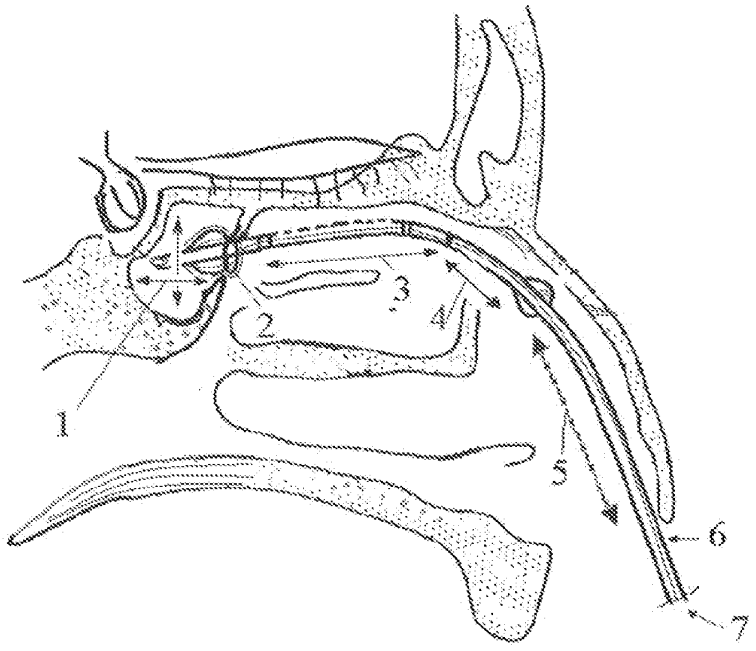


Figure 16

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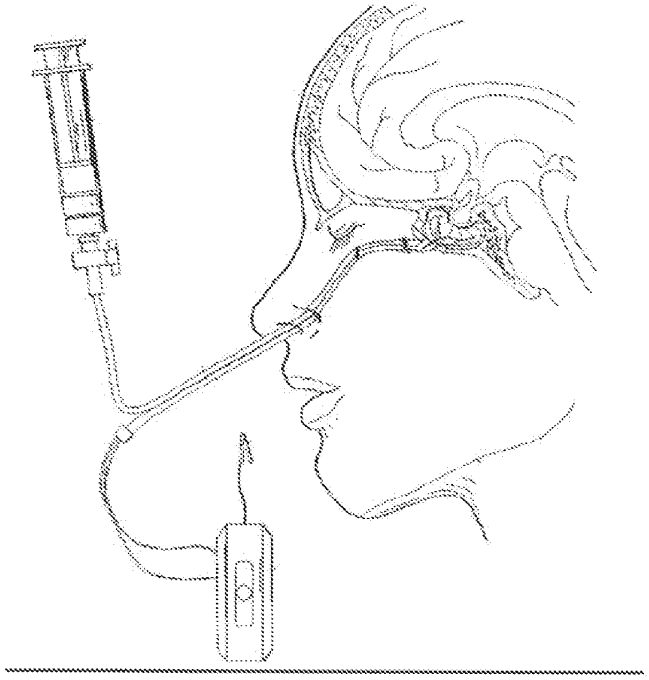


Figure 17

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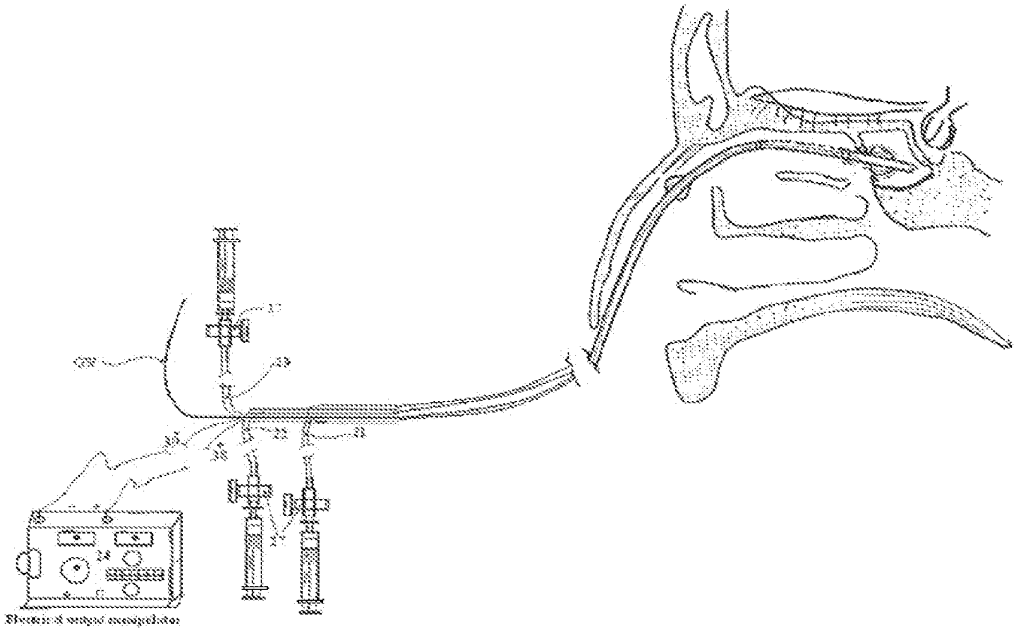


Figure 18

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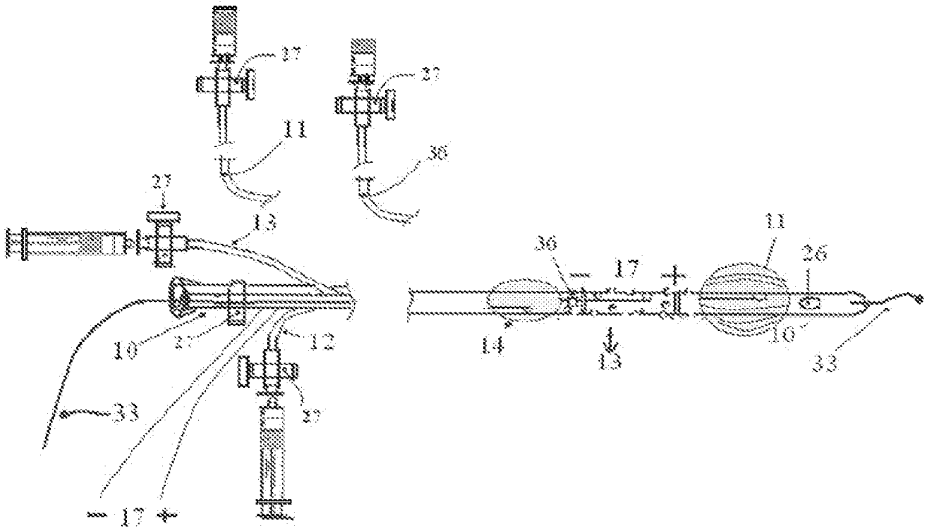


Figure 19

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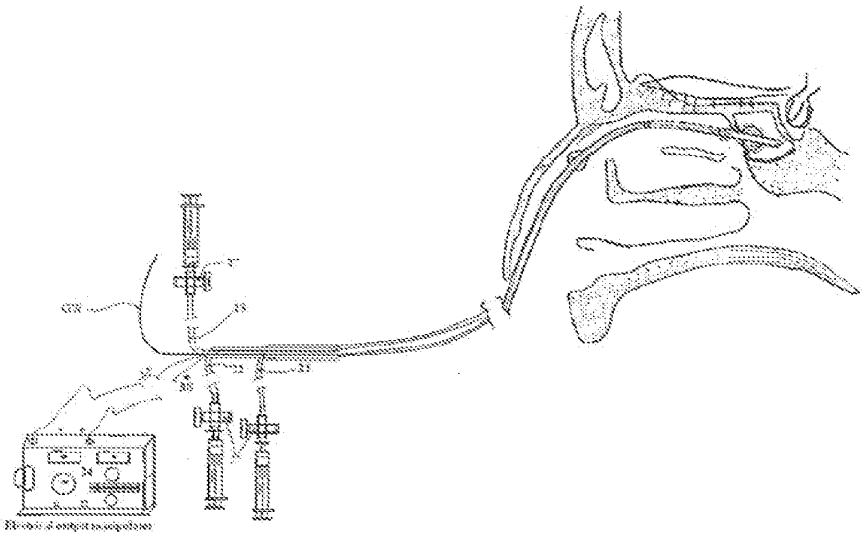


Figure 20

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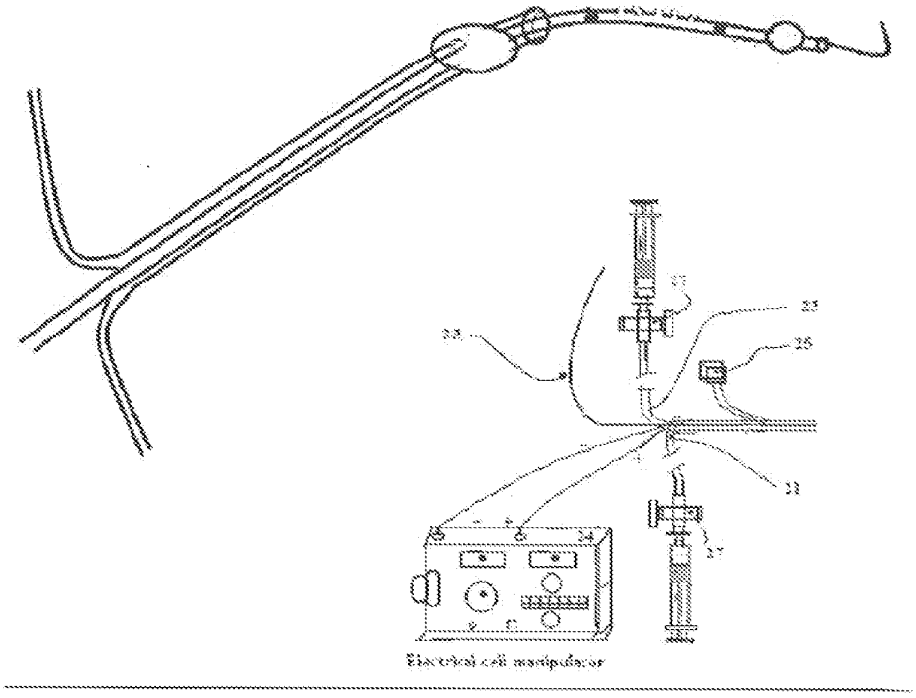


Figure 21

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US14/47566

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61N 1/30 (2014.01)
CPC - A61N 1/00, 1/30, 1/303, 1/306
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)
IPC(8): A61N 1/30 (2014.01)
CPC: A61N 1/00, 1/30, 1/303, 1/306

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)
Database(s) Searched (Patent and Non-Patent Literature (NPL), Including Sub-Databases and Files Searched) and Search Terms Used: MicroPatent (US-G, US-A, EP-A, EP-B, WO, JP-bib, DE-C,B, DE-A, DE-T, DE-U, GB-A, FR-A); ESpacenet; Google/Google Scholar; IP.com; PubMED/MEDLINE: array, balloon, bipolar*, electrode*, sphenoid*, sinus*, nasal*, olfactor*, mucosa*, stimulat*

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 2012/0323214 A1 (SHANTHA, TR) December 20, 2012; figure 5-10; paragraphs [0173]-[0178]	1, 17-18 --- 2, 3/1, 3/2, 4/3/1, 4/3/2
Y	US 2011/0130708 A1 (PERRY, M et al) June 2, 2011; paragraph [0090]	2, 3/1, 3/2, 4/3/1, 4/3/2
A	US 2006/0058854 A1 (ABRAMS, R et al) March 16, 2006; figure 1; paragraphs [0016], [0018], [0029]	2, 3/1, 3/2, 4/3/1, 4/3/2

☐ Further documents are listed in the continuation of Box C. ☐

* 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
06 November 2014 (06.11.2014)	24 NOV 2014
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US14/47566

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. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

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.: 5-16 and 19-34
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 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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IPR2025-01125

Espacenet

Bibliographic data: WO2018087601 (A1) — 2018-05-17

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

Inventor(s): TOWNLEY DAVID [IE]; SHIELDS BRIAN [IE]; KEOGH IVAN [IE]; DOCKERY PETER [IE]; O'BRIEN IAN [IE]; O'HALLORAN MARTIN [IE]; PORTER EMILY [IE]; JONES MARGGIE [IE] ± (TOWNLEY, David, ; SHIELDS, Brian, ; KEOGH, Ivan, ; DOCKERY, Peter, ; O'BRIEN, Ian, ; O'HALLORAN, Martin, ; PORTER, Emily, ; JONES, Marggie)

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Classification: - international: ***A61B5/00; A61B5/053;*** *A61B18/00*
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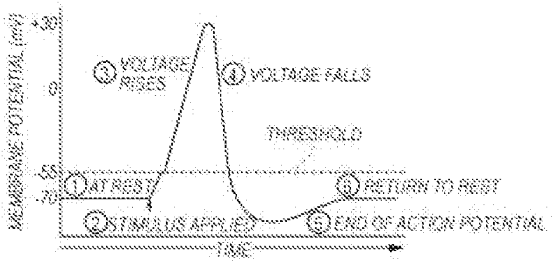
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Devices, systems, and methods for specializing, monitoring, and/or evaluating therapeutic nasal neuromodulation are disclosed herein. A targeted neuromodulation system configured in accordance with embodiments of the present technology can include, 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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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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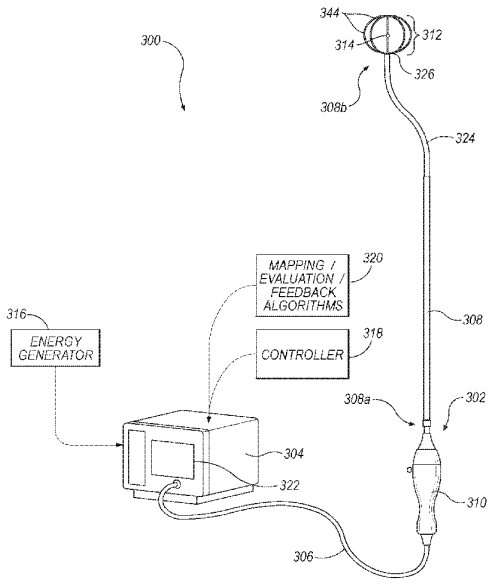


Fig. 3A

(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.

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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.

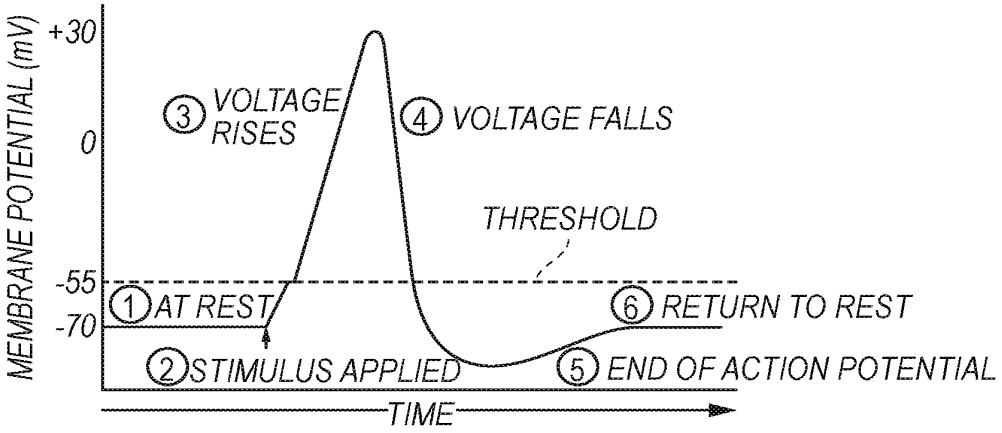


Fig. 1

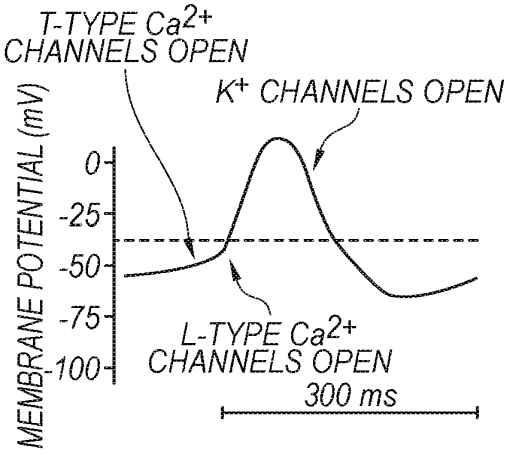


Fig. 2A

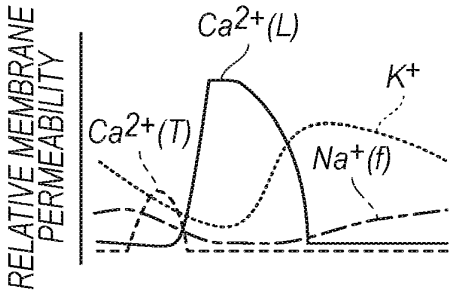


Fig. 2B

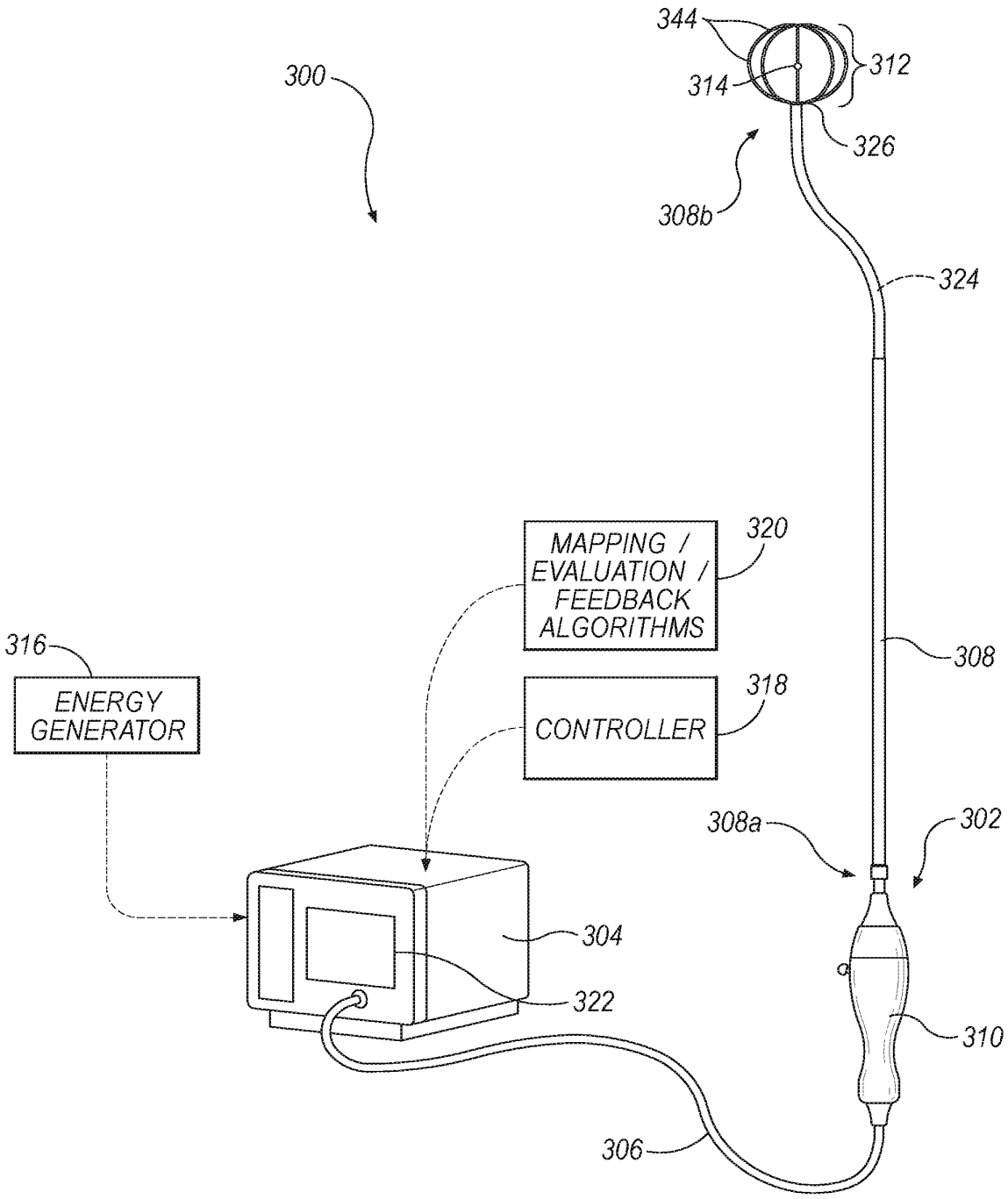

344
312
314
326
300
308b
324
MAPPING / EVALUATION / FEEDBACK ALGORITHMS
320
316
308
ENERGY GENERATOR
318
CONTROLLER
308a
302
304
322
310
306

Fig. 3A

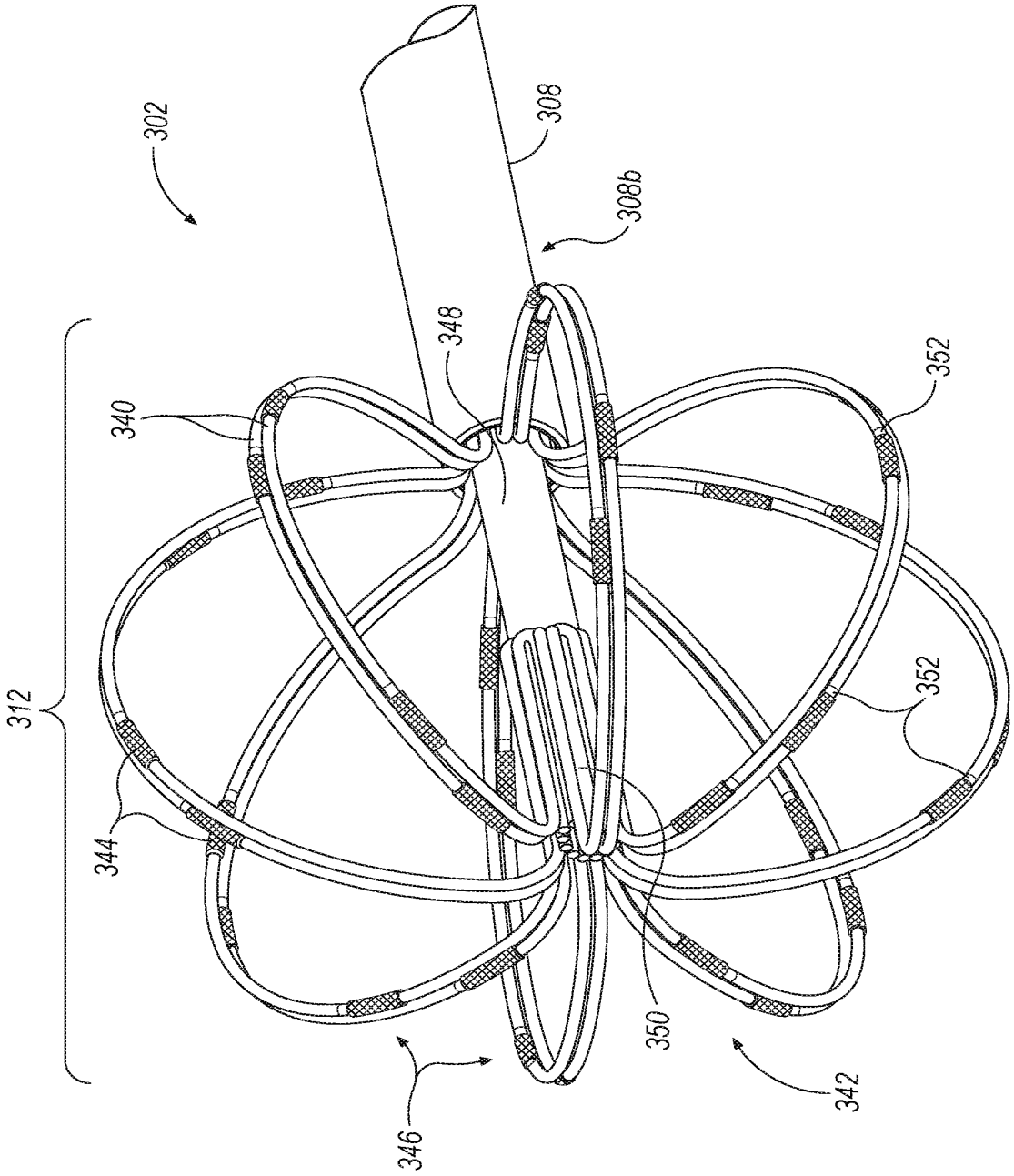


Fig. 3B

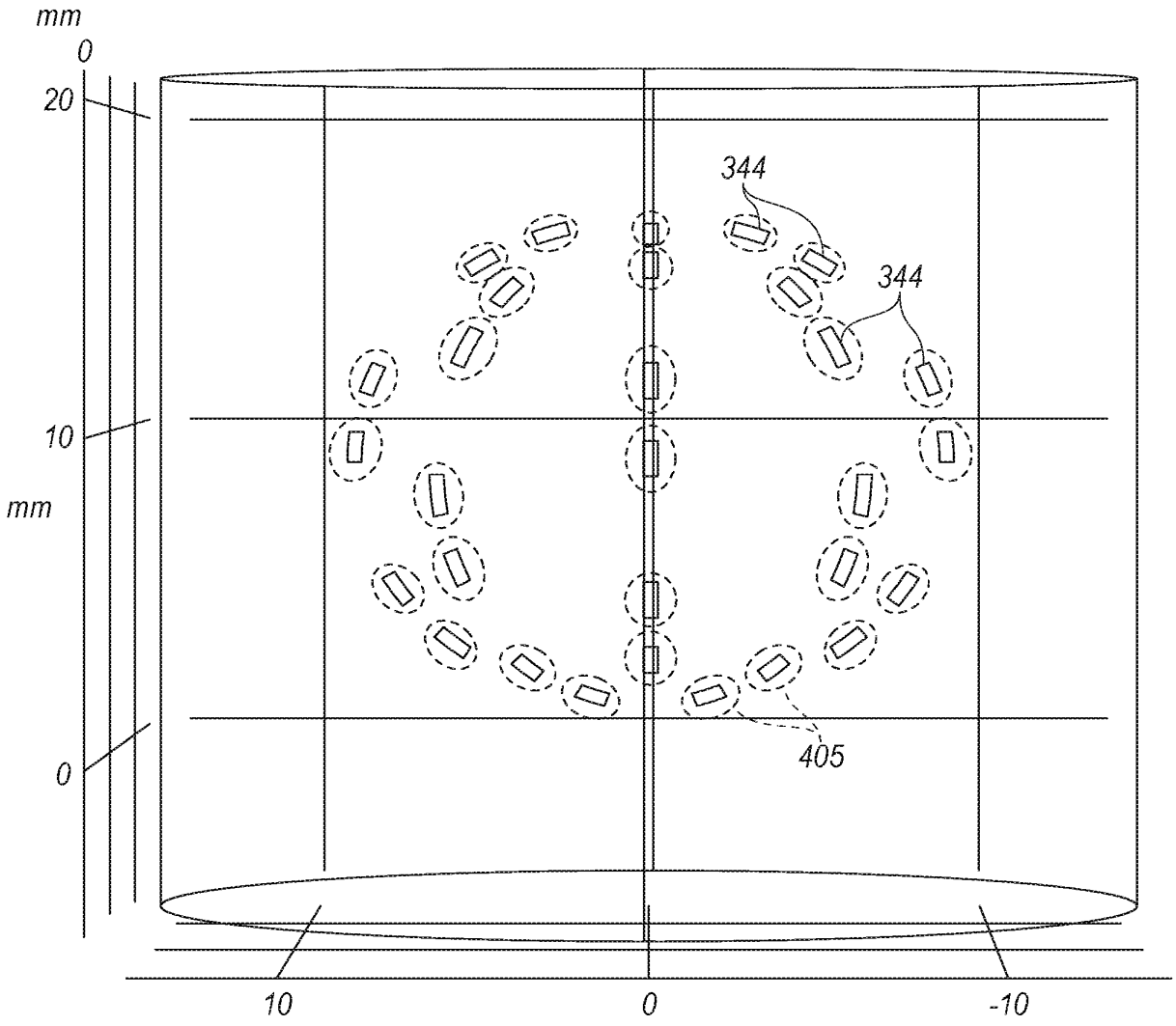


Fig. 4A

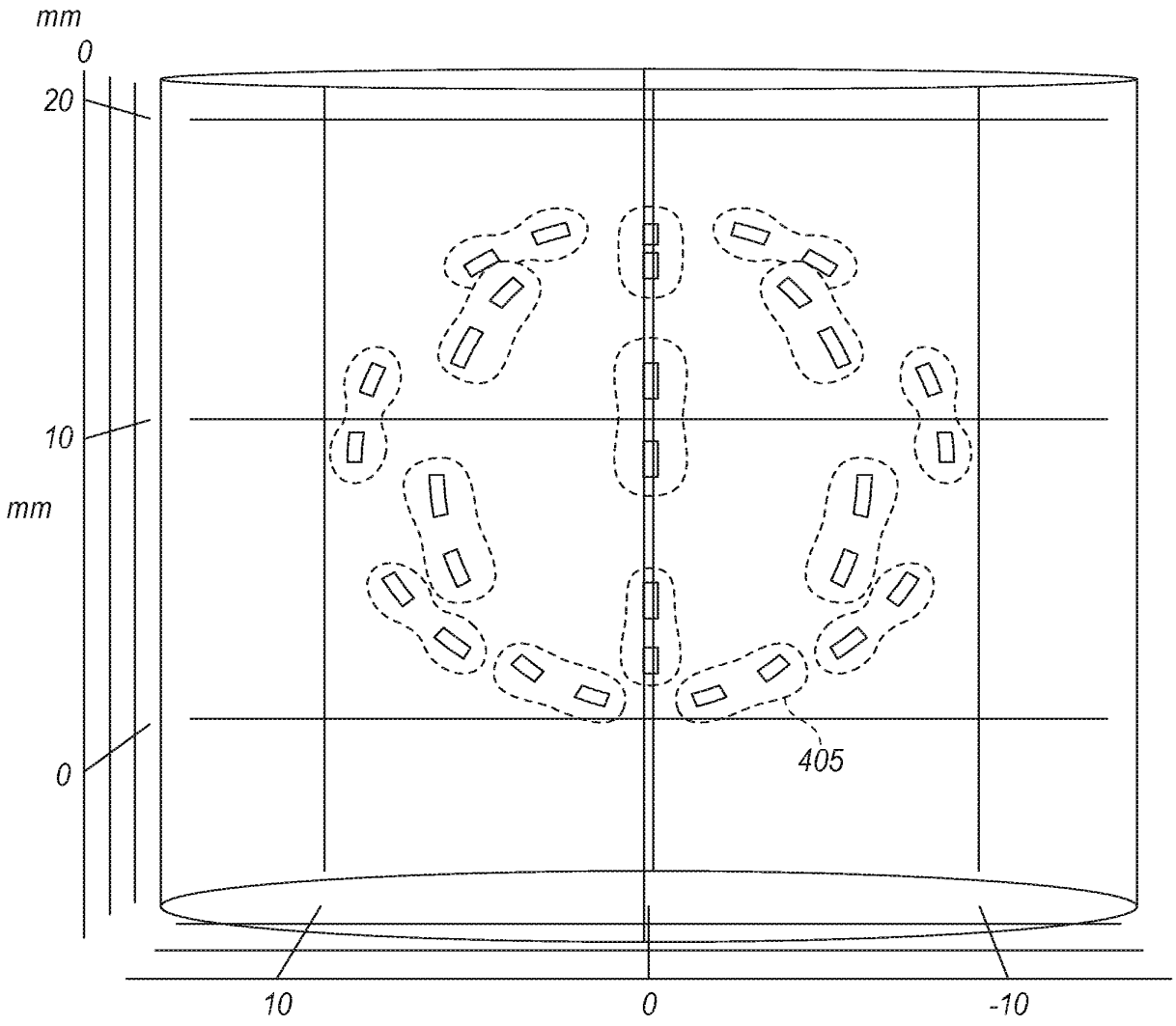


Fig. 4B

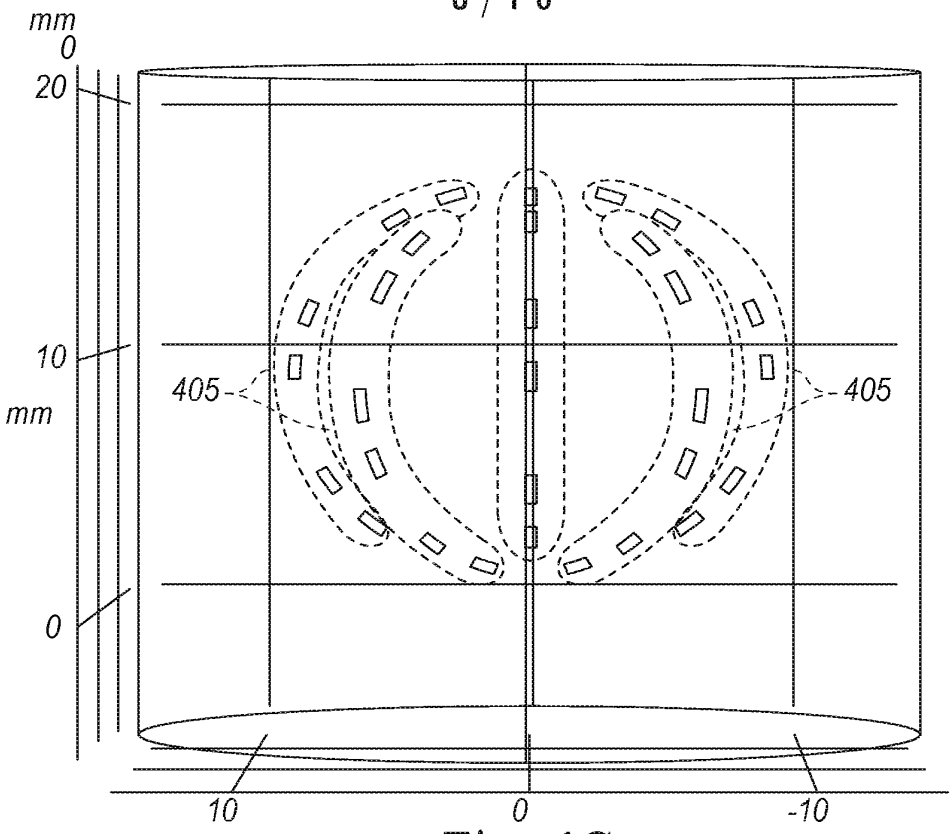


Fig. 4C

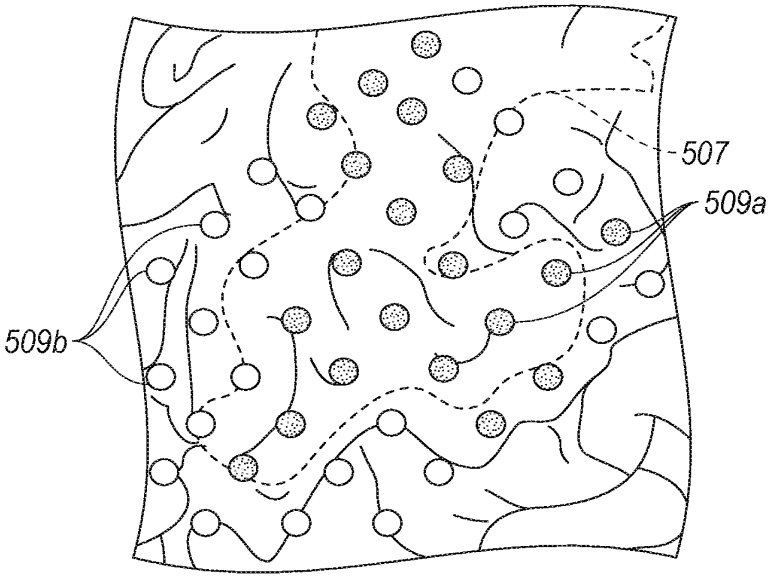


Fig. 5

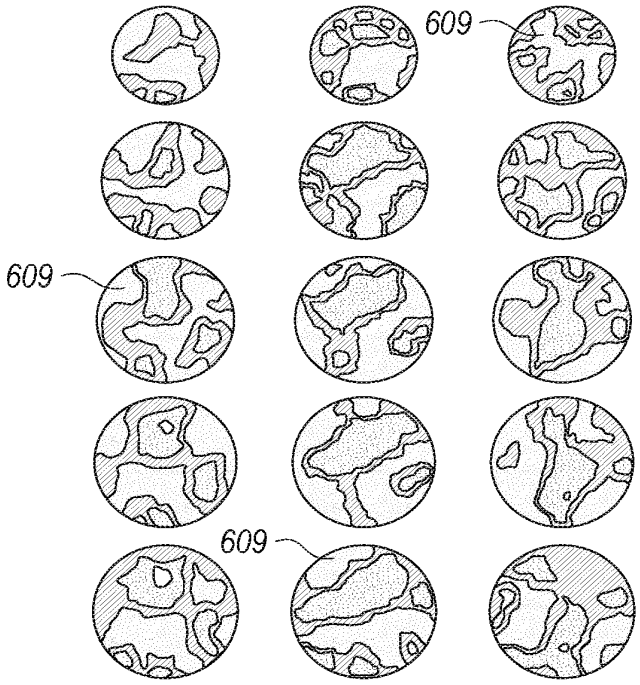


Fig. 6

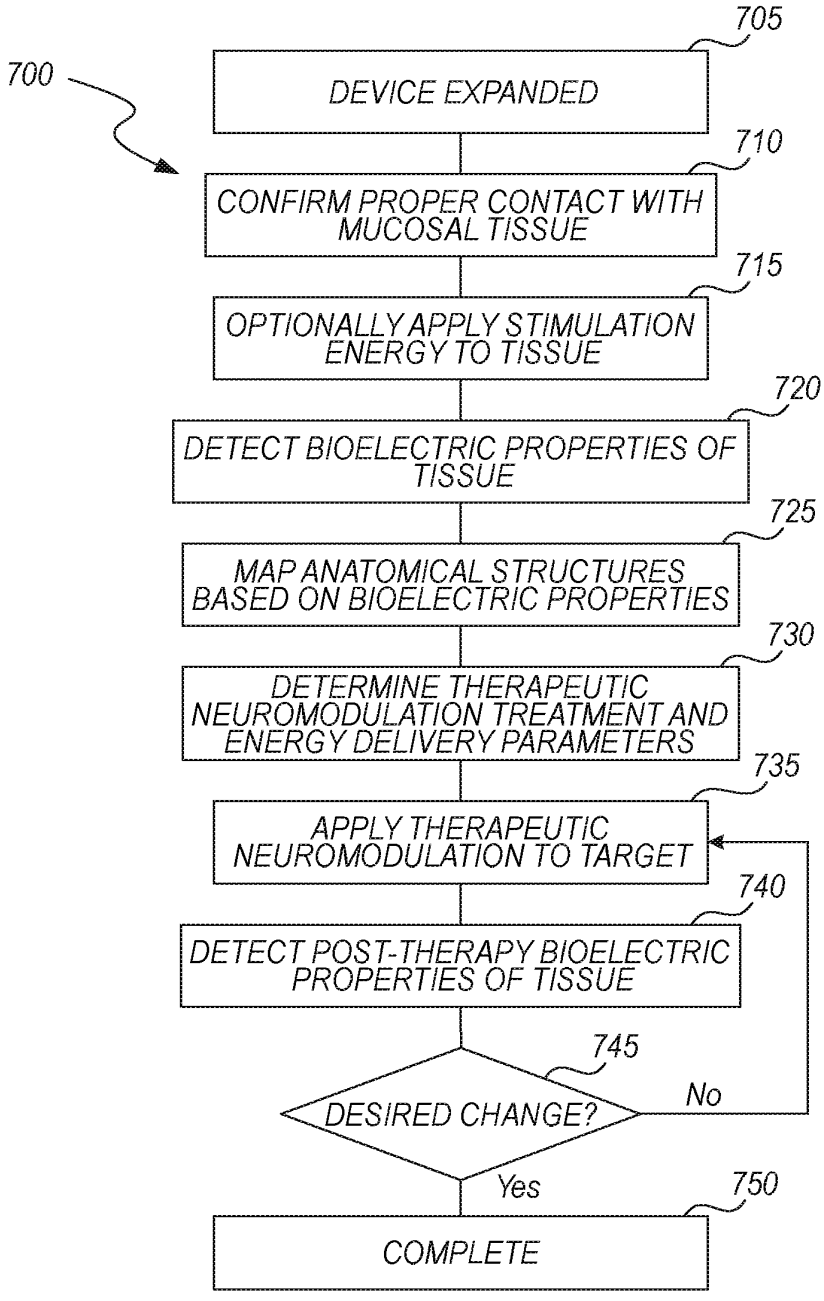

700
705
DEVICE EXPANDED
710
CONFIRM PROPER CONTACT WITH MUCOSAL TISSUE
715
OPTIONALLY APPLY STIMULATION ENERGY TO TISSUE
720
DETECT BIOELECTRIC PROPERTIES OF TISSUE
725
MAP ANATOMICAL STRUCTURES BASED ON BIOELECTRIC PROPERTIES
730
DETERMINE THERAPEUTIC NEUROMODULATION TREATMENT AND ENERGY DELIVERY PARAMETERS
735
APPLY THERAPEUTIC NEUROMODULATION TO TARGET
740
DETECT POST-THERAPY BIOELECTRIC PROPERTIES OF TISSUE
745
DESIRED CHANGE?
No
Yes
750
COMPLETE

Fig. 7

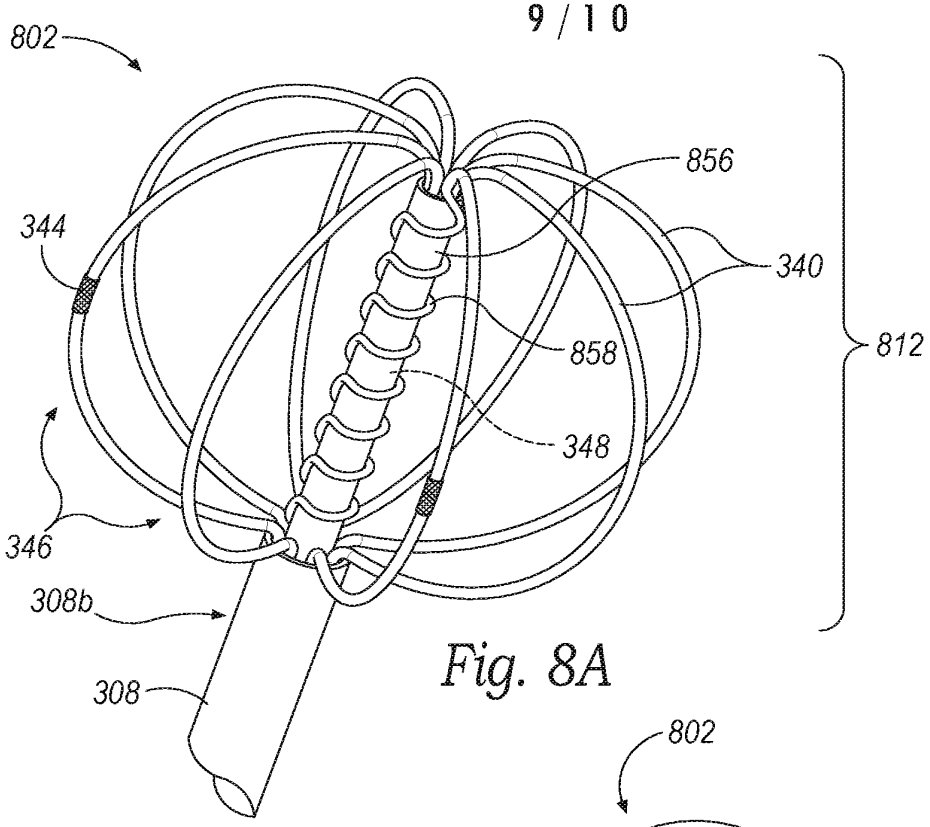

802
856
344
340
858
812
348
346
308b
308

Fig. 8A

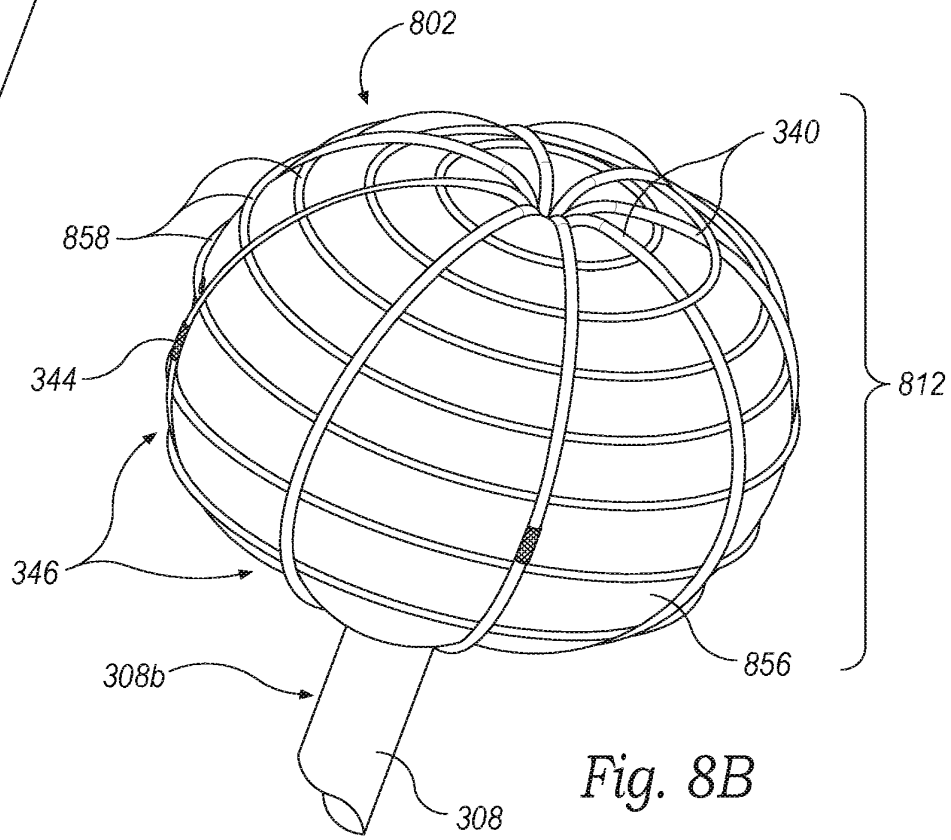

802
340
858
812
344
346
856
308b
308

Fig. 8B

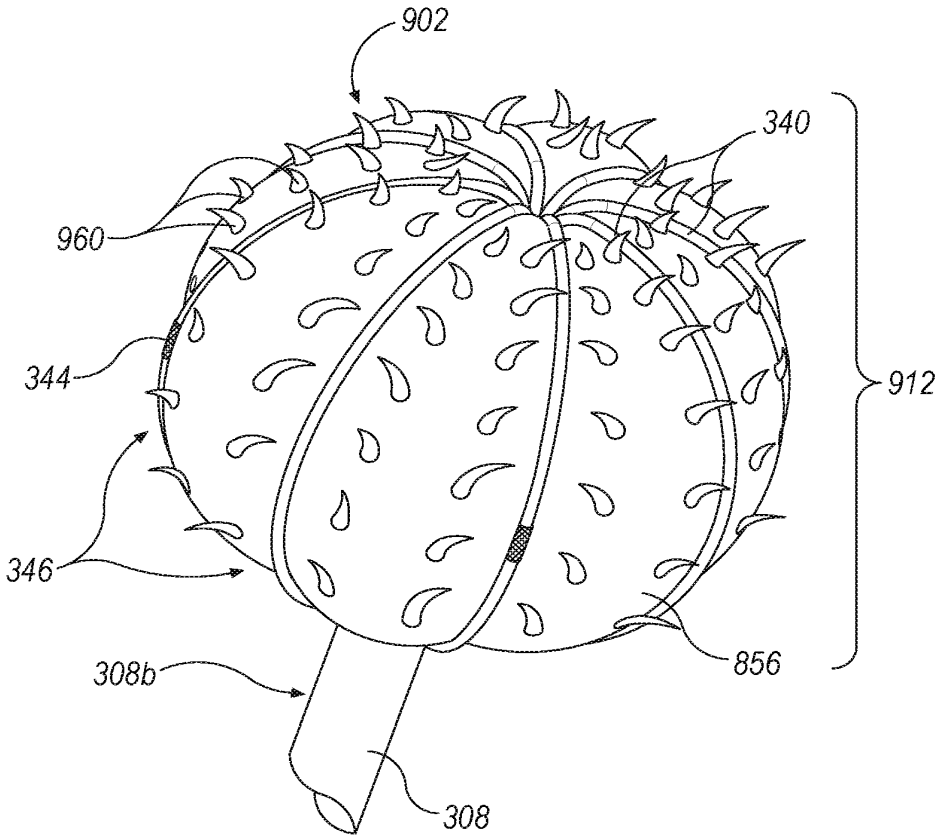


Fig. 9

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

2

Form PCT/ISA/210 (second sheet) (April 2005)

Aerin Exhibit 1011, Page 1350 of 2183
Aerin Medical Inc. v. Neurent Medical Ltd.
IPR2025-01125

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)

Aerin Exhibit 1011, Page 1351 of 2183
Aerin Medical Inc. v. Neurent Medical Ltd.
IPR2025-01125

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

Aerin Exhibit 1011, Page 1352 of 2183
Aerin Medical Inc. v. Neurent Medical Ltd.
IPR2025-01125

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.
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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:
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-018/01WO 35242/93	Date of mailing *(day/month/year)* 4 February 2022 (04-02-2022) **FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/IB2021/000699	International filing date *(day/month/year)* 5 October 2021 (05-10-2021)
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 MUSSON, Frédérique Tel: +31 (0)70 340-2490

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-018/01WO 35242/93		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/IB2021/000699	5 October 2021 (05-10-2021)	6 October 2020 (06-10-2020)
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 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. 1b

[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.
IPR2025-01125

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2021/000699

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.: 1-20
because they relate to subject matter not required to be searched by this Authority, namely:
Refer to the search opinion.

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.

Aerin Exhibit 1011, Page 1357 of 2183
Aerin Medical Inc. v. Neurent Medical Ltd.
IPR2025-01125

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2021/000699

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61B18/14 A61B5/00
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)
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

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	21-33, 36-40
Y	paragraph [0031]; figure 3a paragraph [0036] - paragraph [0038] paragraph [0079] paragraph [0064] - paragraph [0068]; figure 7 paragraph [0048]; figure 3b paragraph [0051]	34,35
E	WO 2021/260435 A1 (NEURENT MEDICAL LTD [IE]) 30 December 2021 (2021-12-30) page 50, line 10 - page 53, line 9; figure 10 page 15, line 26 - page 19, line 15; figures 1a-2 page 47, line 21 - line 31; figure 9c	21-33, 36-40

-/--

[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
26 January 2022	04/02/2022

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	Ekstrand, Vilhelm

3

Form PCT/ISA/210 (second sheet) (April 2005)

Aerin Exhibit 1011, Page 1358 of 2183
Aerin Medical Inc. v. Neurent Medical Ltd.
IPR2025-01125

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 2021/205231 A1 (NEURENT MEDICAL LTD [IE]) 14 October 2021 (2021-10-14) page 14, line 815 - page 15, line 30; figures 1,2 page 38, line 21 - page 45, line 5; figure 9a page 45, line 6 - page 51, line 16; figure 9b page 51, line 17 - page 54, line 15; figure 9c page 55, line 4 - line 13	21-33, 36-40
A	US 2017/215952 A1 (NAIR ANUJA [US]) 3 August 2017 (2017-08-03) paragraph [0093]; figure 3	26
Y	US 2016/331459 A1 (TOWNLEY DAVID [IE] ET AL) 17 November 2016 (2016-11-17) cited in the application paragraph [0111]	34,35
A	US 2019/223944 A1 (COATES PAUL [US]) 25 July 2019 (2019-07-25) paragraph [0157] paragraph [0068]	21-40
A	US 2020/289185 A1 (FORSYTH BRUCE R [US] ET AL) 17 September 2020 (2020-09-17) paragraph [0083]	21-40
A	US 2015/112321 A1 (CADOURI HADAR [US]) 23 April 2015 (2015-04-23) paragraph [0008] - paragraph [0009] paragraph [0059] paragraph [0082] - paragraph [0084]	21-40

3

Aerin Exhibit 1011, Page 1359 of 2183
Aerin Medical Inc. v. Neurent Medical Ltd.
IPR2025-01125

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2021/000699

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 2021260435 A1	30-12-2021	NONE	
WO 2021205231 A1	14-10-2021	US 2021315638 A1	14-10-2021
		WO 2021205231 A1	14-10-2021
US 2017215952 A1	03-08-2017	US 2014180273 A1	26-06-2014
		US 2017215952 A1	03-08-2017
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 2019223944 A1	25-07-2019	CN 111867507 A	30-10-2020
		EP 3742996 A1	02-12-2020
		JP 2021516594 A	08-07-2021
		US 2019223944 A1	25-07-2019
		WO 2019147470 A1	01-08-2019
US 2020289185 A1	17-09-2020	CN 113573656 A	29-10-2021
		EP 3937812 A1	19-01-2022
		US 2020289185 A1	17-09-2020
		WO 2020190693 A1	24-09-2020
US 2015112321 A1	23-04-2015	EP 3060150 A1	31-08-2016
		US 2015112321 A1	23-04-2015
		US 2020030029 A1	30-01-2020
		WO 2015061478 A1	30-04-2015

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/IB2021/000699

TITLE: SYSTEMS AND METHODS FOR THERAPEUTIC NASAL TREATMENT

APPLICANT: NEURENT MEDICAL LIMITED

IPC CLASSIFICATION: A61B18/14, A61B5/00

EXAMINER: Ekstrand, Vilhelm

CONSULTED DATABASES: PRESEARCH, TXT, OMBI

CLASSIFICATION SYMBOLS DEFINING EXTENT OF THE SEARCH:

IPC:

CPC: A61B2018/00327, A61B18/12, A61B2018/00577, A61B2018/00267, A61B2018/00434, A61B2018/00702, A61B2018/00761, A61B2034/101, A61B2018/0016, A61B2090/062, A61B2018/00773, A61B2018/00791, A61B2018/00875, A61B2018/1475, A61B2018/00946, A61B5/40, A61B2018/00839, A61B2018/00779, A61B2018/00714, A61B2017/00154, A61B2018/0072

FI/F-TERMS:

KEYWORDS OR OTHER ELEMENTS FEATURING THE INVENTION:
nose,nasal, cavity, sinus, ablating, electrode, duration, energy, temperature range, treatment, pattern, profile,pulsed.

EPO FORM P04A62

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/IB2021/000699	05.10.2021	06.10.2020

International Patent Classification (IPC) or both national classification and IPC
INV. A61B18/14 A61B5/00

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 P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Fax: +31 70 340 - 3016	see form PCT/ISA/210	Ekstrand, Vilhelm Telephone No. +31 70 340-0

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. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

   see separate sheet

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. 1-20

because:

☒ the said international application, or the said claims Nos. 1-20 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. 1-20

☐ 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	26, 34, 35
	No:	Claims	21-25, 27-33, 36-40
Inventive step (IS)	Yes:	Claims	
	No:	Claims	21-40
Industrial applicability (IA)	Yes:	Claims	21-40
	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

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 2021/260435 A1 (NEURENT MEDICAL LTD [IE]) 30 December 2021 (2021-12-30)

D3 WO 2021/205231 A1 (NEURENT MEDICAL LTD [IE]) 14 October 2021 (2021-10-14)

D4 US 2017/215952 A1 (NAIR ANUJA [US]) 3 August 2017 (2017-08-03)

D5 US 2016/331459 A1 (TOWNLEY DAVID [IE] ET AL) 17 November 2016 (2016-11-17)cited in the application

D6 US 2019/223944 A1 (COATES PAUL [US]) 25 July 2019 (2019-07-25)

D7 US 2020/289185 A1 (FORSYTH BRUCE R [US] ET AL) 17 September 2020 (2020-09-17)

1 Re Item II

The validity of the priority claim cannot be assessed since the search authority does not have the priority document in its possession.

2 Re Item III

Claim 1 refer to treating a condition and includes the step of "delivering treatment energy" which in at least some embodiments is performed on the human body. Thus, claims 1-20 refer to methods of treating the human body by **therapy** and **surgery**. According to Rule 39.1 (iv) PCT and to Art 43bis.1 PCT as well as Rule 67.1 PCT, neither a search nor an international preliminary examination is required to be carried out on these claims.

3 Re Item V

3.1 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 21 is not new in the sense of Article 33(2) PCT. D1 discloses:

A system for treating a condition within a sino-nasal cavity of a patient *(paragraph [0031]; figure 3a)*, the system comprising:

a treatment device including an end effector comprising one or more electrodes *(308),(344)*; and

a controller operably associated with the treatment device and configured to control delivery of treatment energy from the one or more electrodes to tissue at a target site within a sino-nasal cavity of the patient based, at least in part, on a pulsed energy treatment pattern sufficient to maintain a consistent temperature of targeted tissue receiving the treatment energy to thereby cause ablation and/ or modulation of targeted tissue for the treatment of a nasal condition *(paragraph [0036] - paragraph [0038] and [68]:pulsed. The claim does not specify what parameters are controlled. D1 provides a consistent temperature since the treatment always ends at the same temperature in some embodiments).*

3.2 The dependent claims 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 novelty and/or inventive step, refer to the following passages:

claims 22-25: D1, paragraph [0064] - paragraph [0067]; figure 7: Tissue types and their location are identified from stimulation measurements. It is implicit that the different types of tissues have predefined characterisation data associated with them in order to be able to perform a characterisation. Paragraph [0079] discloses that the selection of the ablation pattern can be done autonomously where the treatment parameters are dependent on the position of nerves and tissue type characterisation/nerve mapping.

claim 26: D1: automating the development of the characterisation thresholds for the different tissues cannot be considered to be inventive. Refer also to D4, paragraph [0093]; figure 3.

claim 27-29: D1, [68]: The treatment pattern could be a constant power for a predetermined period or a temperature threshold. It is thus implicit that these parameters are fed back to enable this protocol.

claims 30-32: D1, paragraph [0048]; figure 3b,(352)

claims: 33: D1, [68]: if temperature, duration or impedance is used to control treatment completion, the act of turning off power can be a digital indicator of efficacy. Moreover, to make a ratio of the target vs current parameter values cannot be considered to be inventive.

claims 34-35: D1, [68]: to maintain a temperature is a common alternative regimen to having a temperature threshold for treatment completion. D1 already discloses that different parameters should apply for different tissues and that 60 degree Celsius is a good treatment temperature ([51],[79]). D5, [111] discloses a similar device that maintains a temperature by temperature feed-back using a range. The tolerance will follow implicitly when wanting the specific therapeutic effect of 60 degree Celsius as taught in D1. The division is unsure if the claimed tolerance gives any surprising effects when compared to for example a tolerance of half a degree Celsius. Refer also to D6, paragraph [0157] and paragraph [0068] and D7, paragraph [0083].

claim 36: D1, [68]: last sentence

claims 37,38,39.40: D1 the device is suitable for this.

4 **Re Item VI**

Certain documents cited

4.1 D2
Application: WO2021260435 A1

Publication date: 2021-12-30

Filing date: 2021-06-25

Priority date: 2020-06-26 (US202063044904P)

D2 discloses all features of claims 21-33, 36-40, refer to the cited passages of the search report.

4.2 D3
Application: WO2021205231A1

Publication date: 2021-10-14

Filing date: 2021-04-08

Priority date: 2020-04-09 (US202063007639P)

D3 discloses all features of claims 21-33, 36-40 refer to the cited passages of the search report.

5 **Re Item VII**

5.1 The independent claim(s) is/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 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).

5.2 The features of the claims are not provided with reference signs placed in parentheses (Rule 6.2(b) PCT).

5.3 Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in prior art is not mentioned in the description, nor are these documents identified therein.

6 **Re Item VIII**

Certain observations on the international application

6.1 The application does not meet the requirements of Articles 5,6 PCT, because claims 21,36,37,38,40 are not clear.

claim 21

The claim is formulated in terms of a result to be achieved. A treatment effect can only be achieved if a plan is made and executed or if damage is detected online in the target tissue. These features are considered to be essential to achieve the claimed effect. Moreover, it is not clear how the treatment pattern is used during treatment. Thus, the feed-back loop must be properly described, i.e. what parameters are varied and what parameters are controlled.

claims 34,35

It seems that claim 35 cannot be dependent on claim 34 since this range is not completely within the first range.

claim 36

Refer to claim 1.

claims 37,38,40

The claims refer to use of the device or refer to planner features. However, a planner is not claimed per se.

Aerin Exhibit 1011, Page 1369 of 2183
Aerin Medical Inc. v. Neurent Medical Ltd.
IPR2025-01125

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_____20070401OCR_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).

US 20180133460A1

(19) **United States**

(12) **Patent Application Publication**

Townley et al.

(10) **Pub. No.: US 2018/0133460 A1**

(43) **Pub. Date: May 17, 2018**

(54) **DEVICES, SYSTEMS, AND METHODS FOR SPECIALIZING, MONITORING, AND/OR EVALUATING THERAPEUTIC NASAL NEUROMODULATION**

(71) Applicant: **National University of Ireland, Galway**, Galway (IE)

(72) Inventors: **David Townley**, County Clare (IE); **Brian Shields**, Galway (IE); **Ivan Keogh**, Galway (IE); **Peter Dockery**, Galway (IE); **Ian Stephen O'Brien**, Galway (IE); **Martin O'Halloran**, Galway (IE); **Emily Elizabeth Porter**, Galway (IE); **Marggie Jones**, Galway (IE)

(21) Appl. No.: **15/811,449**

(22) Filed: **Nov. 13, 2017**

Related U.S. Application Data

(60) Provisional application No. 62/421,135, filed on Nov. 11, 2016.

Publication Classification

(51) **Int. Cl.**

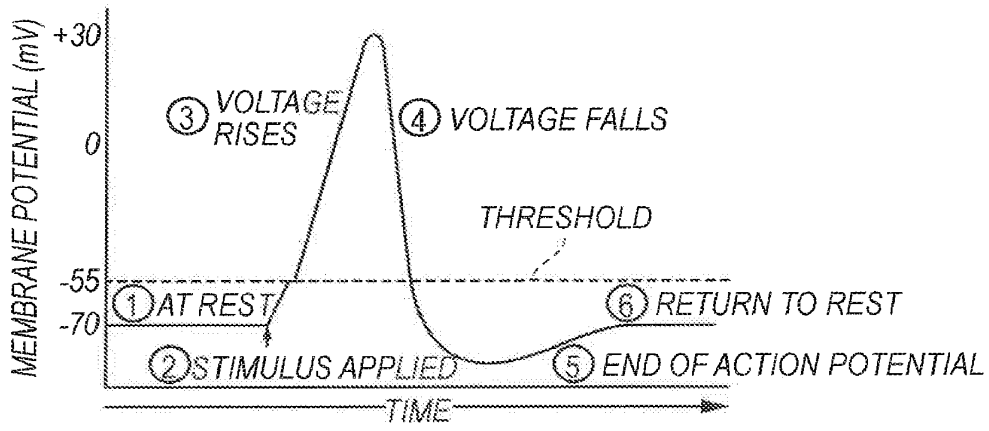
A61N 1/05	(2006.01)
A61N 1/36	(2006.01)

(52) **U.S. Cl.**

CPC *A61N 1/0546* (2013.01); *A61N 1/36075* (2013.01); *A61B 18/1492* (2013.01); *A61N 1/3603* (2017.08); *A61N 1/36021* (2013.01); *A61N 1/36135* (2013.01)

(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.



SNSDOCID: <US_____20180133460A1_I_>

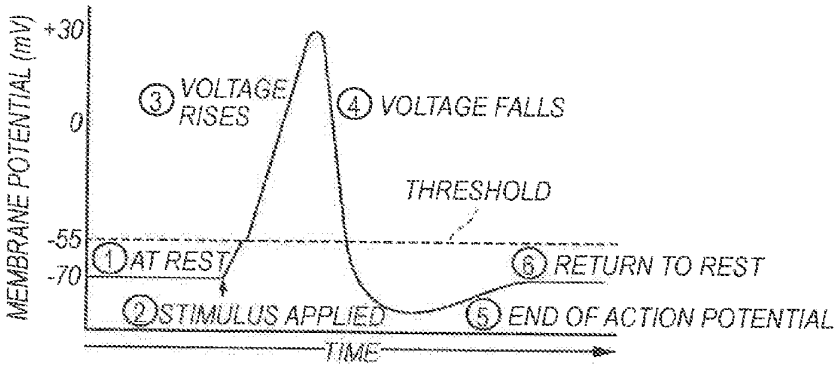


Fig. 1

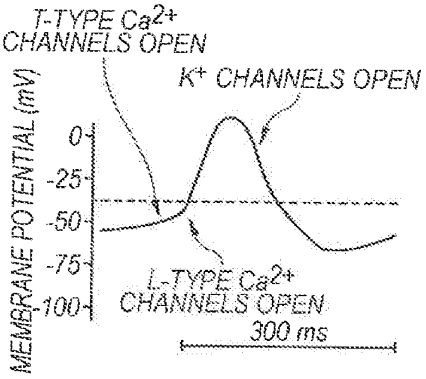


Fig. 2A

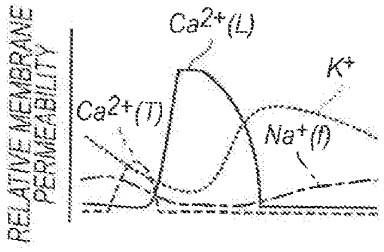


Fig. 2B

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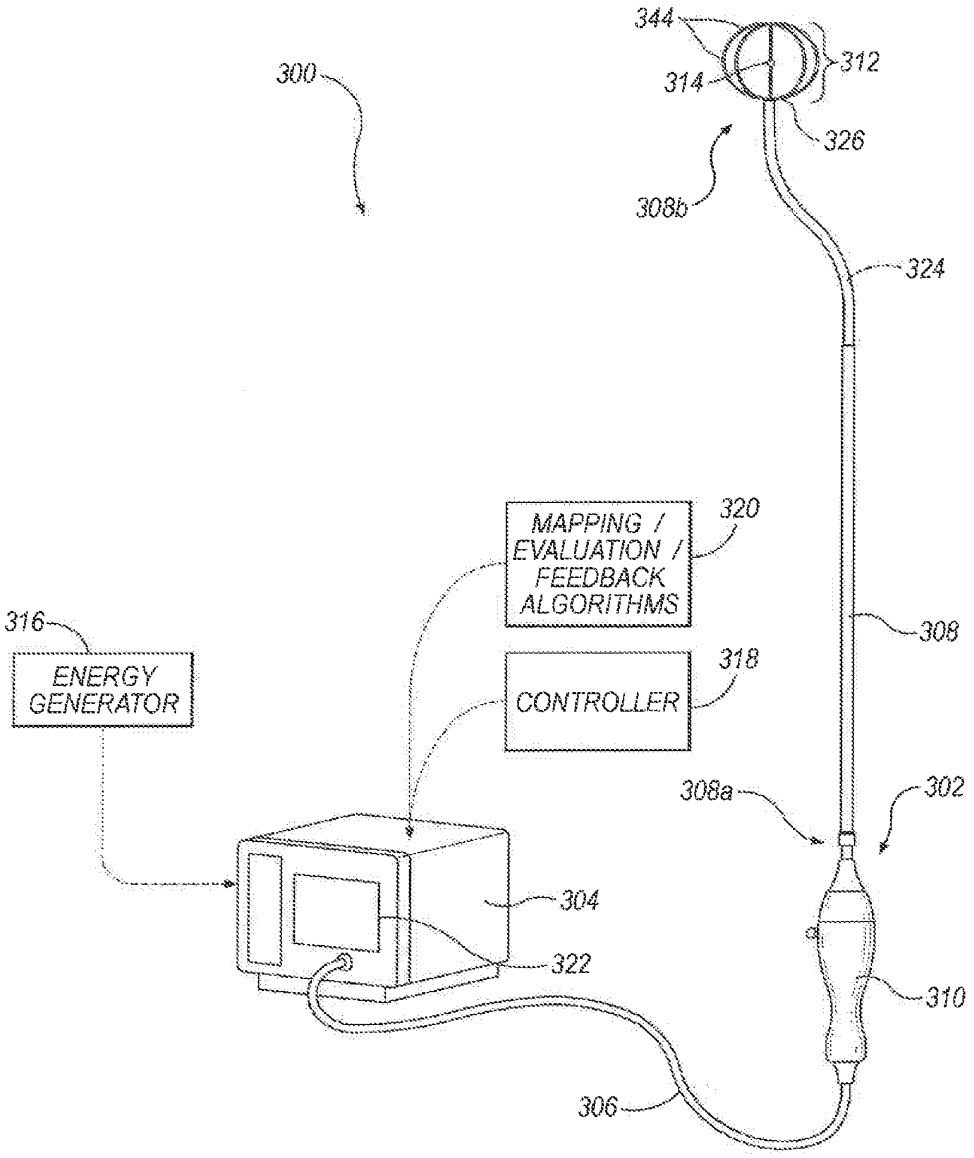


Fig. 3A

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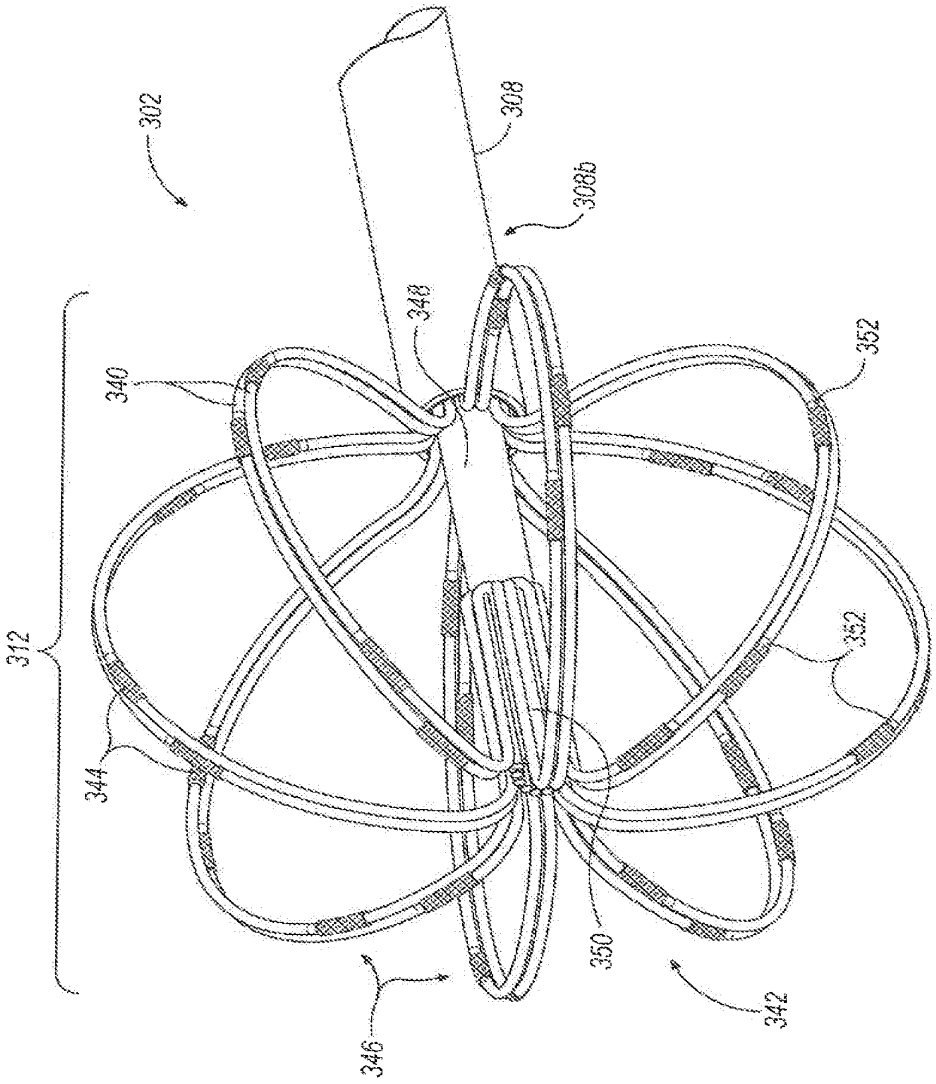


Fig. 3B

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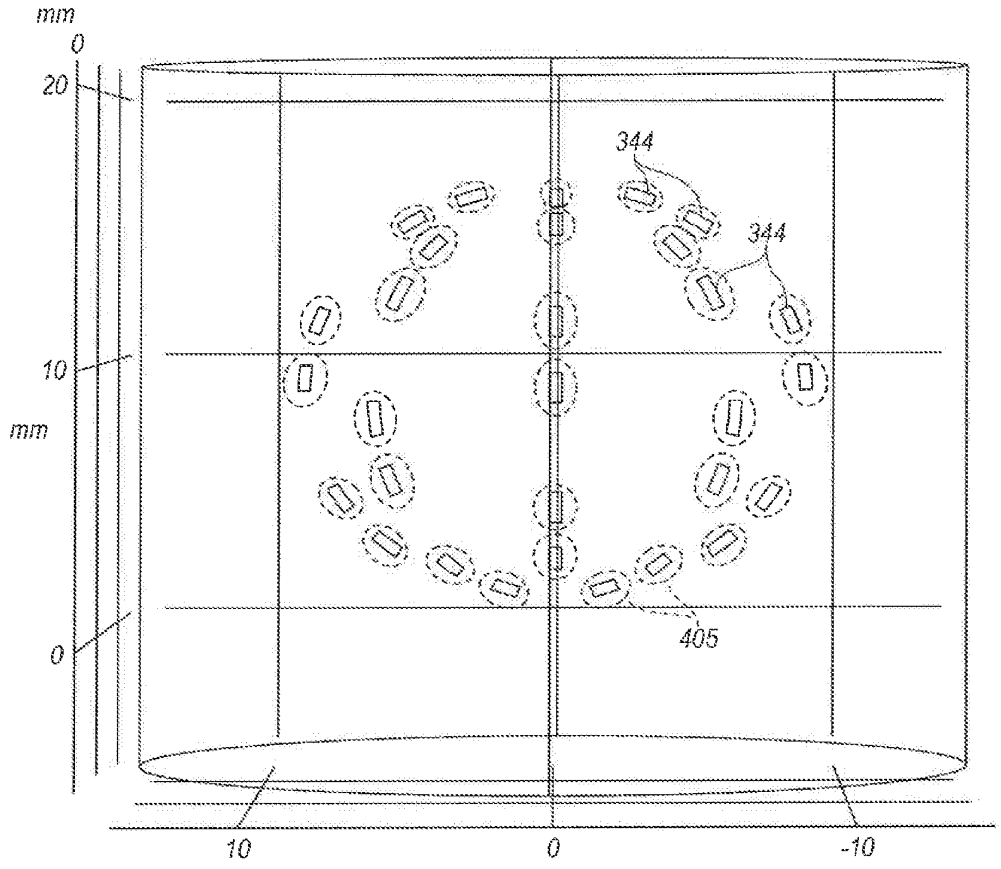


Fig. 4A

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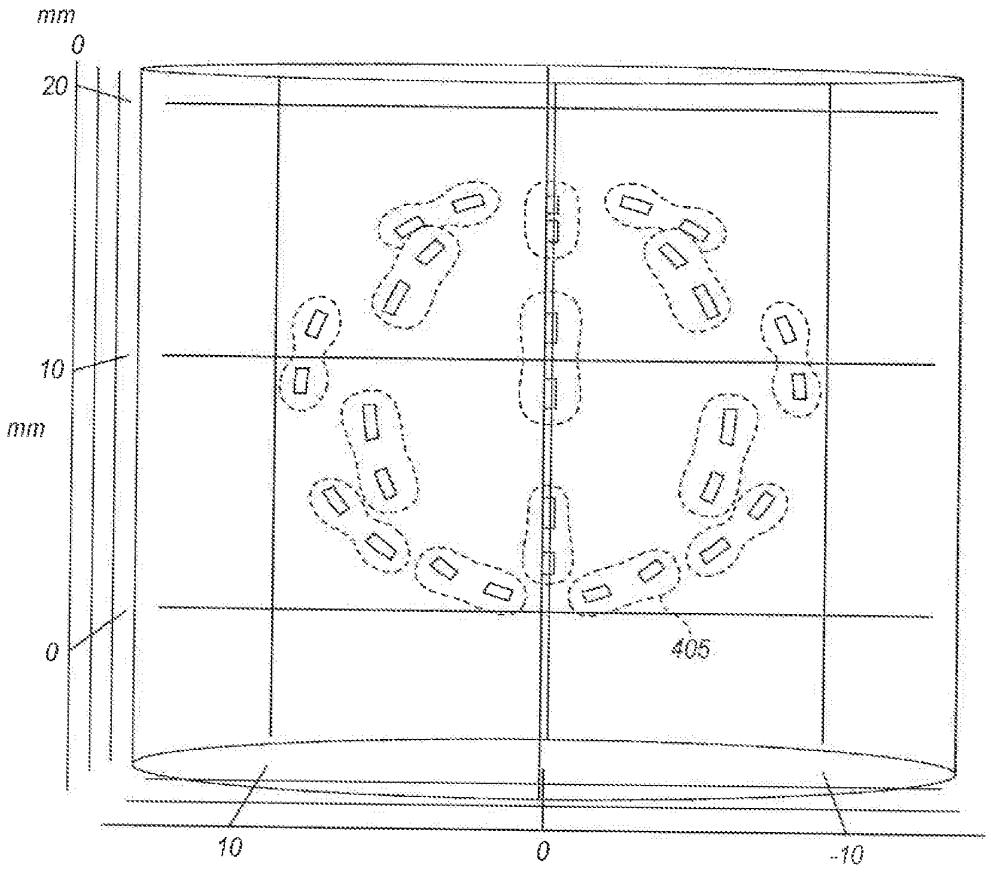


Fig. 4B

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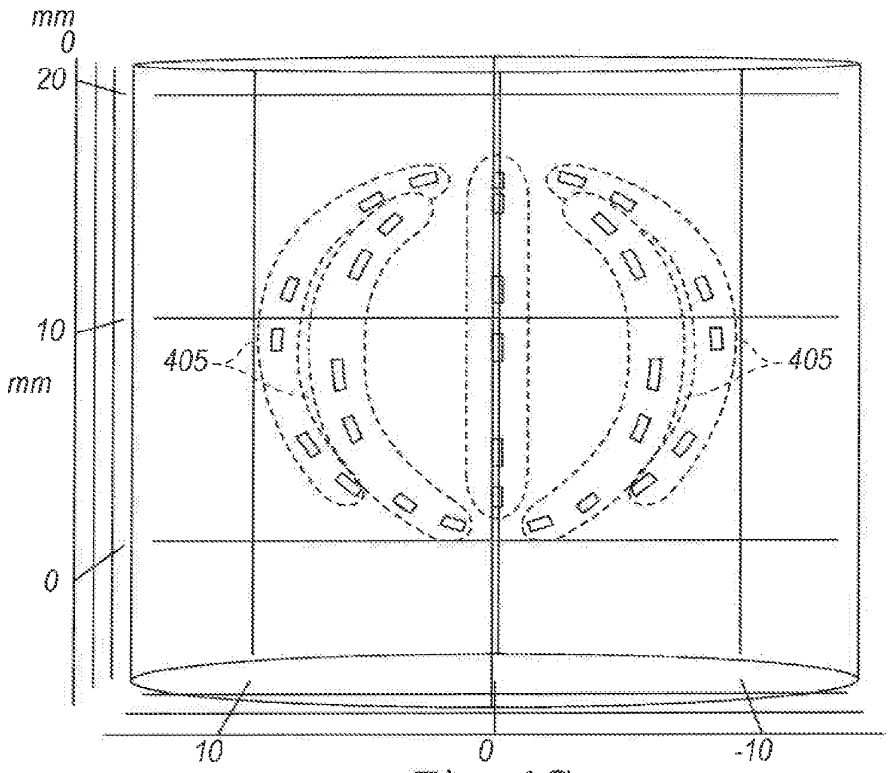


Fig. 4C

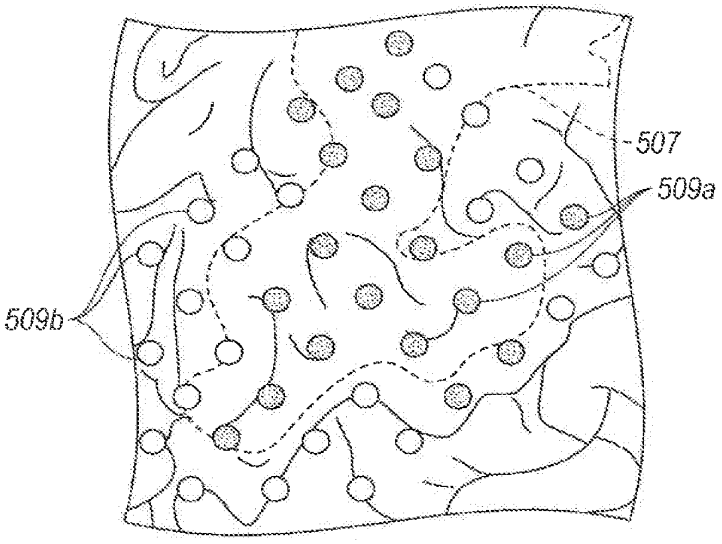


Fig. 5

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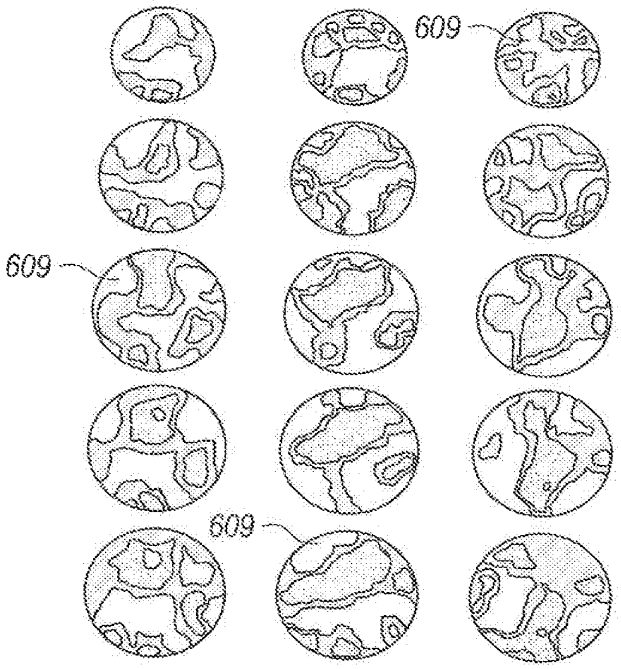


Fig. 6

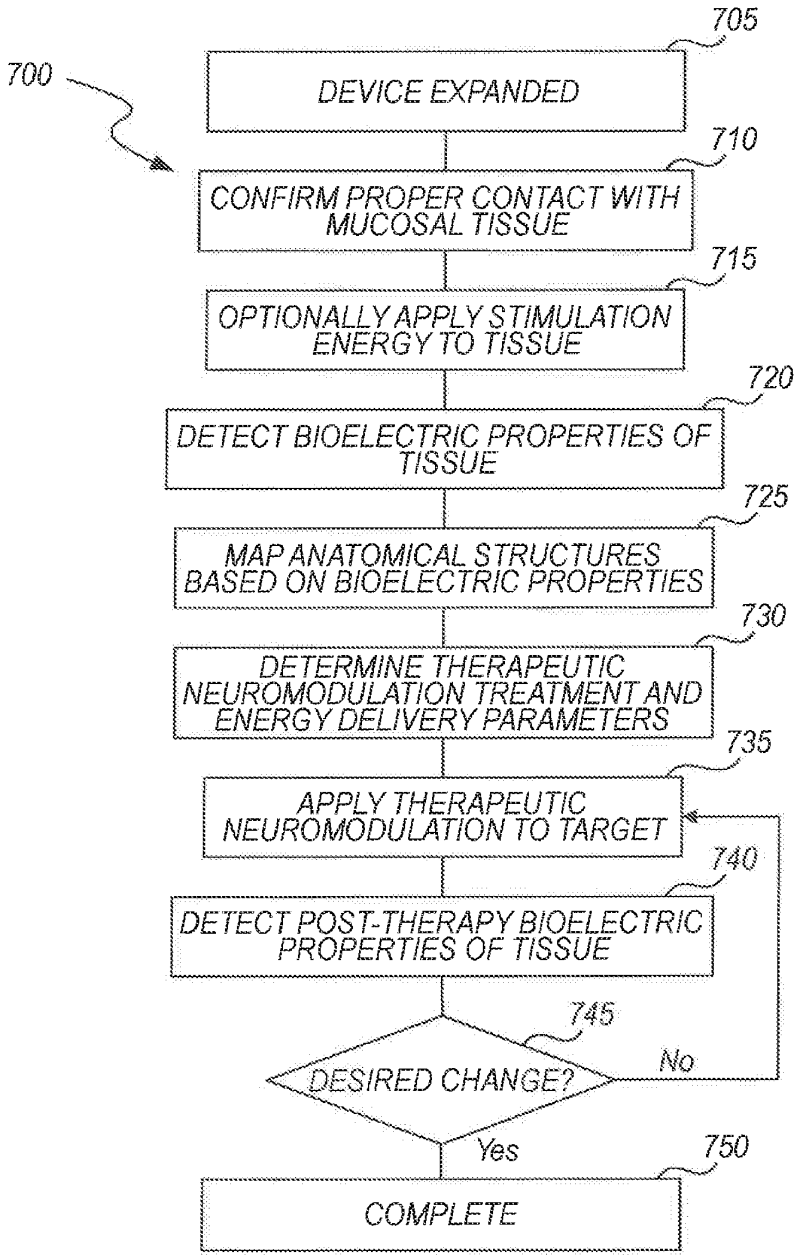


Fig. 7

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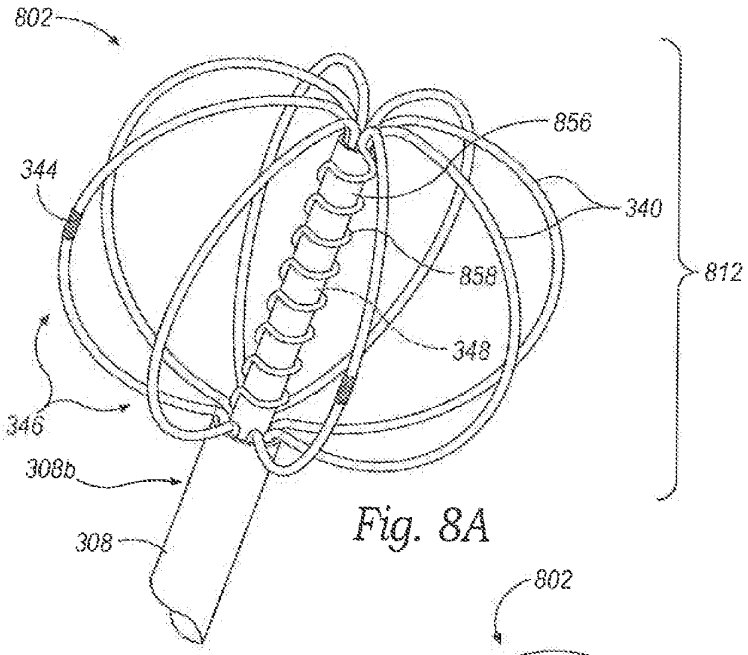


Fig. 8A

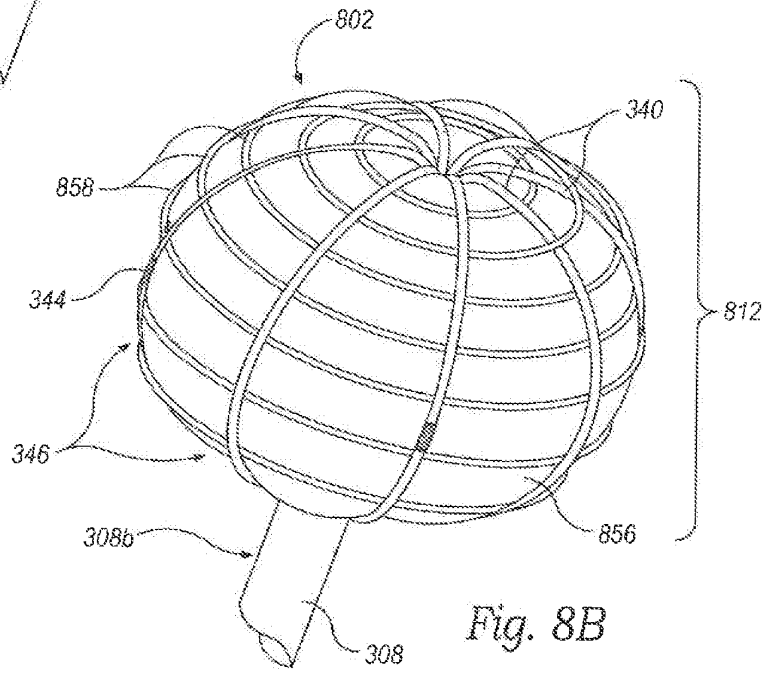


Fig. 8B

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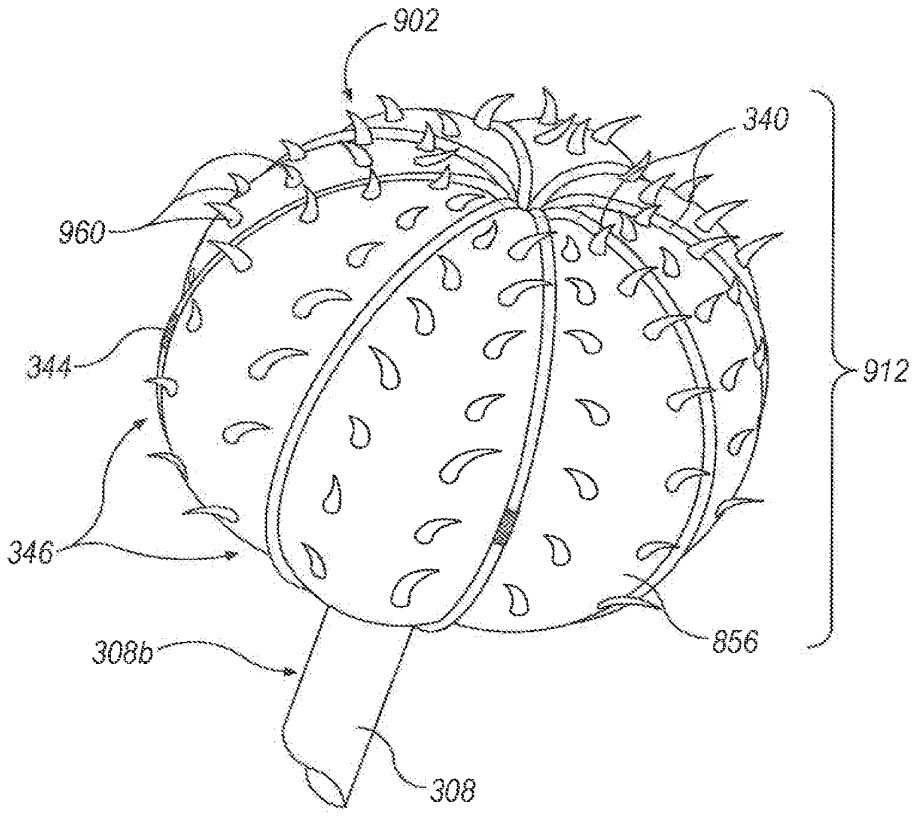


Fig. 9

BNSDOCID: <US_____20180133460A1_|_>

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
2 April 2015 (02.04.2015)

WIPO | PCT

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30 September 2014 (30.09.2014)

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61/884,547 30 September 2013 (30.09.2013) US
62/015,468 22 June 2014 (22.06.2014) US

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(72) Inventor: **SAADAT, Vahid**; 75 Barry Lane, Atherton, California 94027 (US).

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Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

[Continued on next page]

(54) **Title**: APPARATUS AND METHODS FOR TREATING RHINITIS

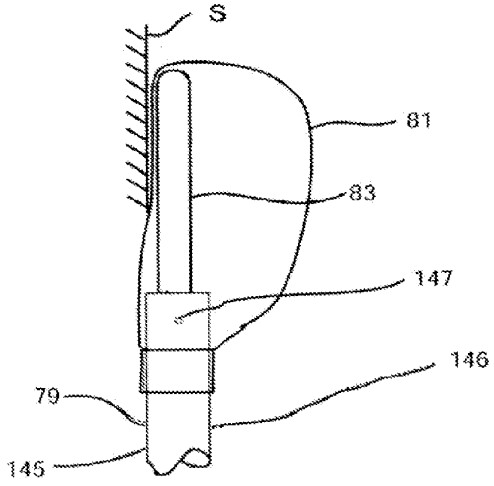


Figure 6H

(57) **Abstract**: Apparatus and methods for treating conditions such as rhinitis are disclosed herein where a distal end of a probe shaft is introduced through the nasal cavity where the distal end has an end effector with a first configuration having a low-profile which is shaped to manipulate tissue within the nasal cavity. The distal end may be positioned into proximity of a tissue region having a post nasal nerve associated with a middle or inferior nasal turbinate. Once suitably positioned, the distal end may be reconfigured from the first configuration to a second configuration which is shaped to contact and follow the tissue region and the post nasal nerve may then be ablated via the distal end. Ablation may be performed using various mechanisms, such as cryotherapy, and optionally under direct visualization.

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APPARATUS AND METHODS FOR TREATING RHINITIS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Patent Application No. 61/884,547 filed September 30, 2013 and 62/015,468 filed June 22, 2014, each of which is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

[0002] The present invention is related to devices and methods for ablating regions of tissue. More particularly, the present invention is related to devices and methods for ablating regions of tissue such as through cryogenic ablation of tissue regions within the nasal cavity for treating conditions such as rhinitis.

BACKGROUND OF THE INVENTION

[0003] The human nose is responsible for warming, humidifying and filtering inspired air. The nose is mainly formed of cartilage, bone, mucous membranes and skin. The right and left nasal cavities extend back to the soft palate, where they merge to form the posterior choanae. The posterior choanae opens into the nasopharynx. The roof of the nose is formed, in part, by a bone known as the cribriform plate. The cribriform plate contains numerous tiny perforations through which sensory nerve fibers extend to the olfactory bulbs. The sensation for smell occurs when inhaled odors contact a small area of mucosa in the superior region of the nose, stimulating the nerve fibers that lead to the olfactory bulbs.

[0004] The nasal turbinates are three bony processes that extend inwardly from the lateral walls of the nose and are covered with mucosal tissue. These turbinates serve to increase the inerior surface area of the nose and to impart warmth and moisture to air that is inhaled through the nose. The mucosal tissue that covers the turbinates is capable of becoming engorged with blood and swelling or becoming substantially devoid of blood and shrinking, in response to changes in physiologic or environmental conditions. The curved edge of each turbinate defines a passage way known as a meatus. For example, the inferior meatus is a passageway that passes beneath the inferior turbinate. Ducts, knows as the nasolacrimal ducts, drain tears from the eyes into the nose through openings located within the inferior meatus. The middle meatus is a passageway that extends inferior to the middle turbinate. The middle meatus contains the semilunar hiatus, with openings or Ostia leading

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into the maxillary, frontal, and anterior ethmoid sinuses. The superior meatus is located between the superior and medial turbinates.

[0005] The turbinates are autonomically innervated by nerves arising from the Vidian nerve which contains sympathetic and parasympathetic afferents that can modulate the function of the turbinates to either increase (parasympathetic) or decrease (sympathetic) activity of the submucosal layer. The pterygoid canal carries both parasympathetic and sympathetic fibers, namely the vidian nerve, to the sphenopalatine ganglion. Exclusive of the sphenopalatine foramen (SPF) contents, additional posterolateral neurovascular rami project from the sphinopaletine ganglion via multiple individual postganglionic rami to supply the nasal mucosa . The most common locations for these rami are within 1 cm posterosuperior to the horizontal attachment of the inferior turbinate, within 5 mm anteroinferior to this attachment, and the palatine bone via a foramen distinct from the SPF. Also, Blier, et.al showed that interfascicle anastomotic loops in some cases, are associated with at least 3 accessory nerves. Based on Blier et.al work each accessory nerve could be proximally traced directly to the PPG or greater palatine nerve.

[0006] Rhinitis is defined as inflammation of the membranes lining the nose, characterized by nasal symptoms, including itching, rhinorrhea, and/or nasal congestion. Chronic Rhinitis affects tens of millions of people in the US and is a leading cause for patients to seek medical care. Medical treatment has been shown to have limited effects for chronic rhinitis sufferers and requires daily medication use or onerous allergy treatments and up to 20% of patients may be refractory.

[0007] In addition to the medications turbinate reduction surgery (RF and micro-debridement) both have temporary duration of effect of 1-2 years and can result in complications including mucosal sloughing, acute pain and swelling, overtreatment and bone damage. Additionally, turbinate reduction does not treat the symptom of rhinorrhea. It is thought that parasympathetic effect of the vidian nerve predominates so that, on transecting it, the result is decreased rhinitis and congestion. This pathophysiology has been confirmed as surgical treatment of the vidian nerve has been tried with great success; however, the procedure is invasive, time consuming and potentially can result in dry eyes due to autonomic fibers in the vidian nerve that supply the lacrimal glands.

[0008] Golding-Wood, who recommended cutting the parasympathetic nerve fibers in the vidian canal to decrease the parasympathetic tone to the nasal mucosa, introduced a different approach for the treatment of hypersecretion in 1961. Various approaches to the

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vidian canal were subsequently developed, and the method was widely employed in the 1970s. However, the original technique was abandoned at the beginning of the 1980s because of its irreversible complications such as dry eyes.

[0009] Recent studies have shown that selectively interrupting the Post Nasal Nerves (PNN) in patients with chronic rhinitis improves their symptoms while avoiding the morbidities associated with vidian neurectomy.[1] The study by Ikeda et.al suggests that the effect of an anticholinergic drug on nasal symptoms resembled that of PNN resection in patients with chronic rhinitis. Based on his study the glandular mucosal acinar cells were significantly reduced after the PNN resection. The reduction in glandular cells may be explained by decreased secretion of the nerve growth factor or epidermal growth factor regulated by acetylcholine, a major neurotransmitter of parasympathetic systems.

[0010] Posterior nasal neurectomy, initially developed by Kikawada in 1998 and later modified by Kawamura and Kubo, is an alternative method in which neural bundles are selectively cut or cauterized from the sphenopalatine foramen. Autonomic and sensory nerve fibers that pass through the foramen anatomically branch into the middle and inferior turbinate and are distributed around the mucosal layer of the nose. Therefore, selective neurectomy at this point enables physicians to theoretically avoid surgical complications such as inhibition of lacrimal secretion.

SUMMARY OF THE INVENTION

[0011] The Posterior Nasal Nerves (PNN) innervate, inferior, middle, and inferior turbinates. Ablating these nerves leads to a decrease in or interruption of parasympathetic nerve signals that contribute to congestion and rhinorrhea in patients with chronic rhinitis (allergic or vasomotor). The devices and methods described herein are configured to be used for ablating one or more of these branches to reduce or eliminate rhinitis, e.g., ablating the Posterior Nasal Nerves (PNN).

[0012] Generally, several various apparatus and methods may be used to ablate the PNN as described below. One method for treating the tissue region within a nasal cavity in proximity to the PNN may be comprised of introducing a distal end of a probe shaft through the nasal cavity, wherein the distal end has an end effector with a first configuration having a low-profile which is shaped to manipulate tissue within the nasal cavity. The distal end may be positioned into proximity of the tissue region having the PNN associated with a middle or inferior nasal turbinate. Once suitably positioned, the distal end may be reconfigured from the first configuration to a second configuration,

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which is shaped to contact and follow the tissue region. The distal end may then be used to ablate the PNN within the tissue region utilizing a number of different tissue treatment mechanisms, e.g., cryotherapy, as described herein.

[0013] In treating the tissue region in one variation, the distal end may be positioned specifically into proximity of the tissue region which is surrounded by the middle nasal turbinate, inferior nasal turbinate, and lateral wall forming a cul-de-sac and having the PNN associated with the middle or inferior nasal turbinate. The distal end may be reconfigured to treat the tissue region accordingly.

[0014] Various configurations for the distal end may be utilized in treating the tissue region so long as the distal end is configured for placement within the narrowed confines of the nasal cavity and more specifically within the confines of the cul-de-sac defined by the tissue region surrounding the middle nasal turbinate, inferior nasal turbinate, and lateral nasal tissue wall.

[0015] One example of a surgical probe configured for ablating the tissue region within such narrowed confines includes a surgical probe apparatus having a surgical probe shaft comprising an elongated structure with a distal end and a proximal end, an expandable structure attached to the distal end of the probe shaft, the expandable structure having a deflated configuration and an expanded configuration. A lumen may be defined through the shaft in fluid communication with an interior of the expandable structure. A member may be attached to the distal end and extend within the expandable structure which encloses the member such that the member is unattached to the interior of the expandable structure. Moreover, the member may define an atraumatic shape, which is sized for pressing against and manipulating through the expandable structure the lateral nasal wall or other tissue proximate to the PNN.

[0016] An example of utilizing such a structure in treating the tissue region may generally comprise advancing the distal end of the surgical probe shaft through the nasal cavity and into proximity of the tissue region having PNN associated with a middle or inferior nasal turbinate and introducing a cryogenic fluid into the expandable structure attached to the distal end of the probe shaft such that the expandable structure inflates from a deflated configuration into an expanded configuration against the tissue region.

[0017] As described above, a position of the member relative to the tissue region may be adjusted where the member is attached to the distal end of the probe shaft and extends within the expandable structure, which encloses the member such that the member is unattached to an interior of the expandable structure. The practitioner may apply a

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pressure against the distal end such that the member is pressed against the interior of the expandable structure which in turn is pressed against the tissue region having the PNN, wherein the member defines an atraumatic shape which is sized for pressing against and manipulating the tissue region. The member may be maintained against the interior of the expandable structure and the tissue region until the tissue region is cryogenically ablated.

[0018] Any of the ablation devices herein can be used to ablate a single nerve branch or multiple nerve branches.

[0019] One aspect of this invention is a surgical probe configured for ablating the posterior nasal nerve associated with a nasal turbinate. The surgical probe, in one example, comprises a surgical shaft with a proximal end and a distal end, a surgical hand piece disposed on the proximal end, and a coiled spring-like structure disposed on the distal end. The coiled spring-like structure is a hollow structure comprising a closely pitched wire coil forming a central lumen, and an outer surface. The surgical hand piece comprises a pressurized liquid cryogen reservoir and a user actuated liquid cryogen flow control valve. There is at least one liquid cryogen path through the probe shaft in fluidic communication with the liquid flow control valve within the hand piece, and the spring-like coiled structure.

[0020] The pressurized cryogen liquid reservoir contains a liquid cryogen, e.g., nitrous oxide, but may also be another cryogenic liquid such as liquid carbon dioxide, or a liquid chlorofluorocarbon compound, etc. The distal spring-like structure may be configured as a liquid cryogen evaporator, either as a closed liquid cryogen evaporator, or as an open liquid cryogen evaporator.

[0021] In the closed evaporator configuration the inner central lumen of the spring-like structure is lined with a polymeric liner. Liquid cryogen is introduced into the central lumen through liquid cryogen supply line that is connected to the liquid cryogen reservoir in the handle, and runs coaxially through the probe shaft. The evaporated liquid cryogen may be vented to the room, e.g., through the probe shaft to a vent port in the hand piece, or in the vicinity of the proximal end of the probe shaft. No liquid or gas cryogen is introduced into the patient's nasal cavity.

[0022] In the open liquid cryogen evaporator configuration, the evaporated cryogen may exit the central lumen of the spring-like structure between the wire coils, and into the nasal cavity of the patient. Precautions to prevent the patient from inhaling the cryogen gas may be taken. As an example, a distal occlusion balloon may be used to occlude the distal nasal passageway.

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[0023] The surgical probe may be configured so that the surgeon can press the distal spring like structure against the lateral nasal wall proximate to the target posterior nasal nerve. The spring-like structure is configured to conform to the morphology of the lateral nasal wall and to evenly engage the lateral nasal wall with a substantially uniform contact pressure. The probe shaft may have a length between, e.g., approximately 4 cm and 10 cm, and a diameter between, e.g., approximately 1 mm and 4 mm. The distal spring-like structure may have an outer diameter that approximates the diameter of the probe shaft, or may be larger or smaller in diameter. The extended length of the spring-like structure may be between, e.g., approximately 0.5 cm and 1.5 cm.

[0024] The surgical probe may be supplied with the distal spring-like structure configured straight and coaxial with the probe shaft. In another embodiment, the distal spring like structure is supplied with a lateral curve with the proximal end of the spring-like structure in a tangential relationship with the distal end of the probe shaft. In another embodiment, the surgical probe may be supplied with the distal spring-like structure in a loop configuration where both ends of the spring-like structure are in a substantially tangential relationship with the distal end of the probe shaft.

[0025] The distal spring-like structure is substantially flexible along its axis; however, the structure may also be at least partly malleable and configured for form shaping by the user. Form shaping of the spring-like structure may be done manually by the surgeon, or alternatively the surgical probe may be supplied with the distal spring like structure in various predetermined/factory configurations. Various lengths, shapes, and diameters of the spring-like structure of the surgical probe may be produced and supplied to the end user.

[0026] In one embodiment, the distal spring-like structure is configured as a cryogenic liquid evaporator, where cryogenic liquid is delivered to the central lumen of the distal spring like structure. The liquid then evaporates at a low temperature, which causes the outer surface of the spring-like structure to reach a temperature that is sufficiently cold to ablate surrounding tissue and the function of the target posterior nasal nerve. The surgical probe may be configured so that the temperature of the outer surface of the spring-like structure is between -20 Deg. C. and -50 Deg. C. during liquid cryogen evaporation.

[0027] The surgical hand piece may comprise a factory filled liquid cryogen reservoir, and a user actuated cryogen flow control valve. The surgical hand piece may be configured so that it is held by the user like a pistol having a pistol grip where the cryogen flow valve actuator is configured like a pistol trigger. In an alternate embodiment, the

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surgical hand piece is configured for the surgeon to grip it substantially like a writing utensil, with a button located in the vicinity of the index finger configured to actuate the cryogen flow control valve. In a third embodiment, the surgical hand piece may be configured to be held by the surgeon substantially like a pistol or a writing utensil, with a pistol like trigger configured to actuate a cryogen flow control valve, and a button in the vicinity of the index finger configured to actuate the same or a second cryogen control valve.

[0028] In another embodiment of this invention, the distal spring-like structure is encompassed by an expandable membranous structure. The expandable membranous structure may be a hollow bulbous structure with a single ostium configured for pressure tight bonding to the distal end of the probe shaft. The expandable membranous structure may be configured as a liquid cryogen evaporation chamber. Liquid cryogen is introduced into the expandable membranous structure from the encompassed spring-like structure.

[0029] The evaporated cryogen may be exhausted into the room through the probe shaft to a vent port in the hand piece, or in the vicinity of the proximal end of the probe shaft. The surgical probe is configured so that the expandable membranous structure expands to a predetermined shape in response to liquid cryogen evaporation. The pressure within the expandable membranous structure during cryogen evaporation may be regulated. The regulation means may comprise a pressure relief valve disposed in the gas exhaust path. The expandable membranous structure may be formed from an elastomeric material such as silicone rubber, or a urethane rubber. Alternatively, the expandable membranous structure may be formed from a substantially non-elastomeric material such as polyurethane or PET. The expandable membranous structure is configured so the shape and the size of the structure matches the shape and the size of the cul-de-sac of the lateral nasal wall defined by the tail of the middle turbinate, lateral nasal wall and the inferior turbinate, which is the target location for the ablation of the posterior nasal nerves for the treatment of rhinitis. Matching the size and shape of the expandable membranous structure to the size and shape of the target anatomy facilitates optimal tissue freezing and ablation of posterior nasal nerves. The expandable membranous structure may have an expanded diameter between approximately 3 mm and 12 mm in one radial axis, and may be configured such that the expanded diameter in one radial axis is different than another radial axis.

[0030] The probe shaft may be straight and rigid, or alternatively may be substantially malleable and configured for form shaping by the user. The probe shaft may be straight and rigid in the proximal region, and substantially malleable in the distal region

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and configured for form shaping by the user.

[0031] The surgical probe may be configured with a camera and a light source disposed in the vicinity of the distal end of the probe shaft. The camera and light source may be configured to provide the surgeon with images of the nasal anatomy in order to identify anatomical landmarks for guiding the surgical placement of the distal spring-like structure against the lateral nasal wall proximate to the target posterior nasal nerve. The camera and light source may be further configured to image tissue freezing to provide the surgeon with visual feedback on the progress of a cryo-ablation of the nasal tissue innervated by posterior nasal nerves.

[0032] The surgical probe may also be configured with at least one temperature sensor disposed in the vicinity of the distal end. The temperature sensor may be configured to sense a temperature indicative of cryogen evaporation temperature, or a temperature indicative of a tissue temperature of surgical interest. Signals from the at least one temperature sensor may be used to servo-control the flow of cryogen in order to control a tissue temperature or to control the evaporation temperature. A temperature sensor may also be used in an informational display, or for system alarms or interlocks.

[0033] The surgical probe may be configured to automatically adjust the flow rate of liquid cryogen in response to one or more of the following parameters: evaporator temperature, evaporator pressure, tissue temperature, evaporator exhaust gas temperature, or elapsed cryogen flow time. The flow rate may be adjusted in a continuous analog manner, or by an alternating on/off flow modulation.

[0034] Another aspect of this invention is a method for treating rhinitis by ablating posterior nasal nerves associated with a middle or inferior nasal turbinate. The method may comprise inserting the distal end of a surgical probe configured for cryoneurolysis into a nostril of a patient with the surgical probe comprising a hollow probe shaft that is, e.g., substantially rigid. The surgical hand piece disposed on the proximal end of the probe shaft may comprise a liquid cryogen reservoir and, e.g., a user actuated liquid cryogen flow control valve. A cryogen liquid evaporator comprising, e.g., a spring-like structure configured as a liquid cryogen evaporator, may be disposed on the distal end of the probe shaft. The distal spring-like structure may be positioned against the lateral nasal wall proximate to a target posterior nasal nerve and then a flow of liquid cryogen to the spring-like structure may be activated for a period of time sufficient to cryo-ablate a target area in the nose containing posterior nasal nerves.

[0035] The method may further involve the targeting of at least one additional

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posterior nasal nerve, either within the ipsilateral nasal cavity, or a posterior nasal nerve in a contralateral nasal cavity.

[0036] The method may comprise the use of a surgical probe which has an expandable membranous or non-membranous structure that encompasses the distal spring-like structure and which is configured as an expandable liquid cryogen evaporation chamber. The expandable membranous structure may be configured to be a predetermined size and shape that matches the size and shape of the nasal wall anatomy proximate to the target posterior nasal nerve. The surgical probe may be configured so the expandable membranous structure expands to its predetermined size and shape in response to liquid cryogen evaporation within.

[0037] The method may comprise controlling the flow of the liquid cryogen into the evaporation chamber based on at least one predetermined parameter, which may comprise one or more of the following parameters: cryogenic liquid flow rate, cryogenic liquid flow elapsed time, cryogenic liquid evaporation pressure, cryogenic liquid evaporation temperature, cryogenic gas exhaust temperature, visual determination of tissue freezing, ultrasonic determination of tissue freezing, or the volume of cryogenic liquid supplied by the cryogenic liquid reservoir.

[0038] The method may comprise determining the location of the target posterior nasal nerve, which may involve one or more of the following targeting techniques: endoscopic determination based on the nasal anatomical landmarks, electrical neuro-stimulation of the target posterior nasal nerve while observing the physiological response to the stimulation, electrical neuro-blockade, while observing the physiological response to the blockade, or identification of the artery associated with the target posterior nasal nerve using, e.g., ultrasonic or optical doppler flow techniques.

[0039] Yet another aspect comprises an embodiment of a surgical probe which is configured for ablation where the surgical probe comprises a surgical probe shaft comprising an elongated structure with a distal end and a proximal end, an expandable structure attached to the distal end of the probe shaft, the expandable structure having a deflated configuration and an expanded configuration, a member attached to the distal end and extending within the expandable structure such that the member is unattached to an interior of the expandable structure, wherein the member defines a flattened shape which is sized for placement against a lateral nasal wall proximate to a posterior nasal nerve, and a lumen in fluid communication with the interior of the expandable structure.

[0040] In use, such a surgical probe may be used for treating a tissue region within

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a nasal cavity, generally comprising advancing a distal end of a surgical probe shaft through the nasal cavity and into proximity of the tissue region having a posterior nasal nerve associated with a middle or inferior nasal turbinate, introducing a cryogenic liquid into an expandable structure attached to the distal end of the probe shaft such that the expandable structure inflates from a deflated configuration into an expanded configuration against the tissue region, positioning a member relative to the tissue region, wherein the member is attached to the distal end of the probe shaft and extends within the expandable structure such that the member is unattached to an interior of the expandable structure, and wherein the member defines a flattened shape which is sized for placement against the tissue region proximate to the posterior nasal nerve, and maintaining the member against the tissue region until the posterior nasal nerve is cryogenically ablated.

[0041] One aspect of the invention is a cryo-surgical probe apparatus for ablation of PNN function comprising a handle at the proximal end, a probe shaft with a spatula shaped cryo-ablation element mounted in vicinity of the distal end of the shaft, whereby the handle is configured for housing a cryogen source, and controlling the flow of the cryogen to the cryo-ablation element, and the geometric parameters of the probe shaft and cryo-ablation element are optimally configured for cryo-ablation of nasal mucosa containing PNN according to the surgical methods disclosed here within.

[0042] One embodiment of this invention is a cryo-surgical probe apparatus for ablation of nasal mucosa innervated by PNN comprise a handle at the proximal end, a probe shaft with a bullet shaped cryo-ablation element mounted in vicinity of the distal end of the shaft, whereby the handle is configured for housing a cryogen source, and controlling the flow of the cryogen to the cryo-ablation element, and the geometric parameters of the probe shaft and cryo-ablation element are optimally configured for cryo-ablation of PNN according to the surgical methods disclosed here within.

[0043] Another embodiment of this invention is a cryo-surgical probe apparatus for ablation of PNN function comprising a handle at the proximal end, a probe shaft with a bullet shaped cryo-ablation element mounted in vicinity of the distal end of the shaft, whereby the handle is configured for housing a cryogen source, and controlling the flow of the cryogen to the cryo-ablation element, wherein the probe shaft is configured with user operable deflectable distal segment, and the geometric parameters of the probe shaft and cryo-ablation element are optimally configured for cryo-ablation of PNN according to the surgical methods disclosed here within.

[0044] Another embodiment of this invention is a cryo-surgical probe apparatus for

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ablation of PNN comprising a handle at the proximal end, a probe shaft with a cylindrically shaped cryo-ablation element mounted in vicinity of the distal end of the shaft, whereby the handle is configured for housing a cryogen source, and controlling the flow of the cryogen to the cryo-ablation element, wherein the cryo-ablation element comprises a linear segmented cryo-ablation element, and the geometric parameters of the probe shaft and cryo-ablation element are optimally configured for cryo-ablation of PNN according to the surgical methods disclosed here within.

[0045] Another embodiment of this invention is a cryo-surgical probe apparatus for ablation of PNN comprising a handle at the proximal end, a probe shaft with a cylindrically shaped cryo-ablation element mounted in vicinity of the distal end of the shaft, whereby the handle is configured for housing a cryogen source, and controlling the flow of the cryogen to the cryo-ablation element, wherein the cryo-ablation element comprises a semi-circular cryo-ablation element, and the geometric parameters of the probe shaft and cryo-ablation element are optimally configured for cryo-ablation of target tissue containing PNN according to the surgical methods disclosed here within.

[0046] Another embodiment of this invention is a cryo-surgical probe apparatus for ablation of PNN function comprising a handle at the proximal end, a probe shaft with a cylindrically shaped cryo-ablation element mounted in vicinity of the distal end of the shaft, whereby the handle is configured for housing a cryogen source, and controlling the flow of the cryogen to the cryo-ablation element, wherein the cryo-ablation element comprises a spiraled cryo-ablation element, and the geometric parameters of the probe shaft and cryo-ablation element are optimally configured for cryo-ablation of target nasal tissue containing PNN according to the surgical methods disclosed here within.

[0047] Another embodiment of this invention is a cryo-surgical probe apparatus for ablation of PNN comprising a proximal end, a probe shaft with a cryo-ablation element comprising a balloon mounted in vicinity of the distal end of the shaft, whereby the proximal end is configured for receiving a cryogen from a cryogen source with the cryogen source comprising a means controlling the flow of the cryogen to the cryo-ablation element, and the geometric parameters of the probe shaft and cryo-ablation element are optimally configured for cryo-ablation of PNN according to the surgical methods disclosed here within.

[0048] Another embodiment of this invention is a cryo-surgical probe apparatus for ablation of PNN comprising a handle at the proximal end, a probe shaft with a cylindrically shaped cryo-ablation element comprising a balloon mounted in vicinity of the distal end of

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the shaft, whereby the handle is configured for housing a cryogen source, and controlling the flow of the cryogen to the cryo- ablation element, and the geometric parameters of the probe shaft and cryo-ablation element are optimally configured for cryo-ablation of target nasal tissue containing PNN according to the surgical methods disclosed here within.

[0049] Another embodiment of this invention is a cryo-surgical probe apparatus for ablation of PNN comprising a handle at the proximal end, a probe shaft with a cylindrically shaped cryo-ablation element mounted comprising a balloon with two lateral chambers disposed in the vicinity of the distal end of the shaft, whereby the handle is configured for housing a cryogen source, and controlling the flow of the cryogen to the cryo-ablation element, wherein one chamber of the balloon is configured as a cryogen expansion chamber, and the second chamber is configured as a thermal insulation chamber, and the geometric parameters of the probe shaft and cryo-ablation element are optimally configured for cryo-ablation of PNN according to the surgical methods disclosed here within.

[0050] Another embodiment of this invention is a cryo-surgical probe apparatus for ablation of PNN comprising a handle at the proximal end, a probe shaft with a "T" shaped cryo-ablation element comprising a balloon mounted in vicinity of the distal end of the shaft, whereby the handle is configured for housing a cryogen source, and controlling the flow of the cryogen to the cryo-ablation element, and the geometric parameters of the probe shaft and cryo-ablation element are optimally configured for cryo-ablation of PNN according to the surgical methods disclosed here within.

[0051] Another embodiment of this invention is a cryo-surgical probe apparatus for ablation of PNN function comprising a handle at the proximal end, a probe shaft with a "J" shaped cryo-ablation element comprising a balloon mounted in vicinity of the distal end of the shaft, whereby the handle is configured for housing a cryogen source, and controlling the flow of the cryogen to the cryo-ablation element, and the geometric parameters of the probe shaft and cryo-ablation element are optimally configured for cryo-ablation of PNN according to the surgical methods disclosed here within.

[0052] Another embodiment of this invention is a cryo-surgical probe apparatus for ablation of PNN comprising a handle at the proximal end, a probe shaft with a cryo-ablation element mounted in vicinity of the distal end of the shaft, whereby the handle is configured for housing a cryogen source, and controlling the flow of the cryogen to the cryo-ablation element, wherein a suction means associated with the cryo-ablation element is configured for stabilizing the position of the cryo-ablation element against the target

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tissue, and the geometric parameters of the probe shaft and cryo-ablation element are optimally configured for cryo-ablation of PNN according to the surgical methods disclosed here within.

[0053] One aspect of this is a method for cryo-surgical ablation of PNN comprising placing a film of oil or gel on the surface of a cryo-ablation element, then pressing the cryo-ablation element against the lateral wall of a nasal cavity adjacent to a PNN, then ablating the function of the PNN with the cryo-ablation element, whereby the oil or gel prevents frozen nasal tissue from adhering to the cryo-ablation element.

[0054] In another aspect of this invention is an electrosurgical probe apparatus for ablation of PNN comprising a handle at the proximal end, a probe shaft with a radiofrequency (RF) ablation element comprising at least one radiofrequency (RF) electrode mounted in the vicinity of the distal end of the shaft, an electrical connector in the vicinity of the handle configured to connect the RF ablation element to a source of radiofrequency energy, whereby the geometric parameters of the probe shaft and RF ablation element are optimally configured for RF ablation of PNN function according to the surgical methods disclosed here within.

[0055] One embodiment of this invention is an electrosurgical probe apparatus for ablation of PNN comprising a handle at the proximal end, a probe shaft with a radiofrequency (RF) ablation element comprising at least one radiofrequency (RF) electrode mounted in the vicinity of the distal end of the shaft, an electrical connector disposed in the vicinity of the handle configured to connect the RF ablation element to a source of radiofrequency energy, and a fluid connector disposed in the vicinity of the handle to connect at least one fluid port associated with the RF ablation element with a source of pressurized liquid, whereby the geometric parameters of the probe shaft and RF ablation element are optimally configured for RF ablation of PNN according to the surgical methods disclosed here within.

[0056] Another embodiment of this invention is an electrosurgical probe apparatus for ablation of PNN comprising a handle at the proximal end, a probe shaft with a radiofrequency (RF) ablation element comprising at least one radiofrequency (RF) electrode mounted in the vicinity of the distal end of the shaft, an electrical connector disposed in the vicinity of the handle configured to connect the RF ablation element to a source of radiofrequency energy, whereby the geometric parameters of the probe shaft and RF ablation element are optimally configured for RF ablation of PNN according to the surgical methods disclosed here within, wherein the RF ablation element comprises a

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monopolar electrosurgical configuration comprising one or more electrodes.

[0057] Another embodiment of this invention is an electrosurgical probe apparatus for ablation of PNN comprising a handle at the proximal end, a probe shaft with a radiofrequency (RF) ablation element comprising at least one radiofrequency (RF) electrode mounted in the vicinity of the distal end of the shaft, an electrical connector disposed in the vicinity of the handle configured to connect the RF ablation element to a source of radiofrequency energy, whereby the geometric parameters of the probe shaft and RF ablation element are optimally configured for RF ablation of PNN according to the surgical methods disclosed here within, wherein the RF ablation element comprises a bi-polar electrosurgical configuration comprising two or more electrodes.

[0058] Another embodiment of this invention is an electrosurgical probe apparatus for ablation of PNN comprising a handle at the proximal end, a probe shaft with a radiofrequency (RF) ablation element comprising at least one radiofrequency (RF) electrode mounted in the vicinity of the distal end of the shaft, an electrical connector disposed in the vicinity of the handle configured to connect the RF ablation element to a source of radiofrequency energy, whereby the geometric parameters of the probe shaft and RF ablation element are optimally configured for RF ablation of PNN according to the surgical methods disclosed here within, wherein the RF ablation element is disposed in the vicinity of the distal end of the shaft on a cylindrical, "J" shaped, "U" shaped or "T" shaped structure.

[0059] Another embodiment of this invention is an electrosurgical probe apparatus for ablation of PNN function comprising a handle at the proximal end, a probe shaft with a radiofrequency (RF) ablation element comprising at least one radiofrequency (RF) electrode mounted in the vicinity of the distal end of the shaft, an electrical connector disposed in the vicinity of the handle configured to connect the RF ablation element to a source of radiofrequency energy, whereby the geometric parameters of the probe shaft and RF ablation element are optimally configured for RF ablation of PNN according to the surgical methods disclosed here within, wherein the RF ablation element is configured in a lateral or radial arrangement.

[0060] Another embodiment of this invention is n electrosurgical probe apparatus for ablation of PNN function comprising a handle at the proximal end, a probe shaft with a radiofrequency (RF) ablation element comprising at least one radiofrequency (RF) electrode mounted in the vicinity of the distal end of the shaft, an electrical connector disposed in the vicinity of the handle configured to connect the RF ablation element to a

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source of radiofrequency energy, whereby the geometric parameters of the probe shaft and RF ablation element are optimally configured for RF ablation of PNN according to the surgical methods disclosed here within, wherein the RF ablation element comprises a circular array of domed electrodes disposed on a flat electrically insulative surface, with the domed electrodes optionally associated with a fluid irrigation port.

[0061] Another embodiment of this invention is an electrosurgical probe for ablation of PNN function comprising a handle at the proximal end, a probe shaft with a radiofrequency (RF) ablation element comprising at least one radiofrequency (RF) electrode mounted in the vicinity of the distal end of the shaft, an electrical connector disposed in the vicinity of the handle configured to connect the RF ablation element to a source of radiofrequency energy, whereby the geometric parameters of the probe shaft and RF ablation element are optimally configured for RF ablation of PNN according to the surgical methods disclosed here within, wherein the RF ablation element comprises a linear array of domed electrodes disposed on a flat electrically insulative surface, with the domed electrodes optionally associated with a fluid irrigation port, and a needle configured for injecting a liquid into a sub-mucosal space.

[0062] Another embodiment of this invention is an electrosurgical probe apparatus for ablation of PNN comprising a handle at the proximal end, a probe shaft with a radiofrequency (RF) ablation element comprising at least one radiofrequency (RF) electrode mounted in the vicinity of the distal end of the shaft, an electrical connector disposed in the vicinity of the handle configured to connect the RF ablation element to a source of radiofrequency energy, whereby the geometric parameters of the probe shaft and RF ablation element are optimally configured for RF ablation of PNN according to the surgical methods disclosed here within, wherein the RF ablation element comprises at least one needle configured for interstitial RF ablation.

[0063] Another embodiment of this invention is an electrosurgical probe apparatus for ablation of PNN comprising a handle at the proximal end, a probe shaft comprising a distal and proximal end, and an integrated circuit comprising an RF generator disposed in the vicinity of the handle and an RF ablation element disposed in the vicinity of the distal end of the shaft, whereby the geometric parameters of the probe shaft and RF ablation element are optimally configured for RF ablation of PNN according to the surgical methods disclosed here within.

[0064] In another aspect of this invention is an ultrasonic energy emitting probe apparatus for ablation of PNN comprising a handle at the proximal end, a probe shaft with

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an ultrasonic energy ablation element comprising at least one ultrasonic energy emitter mounted in the vicinity of the distal end of the shaft, an electrical connector in the vicinity of the handle configured to connect the ultrasonic energy emitter to an ultrasonic energy generator, whereby the geometric parameters of the probe shaft and ultrasonic energy emitter are optimally configured for ultrasonic energy ablation of PNN according to the surgical methods disclosed here within.

[0065] In another embodiment of this invention is an ultrasonic energy emitting probe apparatus for ablation of PNN comprising a handle at the proximal end, a probe shaft with an ultrasonic energy ablation element comprising at least one ultrasonic energy emitter mounted in the vicinity of the distal end of the shaft, an electrical connector in the vicinity of the handle configured to connect the ultrasonic energy emitter to an ultrasonic energy generator; at least one fluid path in communication between at least one fluid connector in the vicinity of the handle and the ultrasonic energy emitter configured to cool the ultrasonic energy emitter during ultrasonic energy emission, whereby the geometric parameters of the probe shaft and ultrasonic energy emitter are optimally configured for ultrasonic energy ablation of PNN according to the surgical methods disclosed here within.

BRIEF DESCRIPTION OF THE DRAWINGS

[0066] Figure 1 is an internal lateral view of the nasal canal showing the relevant nasal anatomy and the targeted region of the lateral nasal wall for cryo-ablation of posterior nasal nerve function.

[0067] Figure 2 is a schematic illustration of a surgical probe configured for cryo-ablation of posterior nasal nerve function for the treatment of rhinitis.

[0068] Figure 3A is a view of the distal end of a surgical probe shaft with the spring-like structure coaxial to the surgical probe shaft.

[0069] Figure 3B is a view of the distal end of a surgical probe shaft with the spring-like structure comprising a lateral curve in a tangential relationship with the surgical probe shaft.

[0070] Figure 3C is a view of the distal end of a surgical probe shaft with the spring-like structure comprising a loop or a continuous structure.

[0071] Figure 4A is a side view of the distal end of the surgical probe shaft with the spring-like structure coaxial to the surgical probe shaft encompassed by an expandable membranous structure in an unexpanded state.

[0072] Figure 4B is a view of the distal end of the surgical probe shaft with the

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spring-like structure coaxial to the surgical probe shaft encompassed by an expandable membranous structure in an expanded state.

[0073] Figure 5A is a side view of the distal end of a surgical probe shaft with the spring-like structure comprising a lateral curve in a tangential relationship with the surgical probe shaft encompassed by an expandable membranous structure in an unexpanded state.

[0074] Figure 5B is a view of the distal end of the surgical probe shaft with the spring-like structure comprising a lateral curve in a tangential relationship with the surgical probe shaft encompassed by an expandable membranous structure in an expanded state.

[0075] Figure 5C is a side view that is 90 degrees from the first side view of Figure 5A.

[0076] Figure 5D is a view that is 90 degrees from the first side view of Figure 5B.

[0077] Figure 6A is a view of the distal end of a surgical probe shaft with the spring-like structure comprising a loop encompassed by an expandable membranous structure in an unexpanded state.

[0078] Figure 6B is a view of the distal end of the surgical probe shaft with the spring-like structure comprising a loop encompassed by an expandable membranous structure in an expanded state.

[0079] Figure 6C is a view that is 90 degrees from the first side view of Figure 6A.

[0080] Figure 6D is a view that is 90 degrees from the first side view of Figure 6B.

[0081] Figure 6E is a view of the distal end of a surgical probe shaft with the structure comprising a continuous member encompassed by a non-distensible structure.

[0082] Figure 6F is a view that is 90 degrees from the first side view of Figure 6E.

[0083] Figure 6G is a view of the embodiment of Figure 6E when pressed longitudinally against a tissue region for treatment.

[0084] Figure 6H is a view of the embodiment of Figure 6E when pressed laterally against a tissue region for treatment.

[0085] Figure 7 is a cross sectional schematic view of the distal end of a surgical probe where the spring-like structure is configured as a closed cryogenic liquid evaporator.

[0086] Figure 8 is a cross sectional schematic view of the distal end of a surgical probe where the spring-like structure is encompassed by an expandable membranous structure with the membranous structure configured as a liquid cryogen evaporation chamber.

[0087] Figure 9 is an internal lateral view of the nasal canal showing a surgical probe with the spring-like structure pressed against a lateral nasal wall in position for a

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cryo-ablation of a posterior nasal nerve function.

[0088] Figure 10A is a front view illustration the distal end of a paddle balloon ablation probe with its expandable structure in its un-expanded state. Figure 10B is a side view illustration of Figure 10A. Figure 10C is a front view illustration of the distal end of a paddle balloon ablation probe with its expandable structure in its expanded state. Figure 10D is a side view illustration of Figure 10C.

[0089] Figure 11A is a front view illustration of the distal end of a paddle porous balloon ablation probe. Figure 11B is a side view illustration of Figure 11A.

[0090] Figure 12A is a front view illustration the distal end of a paddle double balloon ablation probe with its expandable structure in its un-expanded state. Figure 12B is a side view illustration of Figure 12A. Figure 12C is a front view illustration of the distal end of a paddle double balloon ablation probe with its expandable structure in its expanded state. Figure 12D is a side view illustration of Figure 12C.

[0091] Figure 13A through 13D are schematic sectional coronal illustrations of a nasal cavity depicting the surgical access to a middle meatus and cryogenic ablation of a sphenopalatine brand and foramen.

[0092] Figure 14A is an internal lateral view of the nasal cavity showing an anatomical target for ablation of parasympathetic nervous function of the middle turbinate. Figure 14B is an internal lateral view of the nasal cavity showing an anatomical target for ablation of posterior nasal nerves. Figure 14C is an internal lateral view of the nasal cavity showing an anatomical target for ablation of posterior nasal nerves using an intermittent line of ablation. Figure 14D is an internal lateral view of the nasal cavity showing an anatomical target for ablation of posterior nasal nerves.

[0093] Figure 15A is a schematic illustration of a cryosurgical probe configured for cryo-ablation of posterior nasal nerves comprising a spatula shaped cryosurgical tip. Figure 15B defines a section view of the cryosurgical probe's cryosurgical tip. Figure 15C is a cross sectional view of the cryosurgical probe's tip.

[0094] Figure 16A is a schematic illustration of the distal end of an alternative embodiment of the cryosurgical probe comprising a bullet shaped cryo-ablation element at the distal end of an angled shaft. Figure 16B is a schematic illustration of the distal end of an alternative embodiment of the cryosurgical probe comprising a bullet shaped cryo-ablation element at the distal end of a user deflectable probe shaft. Figure 16C is a schematic illustration of the distal end of an alternative embodiment of the cryosurgical probe where the cryo-ablation element is configured for producing multiple discrete cryo-

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ablations simultaneously.

[0095] Figure 17A is a schematic illustration of the distal end of an alternative embodiment of the cryosurgical probe comprising a semi-circular cryo-ablation element. Figure 17B is a schematic illustration of the ablation morphology resulting from use of the semi-circular cryo-ablation element. Figure 17C is a schematic illustration of the distal end of an alternative embodiment of the cryosurgical probe comprising a spiraled cryo-ablation element.

[0096] Figure 18A is a schematic illustration of cryo-ablation balloon probe configured for cryo-ablation of posterior nasal nerves. Figure 18B is a schematic illustration of the distal end of the cryo-ablation balloon probe detailing the geometry of the cryo-ablation balloon. Figure 18C is a schematic illustration of an alternate embodiment of the cryo-ablation balloon probe comprising an insulating chamber within the cryo balloon structure. Figure 18D is a schematic illustration of the distal end of an alternative embodiment of the cryo-ablation balloon probe comprising a tee shaped cryo-ablation balloon. Figure 18E is a schematic illustration of the distal end of an alternative embodiment of the cryo-ablation balloon probe comprising a "J" shaped cryo-ablation balloon.

[0097] Figure 19A is a schematic illustration of the distal end of an alternate embodiment a cryo-ablation probe comprising a cryo-ablation element with suction stabilization. Figure 19B is a cross sectional view of the distal end of the alternative embodiment showing the configuration of the cryo-ablation element and the suction stabilization means.

[0098] Figure 20A is a schematic illustration of a radiofrequency (RF) ablation probe configured for ablation of the posterior nasal nerves with a bi-polar ring electrode ablation element on an "J" shaped distal probe shaft. Figure 20B is a schematic illustration of the distal end of an alternative embodiment of an RF ablation probe comprising a bi-polar ring electrode ablation element on an "J" shaped distal probe shaft. Figure 20C is a schematic illustration of an alternative embodiment of the distal end of an RF ablation probe comprising a bi-polar electrode ablation element on an "J" shaped distal probe shaft with the electrodes disposed in a lateral array. Figure 20D is a schematic illustration of an alternative embodiment of the distal end of an RF ablation probe comprising a bi-polar electrode ablation element on a "U" shaped distal probe shaft with the electrodes disposed in a lateral array. Figure 20E is a schematic illustration of the distal end of an alternative embodiment of an RF ablation probe comprising a bi-polar electrode ablation element on a

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user deployable "T" shaped structure.

[0099] Figure 21A is a schematic illustration of an RF ablation probe configured for ablation of posterior nasal nerves comprising an array of RF ablation electrodes disposed on a planar surface and a fluid irrigation means associated with the electrodes. Figure 21B is a schematic illustration of the distal end of the RF ablation probe showing the arrangement of the ablation electrodes and the associated fluid irrigation means.

[0100] Figure 22A is a schematic illustration of an alternative RF ablation probe comprising an electrode array disposed on a planar surface; a fluid irrigation means associated electrodes, and a deployable needle configured for injecting a liquid into a sub-mucosal space. Figure 22B is a schematic illustration of the distal end of the alternative embodiment RF ablation probe showing the arrangement of the ablation electrodes and the associated fluid irrigation means. Figure 22C is a schematic illustration of the distal end of the alternative embodiment RF ablation probe showing the arrangement of the ablation electrodes and the associated fluid irrigation means with the needle deployed.

[0101] Figure 23A is a schematic illustration of an RF interstitial needle ablation probe configured for interstitial ablation of the parasympathetic nervous function of a nasal turbinate(s). Figure 23B is a schematic illustration of the distal end of the RF interstitial needle ablation probe.

[0102] Figure 24A is a cross sectional view of the distal end of an RF interstitial needle ablation comprising a deployable and retractable array of RF ablation needles configured for lateral deployment showing the needle array retracted. Figure 24B is a cross sectional view of the distal end of an RF interstitial needle ablation comprising a deployable and retractable array of RF ablation needles configured for lateral deployment showing the needle array deployed. Figure 24C is a cross sectional view of the distal end of an RF interstitial needle ablation comprising a deployable and retractable array of RF ablation needles configured for axial deployment showing the needle array retracted. Figure 24D is a cross sectional view of the distal end of an RF interstitial needle ablation comprising a deployable and retractable array of RF ablation needles configured for axial deployment showing the needle array deployed.

[0103] Figure 25A is a schematic illustration of an integrated flexible circuit configured for use with an RF ablation probe comprising an RF energy source and control circuits at one end, and an RF ablation electrode array at the opposite end. Figure 25B is a schematic illustration of the RF ablation electrode array of the flexible circuit mounted on the distal shaft of an RF ablation probe that is configured for ablation of posterior nasal

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nerves.

[0104] Figure 26A is an in situ schematic illustration of the RF ablation probe depicted in Figures 22A through 22C showing the needle injecting an anesthetic into the sub-mucosal space prior to an RF ablation of posterior nasal nerves. Figure 26B is an in situ schematic illustration of the resulting ablation.

[0105] Figure 27 is an in situ schematic illustration of an ablation of posterior nasal nerves using the RF interstitial needle ablation probe depicted in Figures 23A and 23B.

[0106] Figure 28 is an in situ illustration of the ablation of the posterior nasal nerves at the ablation target depicted in Figure 14D.

[0107] Figure 29 is an in situ illustration of the ablation of the posterior nasal nerves at the ablation target depicted in Figure 24A.

[0108] Figure 30 is an in situ illustration of the ablation of the posterior nasal nerves at the ablation target area depicted in Figure 14B.

[0109] Figure 31A is a schematic illustration of the ablation probe and an insulated probe guide configured to protect the nasal septum from thermal injury during an ablation of the posterior nasal nerves. Figure 31B is an in situ illustration of an ablation probe configured for ablation of the posterior nasal nerves which comprises an insulating structure configured to protect the nasal septum. Figure 31C is an in situ illustration of an ablation probe configured for ablation of the parasympathetic nervous function of posterior nasal nerves which comprises a space creating structure configured to protect the nasal septum.

DETAILED DESCRIPTION OF THE INVENTION

[0110] Figure 1 is an internal view of the nasal cavity showing the relevant nasal anatomy. Shown for orientation is the lateral nasal cavity wall 4, the nose 1, nostril 2, and the upper lip 3. The superior turbinate 5, middle turbinate 6, and inferior turbinate 7 are depicted along with the associated nerves relevant to this invention shown in dashed lines. The posterior nasal nerves 10,11 and 12 are responsible for the parasympathetic control of the nasal mucosa including turbinates. These posterior nasal nerves (PNNs) originate from the sphenopalatine ganglion. At times other accessory posterior nasal nerves (APNNs) may originate from the greater palatine nerve or from the bony plate underneath the mucosa.

[0111] Figure 2 is a schematic illustration of surgical probe 29, which is configured for cryo-ablation of posterior nasal nerve function for the treatment of rhinitis. Surgical probe 29 comprises: probe shaft 20, with shaft distal end 21 and shaft proximal end 27; surgical hand piece 23, e.g., with pistol grip 24, finger grip 25, pistol trigger flow control

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valve actuator 26, button flow control flow valve actuator 22, finger grip barrel 28, cryogen reservoir housing 29; and distal end effector 30 (e.g., spring-like structure) with end effector proximal end 31, and end effector distal end 32. Surgical probe shaft 20 is between, e.g., approximately 1 mm and 4 mm in diameter, and between, e.g., approximately 4 cm and 10 cm in length. Surgical probe shaft 20 may be fabricated from various biocompatible materials such as a surgical grade stainless steel hypodermic tube, or may alternatively be fabricated from a polymeric extrusion. Surgical probe shaft 20 comprises at least one liquid cryogen delivery channel between shaft distal end 21 and shaft proximal end 27. Probe shaft 20 is substantially rigid in one variation, and may also be configured to be malleable and shape formable by the user. The distal end effector 30 is shown having multiple variations described herein and may be optionally interchanged depending upon which particular embodiment is utilized by a practitioner.

[0112] Although probe shaft 20 is depicted to be straight, it is well within the scope of this invention probe shaft 20 may be manufactured with at least one curved segment. Surgical hand piece 23 is disposed on the proximal end 22 of probe shaft 20. Surgical hand piece 23 comprises a liquid cryogen reservoir, not shown, that may be conventionally supplied with liquid cryogen and configured for a single patient use. Alternatively, surgical hand piece 23 may be configured for use with a user replaceable liquid cryogen reservoir in the form of a cartridge. Liquid cryogen cartridges are readily commercially available from many sources. In yet another alternative, a reservoir separate from the device may be fluidly coupled to the hand piece 23. Surgical hand piece 23 may further comprise a liquid cryogen flow control valve, not shown, that may be disposed in fluidic communication with the liquid cryogen reservoir and the liquid cryogen channel in probe shaft 20.

[0113] Surgical device 29 may be configured to be held like a pistol by the surgeon or practitioner using pistol grip 24, or the surgeon or practitioner may hold surgical device 29 like a writing utensil using finger grips 25, with finger grip barrel 28 residing between the thumb and index finger of the surgeon. Surgical device 29 may be configured with, e.g., two or more liquid cryogen flow control valve actuators comprising pistol trigger liquid cryogen flow control actuator 26, which may be used to control the flow of liquid cryogen when the surgeon holds surgical device 29 using pistol grip 24. Liquid cryogen flow control actuator button 22 may be used to control the flow of liquid cryogen when the surgeon holds surgical device 29 by finger grips 25. Probe shaft 20 may be configured to be rotatably coupled to the surgical device 29 to facilitate positioning of distal end effector 30 (e.g., spring–like structure) without having to rotate the surgical device 29 excessively.

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Distal end effector 30 (e.g., spring–like structure) , with end effector proximal end 31, and end effector distal end 32 is disposed on the distal end 21 of probe shaft 20 as shown. Distal end effector 30 (e.g., spring–like structure) is configured as a liquid cryogen evaporator, and is configured to be pressed against the lateral nasal wall within the cul-de-sac described above for cryo-ablation of at least one posterior nasal nerve. The construction and the function of distal end effector 30 (e.g., spring–like structure) , and alternative embodiments are described in detail below.

[0114] Surgical device 29 may be configured as a simple mechanical device that is void of electronics as shown. Alternatively, surgical device 29 may be configured with at least one electronic function. In one embodiment, a temperature sensor may be disposed in the vicinity of distal end effector 30 (e.g., spring–like structure) and used to measure, display, or control a temperature of surgical interest. A temperature sensor may be configured to sense the temperature of evaporating cryogen within distal end effector 30 (e.g., spring–like structure) . A temperature sensor may also be configured to sense the temperature of a tissue of surgical interest. The liquid cryogen control valve 22 may also optionally comprise a servo mechanism configured to respond to a sensed temperature to modulate the flow of cryogen in order to control a desired surgical parameter.

[0115] In addition to a temperature sensing capability, surgical device 29 may be configured with a camera and/or a light source disposed in the vicinity of distal end 21 of probe shaft 20. The camera and light source may be used, e.g., to identify nasal anatomical landmarks, and may be used to guide the placement of distal end effector 30 (e.g., spring–like structure) against the lateral nasal wall for a cryo-ablation of the function of a target posterior nasal nerve. An ultrasonic or optical doppler flow sensor may also be disposed in the vicinity of distal end 21 of probe shaft 20 and be used, e.g., to locate the major artery associated with the target posterior nasal nerve, as a means for locating the target posterior nasal nerve. In addition, one or more electrodes may be disposed in the vicinity of distal end 21 of probe shaft 20, which may be used for electrical stimulation or electrical blockade of the function of a target posterior nasal nerve using the observed physiological response to the stimulation or blockade to confirm correct surgical positioning of distal end effector 30 (e.g., spring–like structure) prior to a cryo-ablation, and/or to confirm effectiveness of a cryo-ablation by the determination of a change in the physiological response from before and after a cryo-ablation.

[0116] Any number of temperature sensing, endoscopic instruments, servo controlled cryogen control valves, ultrasonic or optical doppler flow detection, and/or

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electrical nervous stimulation and blockade mechanisms may be optionally incorporated into the devices described herein. Also, providing a surgical probe as described here with a liquid cryogen reservoir that is external to the probe hand piece is also within the scope of this invention.

[0117] Figure 3A is a schematic illustration of an alternative end effector embodiment, which comprises spring-like structure 39 which is configured in a coaxial arrangement with probe shaft 20. Figure 3B is a schematic illustration of the distal end of an alternative embodiment surgical probe 43 which comprises spring-like structure 44, which is configured with a lateral curve as shown with proximal end 46 in a tangential relationship with the distal end 21 of probe shaft 20. Figure 3C is a schematic illustration of the distal end of an alternative embodiment surgical probe 48, with spring-like structure 49 configured as a loop structure as shown, with both ends of spring-like structure 49 in a substantially tangential relationship with distal end 21 of probe shaft 20. The three alternate spring-like structure embodiments 39, 44, and 49 depicted in Figures 3A, 3B, and 3C are configured as liquid cryogen evaporators, where the outer surface of each spring-like structure may achieve a temperature between, e.g., approximately -20 Deg. C to -90 Deg. C., in response to liquid cryogen evaporation within. As previously described, the end effector described here may be optionally replaced by any of the other end effector embodiments described herein.

[0118] Spring-like structures 39, 44, and 49 are substantially flexible and are configured to conform to the morphology of a lateral nasal wall proximate to a target posterior nasal nerve with a substantially uniform contact pressure. Spring-like structures 39, 44, and 49 may be configured to be partially malleable and form shapeable by the user, while retaining a spring-like resilience during use. Spring-like structures 39 and 44 comprise distal end 40 and 45 respectively, and proximal end 41 and 46 respectively. Spring-like structures 39 and 44 comprise end cap 38, which functions as a pressure bulkhead defining the distal end of the liquid cryogen evaporator that resides within, which is described in detail below. Spring-like structures 39, 44, and 49 comprise a tightly coiled wire that forms a central chamber, and an outer surface. A thin polymeric liner is disposed on the inner surface of the central chamber and functions to contain the evaporating cryogen within the central chamber. Cryogen is introduced into the central chamber through a liquid cryogen supply line, which runs through probe shaft 20, and is in fluidic communication with the liquid cryogen flow control valve and the liquid cryogen reservoir previously described. Evaporated cryogen gas may be vented into the room out of the

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central chamber, through probe shaft 20, then out of a vent port disposed in the vicinity of proximal end 22 of probe shaft 20, not shown, or disposed in the surgical hand piece, also not shown. The construction and function of the disclosed embodiments of the spring-like structures is described in detail below.

[0119] Figure 4A is a schematic illustration of a side view of the distal end of alternative embodiment surgical probe 55 comprising expandable membranous structure 58 encompassing spring-like structure 57 in an un-expanded state. Figure 4B is a schematic illustration of a side view of the distal end of surgical probe 55 with expandable structure or expandable membranous structure in an expanded state. In the depicted embodiment, expandable membranous structure 58 is configured as a liquid cryogen evaporation chamber. Liquid cryogen is introduced into the interior of expandable membranous structure 58 from spring-like structure 57. Surgical probe 55 is configured so expandable membranous structure 58 expands to a predetermined size and shape in response to liquid cryogen evaporation within. While structure 58 may be expandable to a predetermined size and shape, the structure 58 may be comprised of a non-distensible material while in other variations, structure 58 may alternatively be comprised of a distensible material which allows for the expanded size and shape to vary depending upon the volume of cryogen introduced. Surgical probe 55 is configured such that the outer surface of expandable membranous structure 58 will be between approximately -20 Deg. C to -90 Deg. C. during cryogen evaporation within. The expanded size or shape of expendable membranous structure 58 is configured to substantially contact the surface of the cul-de-sac (element 13 in Figure 1 which indicates the region of tissue region defined and surrounded by the middle nasal turbinate, inferior nasal turbinate, and lateral wall) when pressed against the lateral nasal wall be the surgeon. Expandable membranous structure 58 may be configured to form a hollow bulbous structure in its expanded state, and comprises a single ostium 59 configured for adhesive bonding to distal end 62 of probe shaft 56 using adhesive bond 60. Cryogen exhaust vent 61 comprises at least one fenestration in distal end 62 of probe shaft 40, which is in fluidic communication with a proximal vent port, not shown, and the room. A pressure relief valve, not shown, may be disposed in the fluid path between the interior of expandable membranous structure 58 and the room to control the pressure within expandable membranous structure 58, and the degree of expansion during liquid cryogen evaporation. The construction and functionality of surgical probe embodiments comprising an expandable membranous structure are described in detail below.

[0120] Figure 5A is a schematic illustration of a side view of the distal end of

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alternate embodiment of surgical probe 68 comprising expandable membranous structure 69 encompassing spring-like structure 70. Spring-like structure 70 is configured with a lateral bend as depicted. Expandable membranous structure 69 is depicted in its un-expanded state. Figure 5B is a schematic illustration of the same side view in Figure 5A of alternate embodiment surgical probe 68 with expandable membranous structure 69 in its expandable state. Figure 5C is a schematic side view illustration taken at view A-A from Figure 5A. Figure 5D is a schematic side view illustration taken at view B-B from Figure 5B. Surgical probe 68 is configured with expandable membranous structure 69 functioning as a liquid cryogen evaporation chamber as depicted in Figures 4A and 4B. Liquid cryogen enters the interior of expandable membranous structure 69 from encompassed spring-like structure 70. Evaporated cryogen gas exits the interior of expandable membranous structure 69 through fenestration(s) 144 in distal end 143 of probe shaft 141 and exits surgical probe 68 proximally into the room. Spring-like structure 70 is configured to pre-tension membranous structure 69 in one radial axis to a greater extent than a second radial axis in a manner that causes expansion to be constrained in the radial axis with greatest pre-tensioning. In Figure 5A and 5B, spring-like structure 70 is configured to pre-tension expandable membranous structure 69 to a greater extent in the radial axis that is normal to the view axis. In Figure 5C and 5D, spring-like structure 70 is configured to pre-tension expandable membranous structure 69 to a greater extent in the radial axis that is parallel to the view axis. Figure 5A and Figure 5C depict surgical probe 68 with expandable membranous structure 69 in its un-expanded state. Figure 5B and 5D depict surgical probe 68 with expandable membranous structure 69 in its expanded state. Pre-tensioning of expandable membranous structure 69 provides a means for achieving a predetermined expanded shape for optimal matching of the morphology of the target area of the lateral nasal wall.

[0121] Figure 6A is a schematic illustration of a side view of the distal end of alternate embodiment of surgical probe 79 comprising expandable membranous structure 80 encompassing spring-like structure 82. Spring-like structure 82 is configured as a loop structure as depicted. Expandable membranous structure 80 is depicted in its un-expanded state. Figure 6B is a schematic illustration of the same side view in Figure 6A of alternate embodiment surgical probe 79 with its expandable membranous structure 80 in its expandable state. Figure 6C is a schematic side view illustration taken at view C-C from Figure 6A. Figure 6D is a schematic side view illustration taken at view D-D from Figure 6B. Surgical probe 79 is configured with expandable membranous structure 80 functioning

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as a liquid cryogen evaporation chamber as depicted in Figures 4A and 4B. Liquid cryogen enters the interior of expandable membranous structure 80 from encompassed spring-like structure 82. Evaporated cryogen gas exits the interior of expandable membranous structure 69 through fenestration(s) 147 in distal end 146 of probe shaft 145 and exits surgical probe 79 proximally into the room. Spring-like structure 82 is configured to pre-tension expandable membranous structure 80 in one radial axis to a greater extent than a second radial axis in a manner that causes expansion to be constrained in the radial axis with greatest pre-tensioning. In Figure 6A and 6B, spring-like structure 82 is configured to pre-tension membranous structure 80 to a greater extent in the radial axis that is normal to the view axis. In Figure 6C and 6D, spring-like structure 82 is configured to pre-tension expandable membranous structure 80 to a greater extent in the radial axis that is parallel to the view axis. Figure 6A and Figure 6C depict surgical probe 79 with expandable membranous structure 80 in its un-expanded state. Figure 6B and 6D depict surgical probe 79 with expandable membranous structure 80 in its expanded state. Pre-tensioning of expandable membranous structure 80 provides a means for achieving a predetermined expanded shape for optimal matching of the morphology of the target area of the lateral nasal wall.

[0122] Another alternative embodiment is illustrated in the side view of Figure 6E which shows a structure or member 83 which is formed into a looped and elongated structure having arcuate edges for presenting an atraumatic surface. Rather than being formed as a spring like structure, the structure 83 may be formed of a relatively rigid wire or member instead which maintains its configuration when pressed against a tissue surface. Structure 83 may form a continuous structure which defines an opening there through such as a looped or elongated and looped member which is open through the loop. The structure 83 may be contained entirely within the expandable structure 81 which may be formed to have a predefined shape which is distensible or non-distensible when inflated by the cryogen. Moreover, the expandable structure 81 may be formed to surround the structure 83 entirely without being supported by or attached to the structure 83 itself. Such a structure 83 may provide a configuration which presents a low-profile as the device is advanced into and through the nasal cavity and between the nasal turbinate tissues. Yet because of the relatively flattened shape and rigidity and integrity of the structure 83, the structure 83 may be used to manipulate, move, or otherwise part the tissues of the nasal cavity without having to rely upon the expandable structure 81. Additionally, the low-profile enables the structure 83 to be positioned desirably within the narrowed confines of,

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e.g., the cul-de-sac in proximity to the posterior nasal nerves (as shown by cul-de-sac 13 shown in Figure 1). When the expandable structure 81 is in its deflated state, it may form a flattened shape and when inflated, the expandable structure 81 may inflate into a configuration which remains unsupported by or attached to the structure 83. Because the structure 83 may be formed of a member which solid along its length, the cryogen may be introduced directly into the expandable structure 81 through a distal opening defined in the probe shaft 145.

[0123] Alternatively, structure 83 may be formed of a hollow tubular member which itself is formed into the continuous or looped shape. In such an embodiment, the cryogen may be optionally introduced through the hollow tubular member and dispersed within the interior of the expandable structure 81 through one or more openings which may be defined along the tubular member. In yet another alternative, the structure 83 may be formed into a flattened shape rather than a looped shape. In this configuration, the structure may be either solid or hollow such that that cryogen may be introduced through the structure and into the interior of the expandable structure 81 via one or more openings defined along the structure.

[0124] The structure 83 may extend and remain attached to the probe shaft 145, but the remainder of the structure 83 which extends within the expandable structure 81 may remain unattached or unconnected to any portion of the expandable structure 81. Hence, once the expandable structure 81 is inflated by the cryogen, the structure 83 may be adjusted in position or moved via manipulating the probe shaft 145 relative to the interior of the expandable structure 81 to enable the targeted positioning and cooling of the tissue region when in contact against the outer surface of the expandable structure 81. For instance, the structure 83 may press laterally upon a particular region of the underlying tissue to stretch or thin out the contacted tissue region to facilitate the cryogenic treatment. When the structure 83 is adjusted in position relative to the expandable structure 81, the expandable structure 81 may remain in a static position against a contacted tissue region allowing for limited repositioning of the structure 83 within.

[0125] Alternatively in other variations, the structure 83 may be attached along the interior of the expandable structure 81 partially at particular portions of the structure 83 or along the entirety of the structure 83. For instance, structure 83 may be attached, adhered, or otherwise coupled over its entirety to expandable structure 81 while in other variations, a distal portion of structure 83 may be attached, adhered, or otherwise coupled to a distal portion of the expandable structure 81 while in yet other variations, portions of the

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structure 83 may be attached, adhered, or otherwise coupled to the expandable structure 81 along its side portions. Any of these variations may be optionally utilized depending upon the desired interaction and treatment between the structure 83, expandable structure 81, and underlying tissue region to be treated.

[0126] In yet another alternative variation, the lumen 84 for introducing the cryogen into the interior of the expandable structure 81 may be extended past the distal end of the probe shaft such that the cryogen is released within the interior at a more distal location. As shown, the cryogen lumen 84 may be supported along the structure 83, e.g., via a bar or member 85 which extends across the structure 83. This particular variation may allow for the cryogen to be introduced into the distal portion of the interior of the expandable member 81. Either this variation or the variation where the cryogen is released from an opening of the probe shaft may be utilized as desired.

[0127] Figure 6F shows a side view of the embodiment of Figure 6E illustrating how the structure 83 can be formed from a relatively flattened configuration relative to the inflated expandable structure 81. Because of the structural integrity of structure 83 and its relatively flattened profile, the structure 83 may provide for targeted treatment of the tissue when contacted by the device. Figure 6G shows the side view of the inflated expandable structure 81 when pressed in a longitudinal direction by its distal tip against the underlying tissue surface S. The relative strength of the structure 83 provides for the ability to press the device against the tissue surface such that the remainder of the expandable structure 81 may maintain its inflated configuration to potentially insulate the other surrounding tissue regions. Figure 6H likewise shows the device when the structure 83 is pressed laterally along its side against the tissue surface S such that the structure 83 lies flat. The contacted tissue region may be treated while the remainder of the surrounding tissue is potentially insulated by the expanded structure 81.

[0128] While the treatment end effector is designed for application along the tissue region defined by the cul-de-sac, the same end effector may be used in other regions of the nasal cavity as well. For instance, once the ablation is performed along the cul-de-sac, the end effector may then be moved to an adjacent tissue region, e.g., region immediately inferior to the cul-de-sac, and ablation treatment may be effected again. Additionally and/or alternatively, the end effector may also be used to further treat additional tissue regions, e.g., posterior aspect of the superior, middle, and/or inferior turbinates (any one, two, or all three regions). In either case, once the cul-de-sac has been ablated, the end effector may remain in place until the tissue region has thawed partially or completely

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before the end effector is moved to the adjacent tissue region for further treatment.

[0129] Once the treatment is completed, or during treatment itself, the tissue region may be assessed utilizing any number of mechanisms. For instance, the tissue region may be visually assessed utilizing an imager during and/or after ablation.

[0130] As described herein, the device may be utilized with a temperature sensor, e.g., thermistor, thermocouple, etc., which may be mounted along the shaft, within or along the expandable structure 81, along the structure 83, etc., to monitor the temperature not only of the cryogen but also a temperature of the tissue region as well under treatment.

[0131] Additionally and/or alternatively, the expandable structure 81 may also be vibrated while maintaining the structure 83 against the interior of the expandable structure 81 and the tissue region utilizing any number of vibrational actuators which may be mounted anywhere along the device as appropriate. The vibrations may be applied directly against the tissue region or, e.g., through a layer of gel to facilitate the vibrational contact with the tissue.

[0132] Additionally and/or alternatively, other biocompatible agents may be used in combination with the cryogenic treatment. For instance, in one variation, an anesthetic may be applied to the tissue region to be treated prior to or during the cryogenic treatment. This and other alternative features described may be utilized not only with the variation shown and described in Figures 6E and 6F but with any other embodiments described herein.

[0133] Figure 7 is a cross sectional schematic illustration of the distal end of a generic surgical probe 89, which represents the construction and functionality of previously described surgical probe end effectors described above. Depicted is the distal end of probe shaft 90, liquid cryogen supply line 91, wire coil 92, inner liner 93, end cap 94, metering orifices 95, liquid cryogen 96, liquid cryogen evaporation chamber 97, and cryogen exhaust path 98. Liquid cryogen evaporation chamber is defined by central channel 134 and inner liner 93 of wire coil 92, end cap 94 at its distal end, probe shaft 90 at its proximal end. Wire coil 92 may be welded to end cap 94 and probe shaft 90 as shown. Alternatively, adhesive may be used for assembly. Probe shaft 90 may be formed from a surgical grade stainless steel hypodermic tube with an outside diameter between, e.g., approximately 1 mm and 4 mm. Wire coil 92 comprises a tightly coiled flat wire with a coil pitch that approximates the axial thickness 136 of wire 135 as shown. Wire 135 may be a stainless steel wire, or may alternatively be a nickel titanium super elastic alloy wire. Wire 135 has an axial thickness 136 between, e.g., approximately 0.5 mm and 1.5 mm, and a radial

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thickness 137 between, e.g., approximately 0.1 mm and 0.5 mm. Wire 135 may alternatively be a round wire with a diameter between, e.g., approximately 0.25 mm and 1.0 mm.

[0134] Inner liner 93 is depicted being disposed on the inner wall of wire coil 92. Inner liner 93 is configured to provide a fluid tight seal of wire coil 92. Inner liner 93 may be a polymeric material such as polyethylene, or PTFE. Alternatively a polymeric line may be disposed on the outer surface 133 to provide a fluid tight seal of wire coil 92. Cryogen supply line 91 in fluidic communication with the supply of liquid cryogen in the liquid cryogen reservoir and liquid cryogen flow control valve in the surgical hand piece, not shown. Cryogen supply line 91 may be made from a thin walled tube with a high pressure rating such as a polyimide tube. Cryogen supply line 91 delivers liquid cryogen 96 into liquid cryogen evaporation chamber 97 through metering orifice(s) 95. Liquid cryogen supply line 91 has an inner diameter between, e.g., approximately 0.2 mm and 0.8 mm, and a wall thickness between, e.g., approximately 0.05 mm and 0.5 mm.

[0135] Metering orifices 95 are configured to comprise a distribution of fenestrations in the distal end of liquid cryogen supply line 91 as shown, and are configured to distribute liquid cryogen 96 into liquid cryogen evaporation chamber 97 in a substantially uniform manner. The diameter and number of metering orifices 95 are configured such that the flow of liquid cryogen 96 into liquid cryogen evaporation chamber 97 is sufficient to lower the temperature of outer surface 133 to between, e.g., approximately - 20 Deg. C., and -50 Deg. C. during liquid cryogen evaporation in order to effect a cryo-ablation, while limiting the flow of liquid cryogen 96 into liquid cryogen evaporation chamber 97 so that substantially all liquid cryogen evaporates within liquid cryogen evaporation chamber 97. As depicted, liquid cryogen evaporation chamber 97 is an empty space. Alternatively, liquid cryogen evaporation chamber 97 may comprise a porous material configured to absorb the liquid cryogen 96 and prevent the liquid cryogen from leaving liquid cryogen evaporation chamber 97 while in a liquid state. Cryogenic gas leaves liquid cryogen evaporation chamber 97 through central channel 139, and is vented into the room.

[0136] Figure 8 is a cross sectional schematic illustration of the distal end of generic surgical probe 104 representing the construction and functionality of surgical probe embodiments 55, 68, and 79 previously described and depicted in Figures 4A and 4B, Figures 5A through 5D, and Figures 6A through 6D, respectively. Depicted is the distal end of probe shaft 105, wire coil structure 106, end cap 107, liquid cryogen supply line

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108, expandable membranous structure 109, in its expanded state, ostium 110, adhesive bond 111 between ostium 110 and probe shaft 105, cryogen gas exhaust vent 112, exhaust gas flow path 113, pressure bulkhead 114, liquid cryogen evaporation chamber 115, and liquid cryogen 116. Wire coil 106, probe shaft 105, end cap 107, and cryogen supply line 108 are substantially similar to corresponding elements described in detail and depicted in Figure 7, therefore, no further description is warranted. Expandable membranous structure 109, ostium 110, adhesive bond 111, cryogen gas exhaust vent 112, and exhaust gas flow path 113 are substantially similar to corresponding elements described in detail and depicted in Figure 4A, 4B, 5A through 5D, and 6A through 6D, therefore no further description is warranted. Liquid cryogen chamber 139 is defined by spring coil 106, end cap 107, and pressure bulkhead 114. Liquid cryogen 116 enters liquid cryogen chamber 139 through liquid cryogen supply line 108, and through liquid cryogen ports 137. Wire coil 106 is configured to meter liquid cryogen 116 from liquid cryogen chamber 139 into liquid cryogen evaporation chamber 115 in a manner that sprays liquid cryogen 116 in the direction of interior surface 141 of expandable membranous structure 109 so that the liquid cryogen rapidly evaporates upon contact with inner surface 141. A perforated polymeric liner, not shown, disposed upon wire coil 106 may be used to provide proper metering and spatial distribution of liquid cryogen 116.

[0137] Figure 9 is an internal view of the nasal cavity showing surgical probe 148 comprising an expandable membranous structure 123, configured as a liquid cryogen evaporator in position for a cryo-ablation of at least one posterior nasal nerve associated with middle nasal turbinate 129, or inferior nasal turbinate 128. Probe shaft 122 is associated with a surgical hand piece, not shown. Endoscope 126, proximal end not shown, with field of view 127 is positioned to guide the correct surgical placement of spring-like structure 125, and expandable membranous structure 123 against lateral nasal wall 130 at region 124 posterior to the middle turbinate as shown. Expandable membranous structure 123 is depicted in an expanded state. Alternatively, an endoscopic imaging means may be incorporated into the surgical probe 148, along its shaft, which may comprise a CCD or CMOS imager

[0138] Figures 10A thru 10D are schematic illustrations of the distal end 151 of alternative embodiment paddle balloon probe 150. Depicted is probe shaft 154, expandable structure 153, and paddle structure 152. Figure 10A is a front view illustration of distal end 151 with expandable structure 153 in an un-expanded state. Expandable structure 153 is maintained in its un-expanded state during introduction to, and removal from the target region of the

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nasal anatomy. Suction may be applied by a suction means to maintain expandable structure 153 in its un-expanded state. Figure 10B is a side view illustration of the distal end 151 of paddle balloon probe 150 with expandable structure 153 in its un-expanded state. Figure 10C is a front view illustration of the distal end 151 of paddle balloon probe 150 with expandable structure 153 in its expanded or inflated state. Figure 10D is a side view illustration of the distal end of paddle balloon probe 150 with expandable structure 153 in its expanded or inflated state. Paddle 152 is configured for access to middle meatus of the lateral nasal wall by means of insertion between the middle nasal turbinate and the inferior nasal turbinate, as illustrated in figures 13A thru 13D below. Paddle structure 152 is a rounded rectangular shape as shown with a major dimension between approximately, e.g. 8mm and 16mm, and a minor dimension between approximately, e.g. 4mm and 10mm. The thickness of paddle structure 152 is between approximately, e.g. 1mm and 3mm. Paddle structure 152 is sufficiently rigid to access the middle meatus between the middle nasal turbinate and the inferior nasal turbinate, and is sufficiently flexible to avoid trauma to the nasal anatomy during use. Expandable structure 153 comprises a membrane that is bonded to paddle structure 152 in a manner that forms a air tight bladder as shown. Paddle balloon probe 150 is configured for introduction of a liquid cryogen into the bladder formed by paddle structure 152 and expandable structure 153, as well as to removed evaporated cryogen from the bladder with an exit to the room. The bladder formed by paddle structure 152 and expandable structure 153 is configured as cryogenic evaporation chamber, and the outer surface of expandable structure 153 is configured as a cryo-ablation surface. Expandable structure 153 is configured apply a force against the middle meatus of the lateral nasal wall between approximately, e.g. 20 grams and 200 grams. Expandable structure 153 is configured for expansion in reaction cryogen evaporation within. Liquid cryogen is introduced into the bladder through probe shaft 154, and evaporated cryogen gas is removed from the bladder and vented to the room trough probe shaft 154. The cryogenic ablation mechanisms and other features are similar to cryo-ablation probe embodiments described above and below.

[0139] Figures 11A and 11 B are schematic illustrations of the distal end 166 of paddle porous balloon probe 163, which is an alternative embodiment of paddle balloon probe 150. Figure 11 A is front view illustration, and Figure 11B is a side view illustration. Paddle porous balloon probe 163 comprises probe shaft 167, porous expandable structure 165, and paddle structure 164. Porous expandable structure 165 is similar to expandable structure 153, described above, comprising a porous membrane versus an air tight

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membrane. Porous expandable structure 165 is configured for the venting of evaporated cryogen gas through the pores168 from within the bladder formed by porous expandable structure 165 and paddle structure 164 into the patient's nostril in the immediate vicinity of the surface of the lateral nasal wall that is targeted for cryo-ablation. Venting the cold gas in the vicinity of the targeted lateral nasal wall enhances cooling effectiveness, while precluding the need to vent the evaporated cryogen gas through probe shaft 167, allowing the probe shaft to be smaller in caliber, and therefore less traumatic. The cryogenic ablation mechanisms and other features are similar to cryo-ablation probe embodiments described above and below.

[0140] Figures 12A thru 12D are schematic illustrations of the distal end 179 of double balloon paddle probe 178. Figure 12A is a front view illustration of double balloon paddle probe 178 with expandable structure 181 in its un-expanded state. Figure 12 B is a side view illustration of double balloon paddle probe 178 with expandable structure in its un-expanded state. Figure 12C is a front view illustration of double balloon paddle probe 178 with expandable structure 181 in its expanded state. Figure 12 D is a side view illustration of double balloon paddle probe 178 with its expandable structure 181 in its expanded state. Double balloon paddle probe 178 comprises probe shaft 180, expandable structure 181, paddle structure 182, liquid cryogen port 183, and cryogen gas exhaust port 184. In this embodiment, expandable structure 181 encompasses paddle structure 182 and comprises a single ostium 185, and an adhesive bond 186 which forms an air tight seal of for expandable structure 181. The configuration and function of this embodiment substantially similar to the embodiment depicted in Figures 6A to 6H, with the difference being in this embodiment a paddle structure 182 is encompassed by expandable structure 181, versus a spring-like structure or a formed wire structure encompassed by an expandable structure as depicted in Figures 6A to 6H. Optionally, the distal inner edge of paddle structure 182 and be bonded to the interior of expandable structure 181 by adhesive bond 187.

[0141] Figures 13A through 13D are schematic sectional coronal illustrations of the nasal cavity depicting ablation probe 201 access to the middle meatus 198 between the middle nasal turbinate 6 and inferior nasal turbinate 7. Ablation probe 201 is a generic representation any of the ablation probes disclosed here within that utilize and expandable structure. Figure 13A depicts the thin edge of the distal end of ablation probe 201 being inserted into the thin gap between middle nasal turbinate 6 and inferior nasal turbinate 7. Figure 13B depicts the distal structure of ablation probe 201 behind middle turbinate against the middle meatus 198 in position for an ablation. Figure 13C depicts the initiation

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of ablation by activation of the flow of cryogenic liquid into the expandable structure 203 resulting in the inflation of the expandable structure 203 as shown. Please note, as depicted, the expandable structure is most similar to that depicted in Figures 10 and 11, but is not intended imply a preference for those embodiments over the other embodiments disclosed here within. Figure 13D depicts the ablation zone 204 resulting from the application of a cryo-ablation of between approximately, e.g. 20 to 300 seconds. Following ablation, the probe may be removed following a thawing period that may be between approximately, e.g. 20 to 30 seconds. As depicted the sphenopalatine branch, comprising the sphenopalatine artery, sphenopalatine vein, and sphenopalatine nerve, and the sphenopalatine foramen are substantially encompassed by the zone of ablation 204. As previously described, and further described below, the targeted tissue may comprise other locations, including the proximity of accessory posterolateral nerves bounded by a sphenopalatine foramen superiorly, an inferior edge of an inferior turbinate inferiorly, a Eustachian tube posteriorly, or a posterior third of the middle and inferior turbinates anteriorly. Other anatomical targets may include the pterygomaxillary fossa, sphenopalatine ganglion, or vidian nerve.

[0142] Figure 14A is an internal lateral view of the nasal cavity showing target 228 for ablation of the parasympathetic nervous function of middle turbinate 6. Ablation target 228 is directly over the posterior superior lateral nasal branches 11 which innervate middle turbinate 6. Ablation target 228 may be circular as shown or non-circular, with a zone of ablative effect between 1 mm and 4 mm deep. Figure 14B is an internal lateral view of the nasal cavity showing target 246 for ablation of parasympathetic nervous function of superior turbinate 5, middle turbinate 6, and inferior turbinate 7. Ablation target 246 is linier as shown and is directly over posterior inferior lateral nasal branch 10, which innervates inferior turbinate 7, posterior superior lateral nasal branch 11 which innervates middle turbinate 6, and superior lateral nasal branch 12 which innervates superior turbinate 5. The depth of ablative effect is ideally between 1mm and 4mm deep. Figure 14C is an internal lateral view of the nasal cavity showing target 247 for ablation of parasympathetic nervous function of superior turbinate 5, middle turbinate 6, and inferior turbinate 7. Ablation target 246 is linier and segmented as shown with ablation segments directly over posterior inferior lateral nasal branch 10, which innervates inferior turbinate 7, posterior superior lateral nasal branch 11 which innervates middle turbinate 6, and superior lateral nasal branch 12 which innervates superior turbinate 5. The depth of ablative effect is ideally between 1mm and 4mm deep. Figure 2D is an internal lateral view of the nasal

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cavity showing target 248 for ablation of the parasympathetic nervous function of middle turbinate 6. Ablation target 228 is directly over the posterior superior lateral nasal branches 11 which innervate middle turbinate 6. Ablation target 248 is oblong as shown and positioned between middle turbinate 6 and inferior turbinate 7 as shown, with a zone of ablative effect between 1 mm and 4 mm deep.

[0143] Figure 15A is a schematic illustration of cryosurgical probe 234 configured for cryo-ablation of parasympathetic nervous function of a nasal turbinate(s) comprising a spatula shaped cryosurgical tip 236. Cryosurgical probe 234 comprises handle 235, probe shaft 237 cryosurgical tip 236 refrigerant cartridge cover 239, and refrigerant control push button 238. Handle 235 may comprise a receptacle, not shown, for receiving a refrigerant filled cartridge, not shown, which may comprise liquid carbon dioxide, which is used for evaporative cryogenic cooling within cryosurgical probe tip 236. Alternatively, the cartridge may comprise a compressed cryogenic gas which may comprise argon or nitrous oxide which is used for Joule-Thompson effect cryogenic cooling within cryosurgical probe tip 236. Those skilled in the art cryosurgical instrumentation are familiar with means for configuring cryosurgical probe 234 for evaporative cryogenic cooling or Joule-Thompson effect cryogenic cooling according to this invention, therefore, further detailed description relating to cryosurgical techniques are not warranted. Refrigerant control push button 238 is in mechanical communication with a valve which is configured to open when push button 238 is depressed by the operator causing the cryogen within the cartridge to flow into cryosurgical probe tip 236 through a conduit within probe shaft 237. Handle 235 further comprises a venting means, not shown for exhausting the expanded cryogen into the atmosphere. Probe shaft 237 is between approximately 2mm and 6mm in diameter, with a length between approximately 4 cm and 10 cm. Figure 15B defines a section view of the cryosurgical probe 234 cryosurgical tip 236. Figure 15C is a cross sectional view of the cryosurgical probe 234 distal end comprising probe shaft 237, refrigerant delivery tube 253, and probe tip 236. Cryogen delivery tube 253 traverses the length of probe shaft 237 in a coaxial relationship and is in fluidic communication with the cryogen cartridge in handle 235 through the cryogen control valve previously described. At the distal end of cryogen delivery tube 253 there is at least one lateral fenestration configured to direct the release of the pressurized cryogen 256 from cryogen delivery tube 253 into expansion chamber 251 of cryosurgical tip 236 in the direction of cryo-ablation surface 249 of cryosurgical tip 236. Cryo-ablation surface 249 is substantially flat. The opposing surface 250 to ablation surface 249 may be cylindrical as shown. By directing the release of

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cryogen towards ablation surface 249, ablation surface 249 achieves cryo-ablation temperatures between approximately -20 to -200 degrees centigrade, and opposing surface 250 remains warmer. The expanded cryogen 255 exits expansion chamber 251 through probe shaft 252 and is vented to atmosphere through handle 235 as previously described. Probe shaft 237, cryogen delivery tube 253, and cryosurgical tip 236 may fabricated from a stainless steel as is typical with cryosurgical probes, or may be fabricated with alternative materials as is familiar to those skilled in the art of cryosurgical probes. Probe shaft 237 may configured as shown with curvatures configured for nasal anatomy, or alternatively may be configured as described below.

[0144] Figure 16A is a schematic illustration of the distal end of an alternative embodiment 262 of the cryosurgical probe comprising a bullet shaped cryo-ablation element 263 at the distal end of angled probe shaft 265. In this embodiment pressurized cryogen is released through an orifice in an axial direction into the expansion chamber in the direction cryo-ablation surface 264. The diameter of shaft 265 is between approximately 2mm and 6mm, and the angle of shaft 265 is between approximately 30 and 60 degrees, and the point of bend is between 1 cm and 3 cm from the distal end of ablation element 263. Figure 16B is a schematic illustration of the distal end of an alternative embodiment 266 of the cryosurgical probe comprising a bullet shaped cryo-ablation element 263 at the distal end of a user deflectable probe shaft 267. Deflectable probe shaft 267 comprises distal deflectable segment 268 and a substantially rigid non-deflectable proximal segment 269. Probe shaft 267 diameter is between approximately 2 mm and 6 mm. The border between deflectable distal segment 268 and proximal non-deflectable segment is between approximately 1 cm and 3 cm from the distal end of ablation element 263. The angle of deflection may be between approximately 60 to 120 degrees and may be configured for deflection in one direction, or in two directions as shown. The deflection means comprises at least one pull wire housed within probe shaft 267 and a deflection actuator disposed in the vicinity of the proximal end of probe 266. Those skilled in the art deflectable tipped surgical probes are familiar means for creating a deflectable tipped cryosurgical probe according to this invention. Figure 4C and 4D are schematic illustrations of the distal end of an alternative embodiment 270 of the cryosurgical probe where the cryo-ablation element 274 is configured for producing multiple discrete cryo-ablations simultaneously. Cryo ablation element 274 comprises an expansion chamber, not shown, discrete lateral cryo-ablation surfaces 272, surrounded by thermal insulation 273. Ablation element 274 comprises a hollow bullet shaped metallic structure with lateral protrusions in the surface

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forming cryo-ablation surfaces 272, with a thermal insulating material covering all remaining external surfaces of ablation element 274 as shown. As with cryo-surgical probe 234, cryogen is released from cryogen delivery tube in a lateral direction towards cryo-ablation surfaces 272.

[0145] Figure 17A is a schematic illustration of the distal end of an alternative embodiment 280 of the cryosurgical probe comprising a semi-circular cryo-ablation element 282. Cryo-ablation element 282 comprises a continuation of probe shaft 281 formed in a semi-circle as shown. Within the semi-circular section cryogen delivery tube 283 comprises an array of lateral fenestration in the one axial direction relative to semi-circular form, making the corresponding surface of the ablation element 282 the cryo-ablation surface. Figure 17B is a schematic illustration of the ablation 284 morphology in the nasal mucosa 288 resulting from use of the semi-circular ablation element 282. The gap 286 in the ablation provides blood perfusion to the mucosa encompassed by the ablation providing a reduction in tissue sloughing as the result of the ablation, as well as a reduction in the chance of infection, and a reduction of patient discomfort. Figure 17C is a schematic illustration of the distal end of an alternative embodiment 287 of the cryosurgical probe comprising a spiraled cryo-ablation element.

[0146] Figure 18A is a schematic illustration of cryo-ablation balloon probe 294 configured for cryo-ablation of parasympathetic nervous function of a nasal turbinate(s). Cryo-ablation balloon probe 294 comprises balloon 295, probe shaft 296, cryogen delivery tube 297, with lateral fenestrations 298 disposed on the distal end of cryogen delivery tube 297 within balloon 295 as shown. Cryo-ablation balloon probe 294 further comprises proximal hub 299 with cryogen exhaust port 299, cryogen supply port 301. Probe shaft 296 may be rigid or flexible. Balloon 295 functions as a cryogen expansion chamber for either a cryogenic evaporation cooling process or a Joules-Thompson effect cooling process. Pressurized cryogen 256 is delivered to the interior of balloon 295 through cryogen delivery tube 297 under pressure. Cryogen 256 exits cryogen delivery tube 297 through lateral fenestrations 298 as shown, in the radial direction towards the wall of balloon 295. The radial wall of balloon 295 is the cryo-ablation surface. Expanded cryogen 255 exits balloon 295 through probe shaft 296, and is vented to atmosphere through exhaust port 300. Exhaust port 300 may comprise a pressure relief valve, which creates a back pressure to inflate balloon 295 at a predetermined pressure. Cryogen supply port 301 is configured to connect cryogen supply tube 297 to a source of cryogen. Proximal hub 299 may be configured as a handle, and comprise a cryogen control valve. Figure 18B is a schematic

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illustration of the distal end of the cryo-ablation balloon probe detailing the geometry of the cryo-ablation balloon. The length 302 of balloon 295 is between approximately 3 mm and 20 mm, and the diameter 303 of balloon 295 is between 1 mm and 5 mm. Figure 18C is a schematic illustration of an alternate embodiment 304 of the cryo-ablation balloon probe 294 comprising an insulating chamber 307 within the cryo balloon 305 structure. Insulating chamber 307 is formed by membrane 306 as shown. Fenestration 308 is a small opening in communication between expansion chamber 311 and insulating chamber 307, which allows insulation chamber to inflate with expanded cryogen gas 255 in a substantially static manner providing thermal insulation to the surface of balloon 305 adjacent to insulation chamber 307. Lateral fenestrations 310 direct pressurized cryogen 301 towards the wall of balloon 305 opposite of insulation chamber 307 forming cryo-ablation surface 312. The length 302 of balloon 305 is between approximately 3 mm and 20 mm, and the diameter of balloon 305 is between approximately 1 mm and 6 mm. Figure 18D is a schematic illustration of the distal end of an alternative embodiment 313 of the cryo-ablation balloon probe 294 comprising a tee shaped cryo-ablation balloon 314. The length 302 of balloon 314 is between approximately 3 mm to 20 mm, and the diameter of balloon 303 is between approximately 1 mm and 6 mm. Cryogen delivery tube 315 is configured to direct pressurized cryogen down the horns 316 of balloon 314 as shown. Figure 18E is a schematic illustration of the distal end of an alternative embodiment 317 of the cryo-ablation balloon probe 294 comprising a "J" shaped cryo-ablation balloon 318. The length 302 of balloon 318 is between approximately 3 mm and 20 mm, and the diameter 303 of balloon 318 is between approximately 1 mm and 6 mm. Cryogen delivery tube 319 is configured to direct pressurized cryogen 256 laterally into the "J" as shown.

[0147] Figure 19A is a schematic illustration of the distal end of an alternate embodiment 325 of cryo-ablation probe 294 comprising a cryo-ablation element 326 with suction stabilization. Figure 19B is a cross sectional view of the distal end of the alternative embodiment 325 showing the configuration of the cryo-ablation element 326 and the suction stabilization means.

[0148] Ablation element 326 is surrounded by suction chamber 329 as shown. Suction chamber 329 is in fluidic communication with a suction source, not shown, by suction tube 331. Suction ports 330 are oriented in the same direction as cryo-ablation surface 332 and are configured to provide suction attachment to the tissue when cryo-ablation surface 332 is placed into contact with the nasal mucosa in the ablation target zone. Probe shaft 325,

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cryogen delivery tube 327, and lateral fenestrations 328 have similar function those previously described.

[0149] Figure 20A is a schematic illustration of radiofrequency (RF) ablation probe 338 configured for ablation of the parasympathetic nervous function of a nasal turbinate(s) with a bi-polar ring electrode ablation element 342 on an "J" shaped distal probe tip 341. RF ablation probe 338 comprises handle 339, probe shaft 340, "J" shaped probe tip 341, bipolar ring electrode pair 342, RF activation switch 345, electrical connector 343, and fluid connector 344. Those skilled in the art of RF ablation probes are familiar with the many possible configurations and construction techniques for RF electrodes and probes that are within the scope of this invention, therefore detailed description of the illustrated electrode configurations described below, and their construction techniques is not warranted. Electrical connector 343 is configured for connection to a radiofrequency energy generator, for which there are many commercially available. Fluid connector 344 is configured for connection to source of liquid irrigant. Fluid connector 344 may be in fluidic communication with at least one fluid irrigation port located the vicinity of the RF ablation electrode, and is embodiment specific. RF activation switch 345 allows the user to activate the RF ablation and terminate the RF ablation. Probe shaft 340 is between approximately 2 mm to 6 mm in diameter, and between approximately 4 cm and 10 cm long, but could be longer. The length of "J" tip 341 is between approximately 0.5 cm and 1.5 cm. Ring the spacing between RF electrode pair 342 is between approximately 2 mm and 6 mm. Figure 20B is a schematic illustration of the distal end of an alternative embodiment 346 of RF ablation probe 338 comprising a bi-polar segmented ring electrode ablation element on an "J" shaped distal probe shaft. The gap 348 shown in the ring electrode is on the side opposite of the side configured for RF ablation. The gap 348 in the ring electrodes protect the nasal septum during RF ensuring that RF energy is only applied to the lateral nasal wall at the ablation target. Figure 20C is a schematic illustration of alternative embodiment 349 of the distal end of RF ablation probe 338 comprising a bi-polar electrode ablation element 350 on a "J" shaped distal probe shaft with the electrodes disposed in a lateral array. Figure 20D is a schematic illustration of alternative embodiment 351 of the distal end of RF ablation probe 338 comprising a bi-polar electrode ablation element 352 on a "U" shaped distal probe shaft 353 with the electrodes disposed in a lateral array. Figure 20E is a schematic illustration of the distal end of alternative embodiment 354 of RF ablation probe 338 comprising a bi-polar electrode ablation element 355 on a user deployable "T" shaped structure356. Element 356 is comprised of two halves which can

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alternately be collapsed and deployed as in Figure 20E. The two halves of the electrode structure 356 are pivoted to allow them to move laterally relative to the catheter shaft 354. Electrodes 355 can operate in a mono polar, bipolar or multipolar fashion as known in the art.

[0150] Figure 21A is a schematic illustration of alternative embodiment 362 to RF ablation probe 338 configured for ablation of the parasympathetic nervous function of a nasal turbinate(s) comprising an array of RF ablation electrodes 363 disposed on a planar surface with a fluid irrigation means associated with the electrodes. Figure 21B is a schematic illustration of the distal end of the RF ablation probe 362 showing the arrangement of the ablation electrode array 363 and the associated fluid irrigation means. Alternative embodiment 362 comprises distal probe tip 119, probe shaft 369, handle 339, fluid connector 344, and electrical connector 343. Electrode array 363 comprises two or more dome shaped electrodes 365, that are electrically configured into a bipolar pair, meaning that if there are 4 electrodes 365, then two of the electrodes are connectable to one pole of an RF generator, and the second two electrodes are connectable to the opposite pole of the RF generator, etc. Electrodes 365 are dome shaped and protrude from planar surface 366. A fluid port 364 is associated with each electrode 365. All fluid ports are in fluidic communication with fluid connector 344. Fluid ports 364 are configured to irrigate the surface of the nasal mucosa that is contact with electrodes 365 to provide cooling of the mucosa and the electrodes 365, to minimize thermal injury to the surface of the mucosa, and to prevent sticking of the electrodes to the surface of the mucosa. Probe tip 371 is between approximately 4 mm and 8 mm in diameter, and between approximately 3 mm to 8 mm thick. The number of electrodes 365 of electrode array 363 may be between 2 and approximately 10.

[0151] Figure 22A is a schematic illustration of an alternative embodiment 377 of RF ablation probe 362 comprising a linear electrode array 378 disposed on a planar surface; a fluid irrigation ports 387 associated electrodes 379, and a deployable needle 380 configured for injecting a liquid into a sub-mucosal space. Figure 22B is a schematic illustration of the distal end of the alternative embodiment 377 RF ablation probe showing the arrangement of the ablation electrodes 379 and the associated fluid irrigation ports 387. Figure 22C is a schematic illustration of the distal end of the alternative embodiment 377 RF ablation probe showing the arrangement of the ablation electrodes 379 and the associated fluid irrigation ports 387 with the needle 380 deployed. The function, of domed electrodes 379, fluid ports 387, electrical connector 343, fluid connector 344, RF activation

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switch 345, handle 382, and shaft 384 all function in essentially the same manner as described for prior embodiment 362. This embodiment has a linear electrode array 378, and a deployable needle configured for injecting a liquid into the sub-mucosal space where the liquid may comprise an anesthetic. Needle actuator 383 provides the user a means actuating needle 380. Fluid connector 389 is in fluidic communication with needle 380, through needle shaft 385, and is configured with a female luer connector for mating with a syringe, not shown. Shaft 384 contains needle shaft 385, electrical cable 386, and provides a conduit for irrigation fluid, not shown.

[0152] Figure 23A is a schematic illustration of an RF interstitial needle ablation probe 395 configured for interstitial ablation of a posterior nasal nerve. Figure 23B is a schematic illustration of the distal end 396 of the RF interstitial needle ablation probe 395. RF interstitial needle probe 395 comprises distal tip 396, probe shaft 398, handle 399, electrical connector 400, fluid connector 401, RF activation switch 402. Distal tip 396 comprises interstitial needle electrode array 397, which comprises more than one interstitial needle 464 Handle, 399, RF activation switch 402, electrical connector 400, and probe shaft 398 function in a manner previously described. Fluid port 401 is in fluidic communication with at least one RF ablation needle 464, with the at least one RF ablation needle 464 being hollow and configured for injecting a liquid into the nasal sub-mucosal space. Each RF ablation needle 464 has a proximal electrically insulating coating 405, and a distal electrically insulating coating 404, forming RF electrode surface 403. Proximal insulator 405, and distal insulator 404 are configured for limiting the ablation effects to the sub-mucosal space, which will be described in further detail below. Interstitial needle electrode array 397 may be configured as a mono-polar electrode array, or a bipolar electrode array. Interstitial needle electrode array 397 may be configured as a linear array, a circular array, a triangular array, or any other geometric form. Interstitial needle electrode array 397 may comprise two or more RF ablation needles 464. RF ablation needles 464 are between approximately 18 and 28 gauge, and between approximately 3 mm and 10 mm long.

[0153] Figure 24A is a cross sectional view of the distal end of an alternative embodiment 411 to RF interstitial needle ablation probe 395 comprising a deployable and retractable array of RF ablation needles 412 configured for lateral deployment showing the needle array retracted. Figure 24B is a cross sectional view of the distal end of an alternative embodiment 411 of RF interstitial needle ablation probe 395 comprising a deployable and retractable array of RF ablation needles configured for lateral deployment showing the

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needle array deployed. Interstitial needle array 412 is housed in a hollow sheath with a "J" tip 413 as shown. Linear actuator shaft 414 is in mechanical communication with a user actuator lever at the proximal end not shown. Linear actuator shaft 414 is moved in the distal direction to deploy needle array 412, and moved in the proximal direction to retract needle array 412 as shown. Figure 24C is a cross sectional view of the distal end of an alternative embodiment 415 of RF interstitial needle ablation probe 395 comprising a deployable and retractable array of RF ablation needles configured for axial deployment showing the needle array retracted. Figure 24D is a cross sectional view of the distal end of an alternative embodiment 415 of RF interstitial needle ablation probe 395 comprising a deployable and retractable array of RF ablation needles configured for axial deployment showing the needle array deployed.

[0154] Figure 25A is a schematic illustration of an integrated flexible circuit 421 configured for use with an RF ablation probe comprising an RF energy source and control circuits 422 at one end, and an RF ablation electrode array 423 at the opposite end, connected by electrical conduits 426. Figure 25B is a schematic illustration of the RF ablation electrode array 423 of the flexible circuit mounted on the distal shaft of an RF ablation probe that is configured for ablation of the parasympathetic nervous function of a nasal turbinate. Also shown are optional fluid ports associated with the RF ablation electrode array as shown, with irrigation fluid 427 supplied to irrigation ports 425 through distal shaft 424.

[0155] Figure 26A is an in situ schematic illustration of the RF ablation probe 377 depicted in Figures 10 through 10C showing needle 380 injecting an anesthetic into the sub-mucosal space 433 prior to an RF ablation of the posterior nasal nerve 434. Figure 26B is an in situ schematic illustration of the resulting RF ablation 436 showing the ablation zone 436 encompassing posterior nasal nerve 434, and residing below the mucosal surface 437 due to the cooling effect of liquid irrigant 435.

[0156] Figure 27 is an in situ schematic illustration of an RF ablation of the parasympathetic nerve of a posterior nasal nerve 434 using the RF interstitial needle ablation probe 395 depicted in Figures 11A and 11B showing ablation zone 436 encompassing posterior nasal nerve434 and residing below the mucosal surface 437 due to the arrangement of needle electrode surface(s) 403 and needle insulation zones 404 & 405.

[0157] Figure 28 is an in situ illustration of the ablation of the posterior nasal nervedepicted in Figure 14D. Generic ablation device 441 is shown with cylindrical ablation element 442, which could be a cryo ablation element, an RF ablation element, or

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some other type of thermal ablation element. Also shown is endoscope 443, which provides the surgeon an image for positioning ablation element 442 at the target location, and a means for monitoring the ablation.

[0158] Figure 29 is an in situ illustration of the ablation of the posterior nasal nerveof a nasal turbinate at the ablation target depicted in Figure 14B. Generic ablation device 441 is shown with cylindrical ablation element 442, which could be a cryo ablation element, an RF ablation element, or some other type of thermal ablation element. Also shown is endoscope 443, which provides the surgeon an image for positioning ablation element 442 at the target location, and a means for monitoring the ablation.

[0159] Figure 30 is an in situ illustration of the ablation of the posterior nasal nerve using a generic "T" tipped ablation device 448. Generic "T" tipped ablation device 448 is shown with ablation elements 449, which could be cryo ablation elements, RF ablation elements, or some other type of thermal ablation elements. Also shown is endoscope 443, which provides the surgeon an image for positioning ablation element 442 at the target location, and a means for monitoring the ablation.

[0160] Figure 31A is a schematic illustration of generic ablation probe 455 and an insulated probe guide 457 configured to protect the nasal septum from thermal injury during an ablation of the parasympathetic nervous function of a nasal turbinate(s). Probe guide 457 is configured to press ablation element 456 of probe 455 against the lateral wall of a nasal cavity 458 and create a thermally insulative space between the lateral wall of the nasal cavity 458 and the nasal septum 459 as shown in Figures 31B and 31C. Probe guide 457 may be fabricated from foam material, or any other suitable thermally insulative material. Figure 31B is an in situ illustration of generic ablation probe 437 configured for ablation of the posterior nasal nerve which comprises an insulating structure 460 configured to protect the nasal septum 459 from thermal injury. Structure 460 may comprise an inflatable balloon. Figure 31C is an in situ illustration of generic ablation probe 455 configured for ablation of the parasympathetic nervous function of a nasal turbinate(s) which comprises a space creating structure 461 configured to protect the nasal septum 459 from thermal injury. Structure 461 may comprise a deployable wire structure or surgical basket structure.

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CLAIMS

What is claimed is:

1. A method for treating a tissue region within a nasal cavity, comprising:

introducing a distal end of a probe shaft through the nasal cavity, wherein the distal end has an end effector with a first configuration having a low-profile which is shaped to manipulate tissue within the nasal cavity;

positioning the distal end into proximity of a tissue region having at least one posterior nasal nerve;

reconfiguring the distal end from the first configuration to a second configuration which is shaped to contact and follow the tissue region; and

ablating the at least one posterior nasal nerve within the tissue region via the distal end.

2. The method of claim 1 wherein ablating the at least one posterior nasal nerve comprises ablating the posterior nasal nerve such that symptoms of rhinitis are reduced.

3. The method of claim 1 wherein introducing a distal end comprises introducing the distal end through a nostril and into the nasal cavity.

4. The method of claim 1 wherein positioning the distal end comprises positioning the distal end at least 2 cm beyond an anterior entrance to a middle meatus.

5. The method of claim 1 wherein positioning the distal end comprises:

advancing the distal end along an upper surface of the inferior nasal turbinate to a mid-portion of the middle nasal turbinate;

advancing the distal end into a middle meatus; and

further advancing the distal end posteriorly up into a cul-de-sac.

6. The method of claim 1 wherein positioning the distal end comprises positioning the distal end between the middle and inferior nasal turbinate.

7. The method of claim 1 wherein positioning the distal end comprises

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positioning the distal end relative to the tissue region surrounded by the middle nasal turbinate, inferior nasal turbinate, and lateral wall forming a cul-de-sac.

8. The method on claim 1 wherein positioning the distal end positioning the distal end to contact a lateral nasal wall defined by a tail of a nasal turbinate, lateral wall, and an inferior turbinate.

9. The method of claim 1 wherein positioning the distal end comprises positioning the distal end into proximity of the Pterygomaxillary fossa, sphenopalatine ganglion, sphenopalatine ganglion, or vidian nerve.

10. The method of claim 1 wherein positioning the distal end comprises positioning the distal end into proximity of accessory posterolateral nerves bounded by an sphenopalatine foramen superiorly, an inferior edge of an inferior turbinate inferiorly, a Eustachian tube posteriorly, or a posterior third of the middle and inferior turbinates anteriorly.

11. The method of claim 1 wherein reconfiguring the distal end comprises inflating an expandable structure projecting from the probe shaft into contact against the tissue region.

12. The method of claim 11 further comprising positioning a member extending within the expandable structure, wherein the expandable structure encloses the member such that the member is unattached to the interior of the expandable structure, into contact against the tissue region through the expandable structure.

13. The method of claim 1 wherein ablating the at least one posterior nasal nerve comprises introducing a cryogenic fluid into or through the distal end.

14. The method of claim 1 wherein ablating the at least one posterior nasal nerve comprises cryogenically ablating the tissue region between approximately 20 seconds to 300 seconds.

15. The method of claim 1 wherein ablating the at least one posterior nasal

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nerve comprises cryogenically ablating the tissue region between approximately 20 seconds to 120 seconds.

16. The method of claim 1 further comprising introducing an imaging device in proximity to the distal end.

17. The method of claim 1 further comprising visualizing the tissue region while advancing the distal end of the probe shaft through the nasal cavity.

18. The method of claim 17 wherein visualizing comprises visualizing via a CCD or CMOS imager positioned along the surgical probe shaft.

19. The method of claim 17 wherein visualizing comprises visualizing infrared wavelengths.

20. The method of claim 17 wherein visualizing comprises visualizing via a nasal endoscope.

21. The method of claim 20 wherein visualizing comprises advancing the nasal endoscope with the surgical probe shaft.

22. The method of claim 1 further comprising introducing a temperature sensor in proximity to the distal end of the surgical probe shaft.

23. The method of claim 1 further comprising applying a pressure to the tissue region via the distal end with a force of 20 to 200 grams.

24. The method of claim 1 further comprising waiting 10 to 20 seconds after ablating the at least one posterior nasal nerve prior to removing the distal end from the tissue region.

25. The method of claim 1 wherein ablating the at least one posterior nasal nerve comprises ablating the tissue region through a layer of gel.

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26. The method of claim 1 further comprising assessing the tissue region during and/or after ablation.

27. The method of claim 26 wherein assessing comprises inspecting the tissue region visually or via ultrasound.

28. The method of claim 26 wherein assessing comprises detecting or a temperature of the tissue region.

29. The method of claim 1 further comprising vibrating the distal end while maintaining the distal end against the tissue region.

30. The method of claim 1 further comprising applying an anesthetic to the tissue region to be treated prior to ablating the post nasal nerve.

31. A method for treating rhinitis, comprising:

introducing a distal end of a probe shaft through the nasal cavity, wherein the distal end has an end effector with a first configuration having a low-profile which is shaped to manipulate tissue within the nasal cavity;

positioning the distal end into proximity of a tissue region surrounded by the middle nasal turbinate, inferior nasal turbinate, and lateral wall forming a cul-de-sac;

reconfiguring the distal end from the first configuration to a second configuration which is shaped to contact and follow the tissue region; and

ablating the at least one posterior nasal nerve within the tissue region via the distal end.

32. The method of claim 31 wherein ablating the at least one posterior nasal nerve comprises ablating the posterior nasal nerves such that symptoms of rhinitis are reduced.

33. The method of claim 31 wherein introducing a distal end comprises introducing the distal end through a nostril and into the nasal cavity.

34. The method of claim 31 wherein positioning the distal end comprises

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positioning the distal end at least 2 cm beyond an anterior entrance to a middle meatus.

35. The method of claim 31 wherein positioning the distal end comprises:

advancing the distal end along an upper surface of the inferior nasal turbinate to a mid-portion of the middle nasal turbinate;

advancing the distal end into a middle meatus; and

further advancing the distal end posteriorly up into a cul-de-sac.

36. The method of claim 31 wherein positioning the distal end comprises positioning the distal end between the middle and inferior nasal turbinate.

37. The method on claim 31 wherein positioning the distal end positioning the distal end to contact a lateral nasal wall defined by a tail of a nasal turbinate, lateral wall, and an inferior turbinate.

38. The method of claim 31 wherein positioning the distal end comprises positioning the distal end into proximity of the Pterygomaxillary fossa, sphenopalatine ganglion, sphenopalatine ganglion, or vidian nerve.

39. The method of claim 31 wherein positioning the distal end comprises positioning the distal end into proximity of accessory posterolateral nerves bounded by an sphenopalatine foramen superiorly, an inferior edge of an inferior turbinate inferiorly, a Eustachian tube posteriorly, or a posterior third of the middle and inferior turbinates anteriorly.

40. The method of claim 31 wherein reconfiguring the distal end comprises inflating an expandable structure projecting from the probe shaft into contact against the tissue region.

41. The method of claim 40 further comprising positioning a member extending within the expandable structure, wherein the expandable structure encloses the member such that the member is unattached to the interior of the expandable structure, into contact against the tissue region through the expandable structure.

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42. The method of claim 31 wherein ablating the at least one posterior nasal nerve comprises introducing a cryogenic fluid into or through the distal end.

43. The method of claim 31 wherein ablating the at least one posterior nasal nerve comprises cryogenically ablating the tissue region between approximately 20 seconds to 300 seconds.

44. The method of claim 31 wherein ablating the at least one posterior nasal nerve comprises cryogenically ablating the tissue region between approximately 20 seconds to 120 seconds.

45. The method of claim 31 further comprising introducing an imaging device in proximity to the distal end.

46. The method of claim 31 further comprising visualizing the tissue region while advancing the distal end of the probe shaft through the nasal cavity.

47. The method of claim 46 wherein visualizing comprises visualizing via a CCD or CMOS imager positioned along the surgical probe shaft.

48. The method of claim 46 wherein visualizing comprises visualizing infrared wavelengths.

49. The method of claim 46 wherein visualizing comprises visualizing via a nasal endoscope.

50. The method of claim 49 wherein visualizing comprises advancing the nasal endoscope with the surgical probe shaft.

51. The method of claim 31 further comprising introducing a temperature sensor in proximity to the distal end of the surgical probe shaft.

52. The method of claim 31 further comprising applying a pressure to the tissue region via the distal end with a force of 20 to 200 grams.

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53. The method of claim 31 further comprising waiting 10 to 20 seconds after ablating the posterior nasal nerves prior to removing the distal end from the tissue region.

54. The method of claim 31 wherein ablating the at least one posterior nasal nerve comprises ablating the tissue region through a layer of gel.

55. The method of claim 31 further comprising assessing the tissue region during and/or after ablation.

56. The method of claim 55 wherein assessing comprises inspecting the tissue region visually or via ultrasound.

57. The method of claim 55 wherein assessing comprises detecting or a temperature of the tissue region.

58. The method of claim 31 further comprising vibrating the distal end while maintaining the distal end against the tissue region.

59. The method of claim 31 further comprising applying an anesthetic to the tissue region to be treated prior to ablating the posterior nasal nerves.

60. A surgical probe configured for ablation, comprising:

a surgical probe shaft comprising an elongated structure with a distal end and a proximal end;

an expandable structure attached to the distal end of the probe shaft, the expandable structure having a deflated configuration and an expanded configuration;

a lumen in fluid communication with an interior of the expandable structure; and

a member attached to the distal end and extending within the expandable structure which encloses the member such that the member is unattached to the interior of the expandable structure,

wherein the member defines an atraumatic shape which is sized for pressing against and manipulating through the expandable structure a lateral nasal wall proximate to at least one posterior nasal nerve.

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61. The surgical probe of claim 60 wherein the surgical probe shaft is between 1 mm and 4 mm in diameter and between approximately 4 cm and 10 cm in length.

62. The surgical probe of claim 60 wherein the lumen is defined through the probe shaft.

63. The surgical probe of claim 60 wherein surgical probe shaft is malleable and is configured for shape forming by the user.

64. The surgical probe of claim 60 further comprising a surgical hand piece attached to the proximal end, where the surgical hand piece is configured to be held like writing utensil or like a pistol.

65. The surgical probe of claim 64 wherein the surgical hand piece comprises a flow control valve actuator.

66. The surgical probe of claim 60 further comprising a pressurized reservoir in fluid communication with interior of the expandable structure through the lumen.

67. The surgical probe of claim 66 wherein the reservoir contains a liquid cryogen.

68. The surgical probe of claim 60 wherein the member comprises a looped structure defining an opening therethrough.

69. The surgical probe of claim 60 wherein the member comprises a coiled spring-like structure.

70. The surgical probe of claim 69 wherein the coiled spring-like structure is curved and tangent to the distal end of the surgical probe shaft.

71. The surgical probe of claim 69 wherein the coiled spring-like structure is at least partially malleable and is configured for shape forming by the user.

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72. The surgical probe of claim 69 wherein the coiled spring-like structure comprises a tightly coiled metal wire defining a central lumen and an outer surface.

73. The surgical probe of claim 72 wherein the central lumen is in fluidic communication with the lumen.

74. The surgical probe of claim 72 wherein the central lumen comprises a polymeric liner.

75. The surgical probe of claim 60 wherein the expandable structure comprises a distensible or non-distensible material.

76. The surgical probe of claim 60 wherein the expandable structure is configured as a hollow bulbous structure with an ostium configured for fluid tight bonding to the distal end of the surgical probe shaft.

77. The surgical probe of claim 60 wherein the expandable structure is configured to expand to a greater extent in a first radial axis than a second radial axis.

78. The surgical probe of claim 60 further comprising an imaging device in proximity to the distal end of the surgical probe shaft.

79. The surgical probe of claim 60 further comprising a temperature sensor in proximity to the distal end of the surgical probe shaft.

80. The surgical probe of claim 60 further comprising an indicator or marker along the shaft.

81. A method for treating a tissue region within a nasal cavity, comprising:

advancing a distal end of a surgical probe shaft through the nasal cavity and into proximity of the tissue region having at least one posterior nasal nerve;

introducing a cryogenic fluid into an expandable structure attached to the distal end of the probe shaft such that the expandable structure inflates from a deflated configuration

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into an expanded configuration against the tissue region;

adjusting a position of a member relative to the tissue region, wherein the member is attached to the distal end of the probe shaft and extends within the expandable structure which encloses the member such that the member is unattached to an interior of the expandable structure;

applying a pressure against the tissue region having the at least one posterior nasal nerve via the member pressing against the interior of the expandable structure, wherein the member defines an atraumatic shape which is sized for pressing against and manipulating the tissue region through the expandable structure; and

maintaining the member against the interior of the expandable structure and the tissue region until the tissue region is cryogenically ablated.

82. The method of claim 81 wherein maintaining the member further comprises cryogenically ablating the at least one posterior nasal nerve such until symptoms of rhinitis are reduced.

83. The method of claim 81 wherein advancing a distal end comprises advancing the distal end through a nostril and into the nasal cavity.

84. The method of claim 81 wherein advancing a distal end comprises advancing the distal end at least 2 cm beyond an anterior entrance to a middle meatus.

85. The method of claim 81 wherein advancing a distal end comprises:

advancing the distal end along an upper surface of the inferior nasal turbinate to a mid-portion of the middle nasal turbinate;

advancing the distal end into a middle meatus; and

further advancing the distal end posteriorly up into a cul-de-sac.

86. The method of claim 81 wherein advancing a distal end comprises positioning the member between the middle and inferior nasal turbinate.

87. The method of claim 81 wherein advancing a distal end comprises positioning the member relative to the tissue region surrounded by the middle nasal turbinate, inferior nasal turbinate, and lateral wall forming a cul-de-sac.

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88. The method of claim 81 wherein advancing a distal end comprises positioning the member into proximity of the Pterygomaxillary fossa, sphenopalatine ganglion, sphenopalatine ganglion, or vidian nerve.

89. The method of claim 81 wherein advancing a distal end comprises positioning the member into proximity of accessory posterolateral nerves bounded by an sphenopalatine foramen superiorly, an inferior edge of an inferior turbinate inferiorly, a Eustachian tube posteriorly, or a posterior third of the middle and inferior turbinates anteriorly.

90. The method of claim 81 wherein introducing a cryogenic fluid comprises evaporating the cryogenic fluid within the expandable structure.

91. The method of claim 81 wherein the expandable structure is inflated in response to evaporation of the cryogenic fluid within the interior.

92. The method of claim 81 wherein introducing a cryogenic fluid further comprises expanding the expandable structure to a greater extent in one radial axis compared to a second radial axis.

93. The method on claim 81 wherein adjusting a position of a member further comprises positioning the member to contact a lateral nasal wall defined by a tail of a nasal turbinate, lateral wall, and an inferior turbinate.

94. The method of claim 81 wherein introducing a cryogenic fluid further comprises flowing the cryogenic fluid into the interior between approximately 20 seconds to 300 seconds.

95. The method of claim 81 wherein introducing a cryogenic fluid further comprises flowing the cryogenic fluid into the interior between approximately 20 seconds to 120 seconds.

96. The method of claim 81 wherein the cryogenic fluid comprises nitrous

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oxide, liquid nitrogen, or carbon dioxide.

97. The method of claim 81 further comprising introducing an imaging device in proximity to the distal end.

98. The method of claim 81 further comprising visualizing the tissue region while advancing the distal end of the surgical probe through the nasal cavity.

99. The method of claim 98 wherein visualizing comprises visualizing via a CCD or CMOS imager positioned along the surgical probe shaft.

100. The method of claim 98 wherein visualizing comprises visualizing infrared wavelengths.

101. The method of claim 98 wherein visualizing comprises visualizing via a nasal endoscope.

102. The method of claim 101 wherein visualizing comprises advancing the nasal endoscope with the surgical probe shaft.

103. The method of claim 81 further comprising introducing a temperature sensor in proximity to the distal end of the surgical probe shaft.

104. The method of claim 81 wherein advancing a distal end comprises positioning the surgical probe shaft into proximity of an anterior region of middle or inferior nasal turbinate.

105. The method of claim 81 wherein applying a pressure comprises applying a force of 20 to 200 grams via the member pressing against the interior of the expandable structure.

106. The method of claim 81 further comprising stopping the cryogenic fluid and waiting 10 to 20 seconds prior to removing the distal end of the surgical probe shaft from the tissue region.

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107. The method of claim 81 wherein maintaining the member comprises ablating the tissue region through a layer of gel.

108. The method of claim 81 further comprising assessing the tissue region during and/or after ablation.

109. The method of claim 108 wherein assessing comprises inspecting the tissue region visually or via ultrasound.

110. The method of claim 81 wherein assessing comprises detecting or a temperature of the tissue region.

111. The method of claim 81 further comprising vibrating the expandable structure while maintaining the member against the interior of the expandable structure and the tissue region.

112. The method of claim 81 further comprising applying an anesthetic to the tissue region to be treated prior to applying a pressure against the tissue region.

113. A method for treating rhinitis, comprising:

advancing a distal end of a surgical probe shaft through the nasal cavity and into proximity of a tissue region surrounded by the middle nasal turbinate, inferior nasal turbinate, and lateral wall forming a cul-de-sac and having at least one posterior nasal nerve;

introducing a cryogenic fluid into an expandable structure attached to the distal end of the probe shaft such that the expandable structure inflates from a deflated configuration into an expanded configuration against the tissue region, wherein the distal end has an attached member which extends within the expandable structure such that the member is unattached to the interior of the expandable structure;

applying a pressure against the tissue region via the member pressing against the interior of the expandable structure, wherein the member defines an atraumatic shape and is unattached to the interior of the expandable structure; and

maintaining the member against the interior of the expandable structure and the

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tissue region until the tissue region is cryogenically ablated.

114. The method of claim 113 wherein advancing a distal end comprises advancing the distal end at least 2 cm beyond an anterior entrance to a middle meatus.

115. The method of claim 113 wherein advancing a distal end comprises:

advancing the distal end along an upper surface of the inferior nasal turbinate to a mid-portion of the middle nasal turbinate;

advancing the distal end into a middle meatus; and

further advancing the distal end posteriorly up into a cul-de-sac.

116. The method of claim 113 wherein advancing a distal end comprises positioning the member between the middle and inferior nasal turbinate.

117. The method of claim 113 wherein advancing a distal end comprises positioning the member into proximity of the Pterygomaxillary fossa, sphenopalatine ganglion, sphenopalatine ganglion, or vidian nerve.

118. The method of claim 113 wherein advancing a distal end comprises positioning the member into proximity of accessory posterolateral nerves bounded by an sphenopalatine foramen superiorly, an inferior edge of an inferior turbinate inferiorly, a Eustachian tube posteriorly, or a posterior third of the middle and inferior turbinates anteriorly.

119. The method of claim 113 wherein introducing a cryogenic fluid comprises evaporating the cryogenic fluid within the expandable structure.

120. The method of claim 113 wherein the expandable structure is inflated in response to evaporation of the cryogenic fluid within the interior.

121. The method on claim 113 wherein advancing a distal end further comprises positioning the member to contact a lateral nasal wall defined by a tail of a nasal turbinate, lateral wall, and an inferior turbinate.

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122. The method of claim 113 wherein introducing a cryogenic fluid comprises flowing the cryogenic fluid into the interior between approximately 20 seconds to 300 seconds.

123. The method of claim 113 wherein introducing a cryogenic fluid further comprises flowing the cryogenic fluid into the interior between approximately 20 seconds to 120 seconds.

124. The method of claim 113 wherein the cryogenic fluid comprises nitrous oxide, liquid nitrogen, or carbon dioxide.

125. The method of claim 113 further comprising introducing an imaging device in proximity to the distal end.

126. The method of claim 113 further comprising visualizing the tissue region while advancing the distal end of the surgical probe through the nasal cavity.

127. The method of claim 126 wherein visualizing comprises visualizing via a CCD or CMOS imager positioned along the surgical probe shaft.

128. The method of claim 126 wherein visualizing comprises visualizing infrared wavelengths.

129. The method of claim 126 wherein visualizing comprises visualizing via a nasal endoscope.

130. The method of claim 129 wherein visualizing comprises advancing the nasal endoscope with the surgical probe shaft.

131. The method of claim 113 further comprising introducing a temperature sensor in proximity to the distal end of the surgical probe shaft.

132. The method of claim 113 wherein applying a pressure comprises applying a force of 20 to 200 grams via the member pressing against the interior of the expandable

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structure.

133. The method of claim 113 further comprising stopping the cryogenic fluid and waiting 10 to 20 seconds prior to removing the distal end of the surgical probe shaft from the tissue region.

134. The method of claim 113 wherein maintaining the member comprises ablating the tissue region through a layer of gel.

135. The method of claim 113 further comprising assessing the tissue region during and/or after ablation.

136. The method of claim 135 wherein assessing comprises inspecting the tissue region visually or via ultrasound.

137. The method of claim 113 wherein assessing comprises detecting or a temperature of the tissue region.

138. The method of claim 113 further comprising vibrating the expandable structure while maintaining the member against the interior of the expandable structure and the tissue region.

139. The method of claim 113 further comprising applying an anesthetic to the tissue region to be treated prior to applying a pressure against the tissue region.

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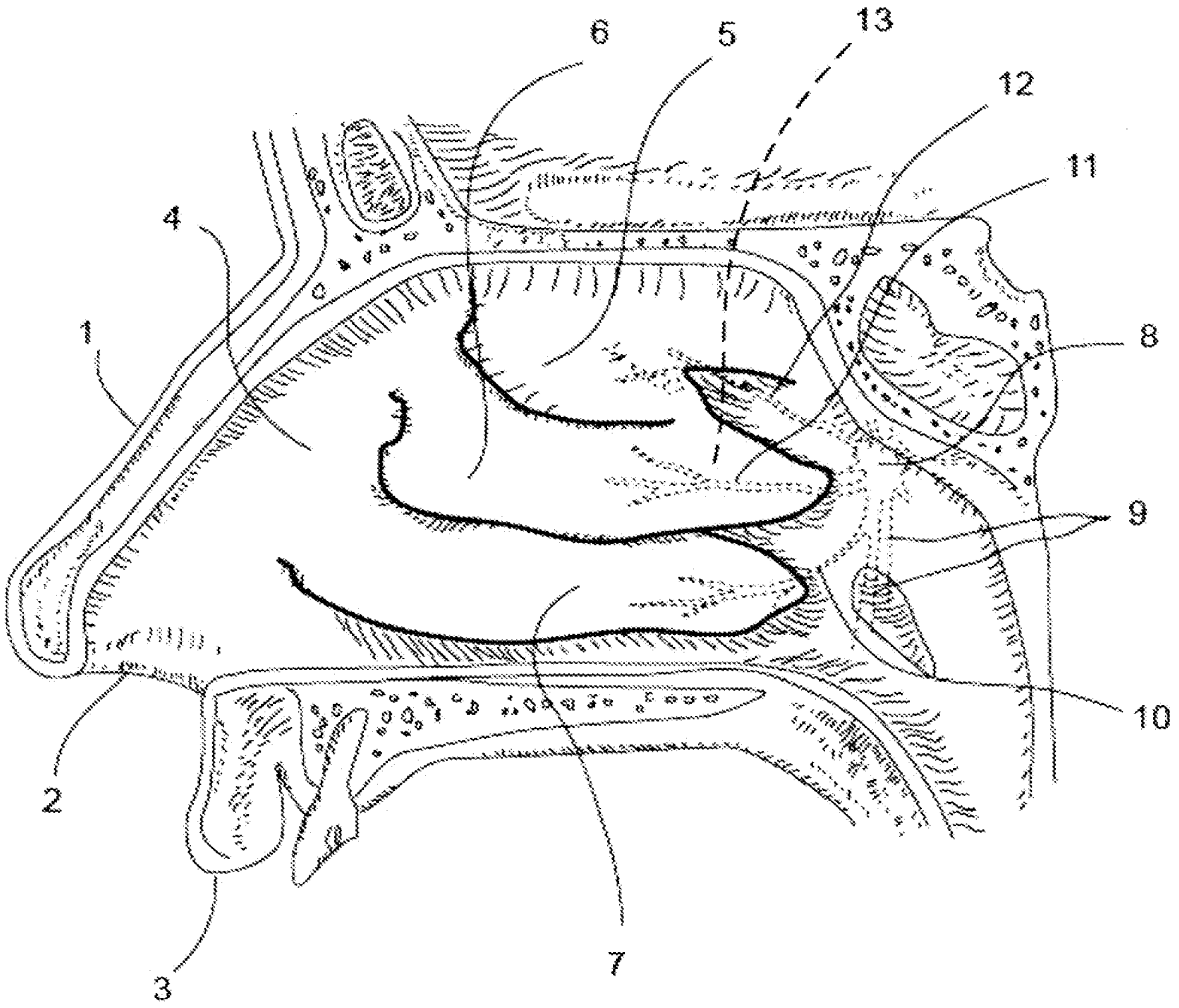


Figure 1

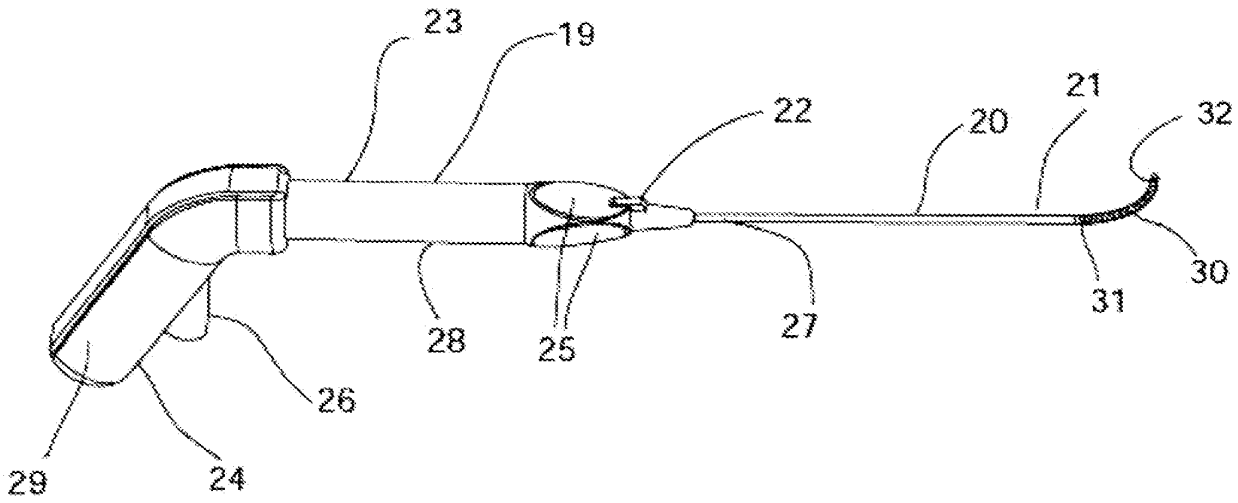


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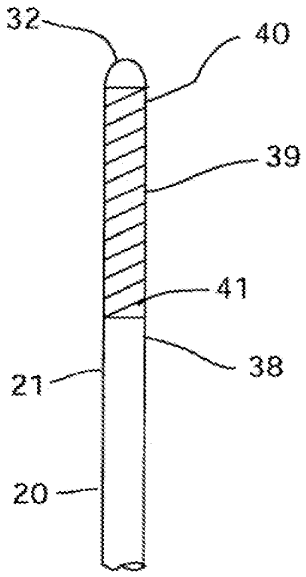


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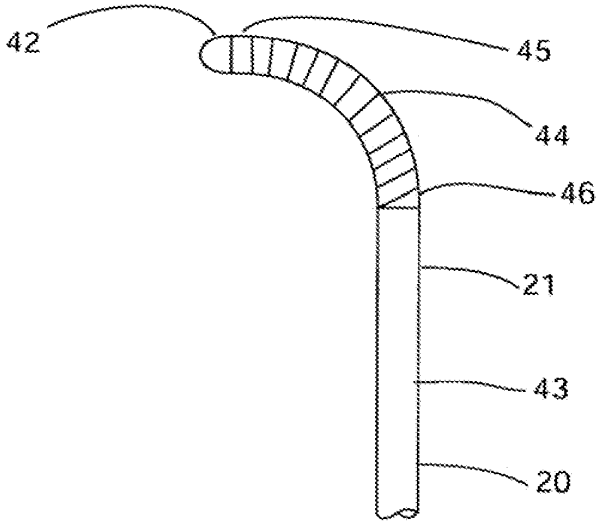


Figure 3B

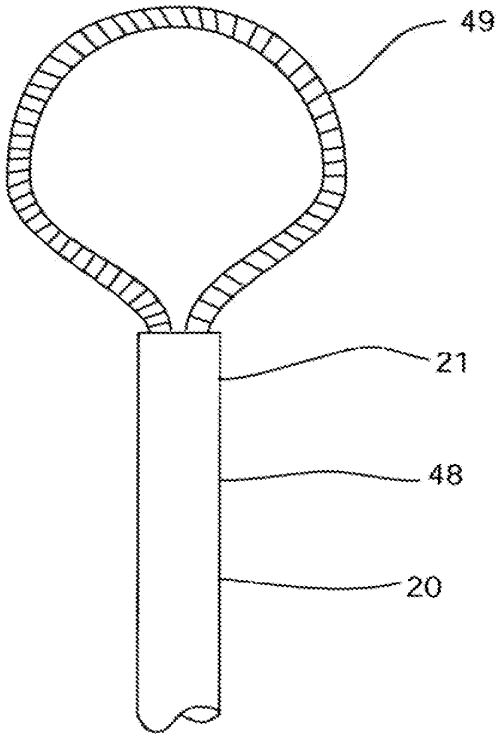


Figure 3C

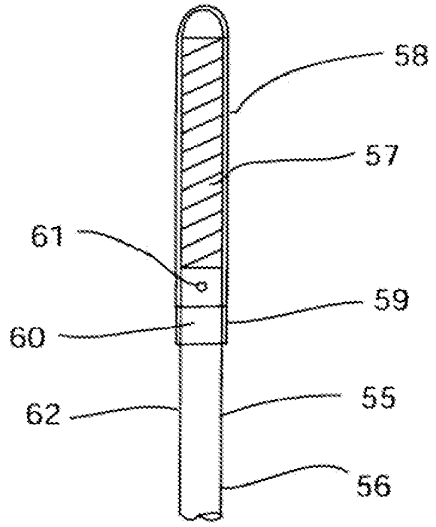


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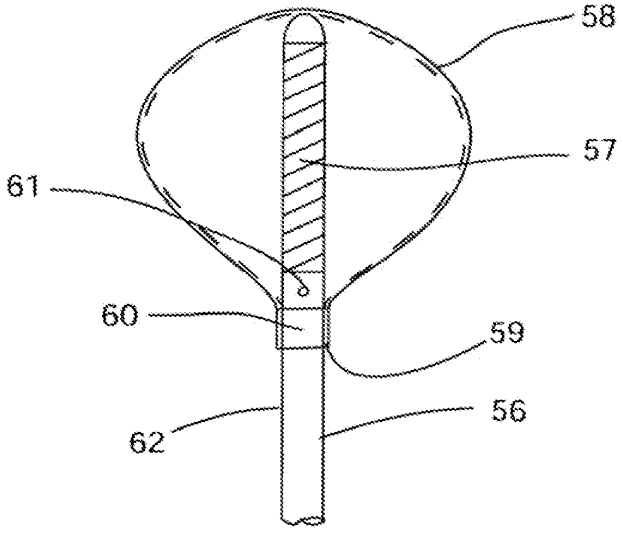


Figure 4B

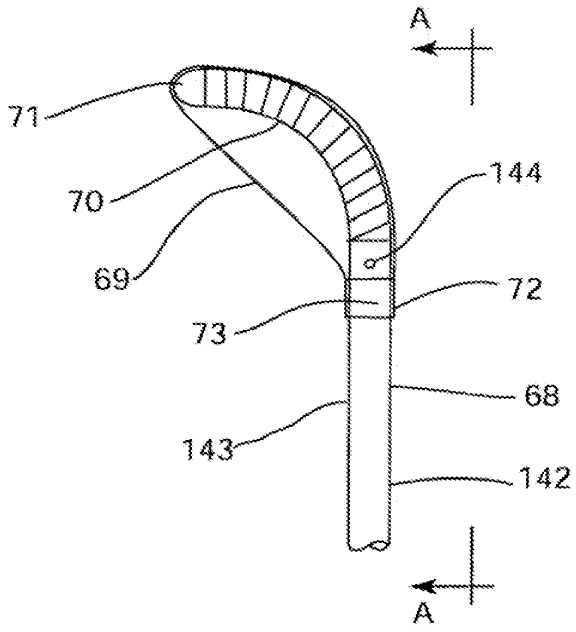


Figure 5A

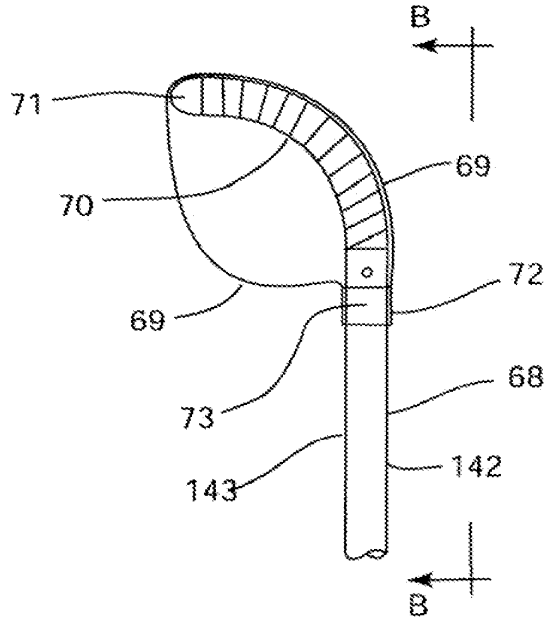
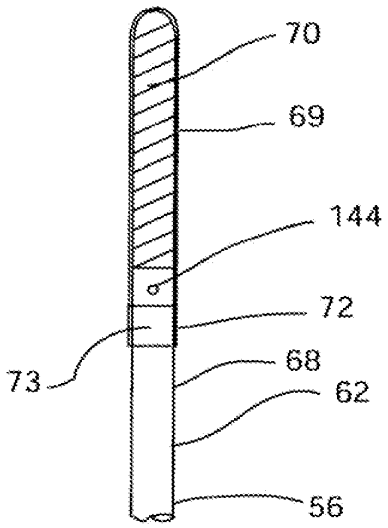
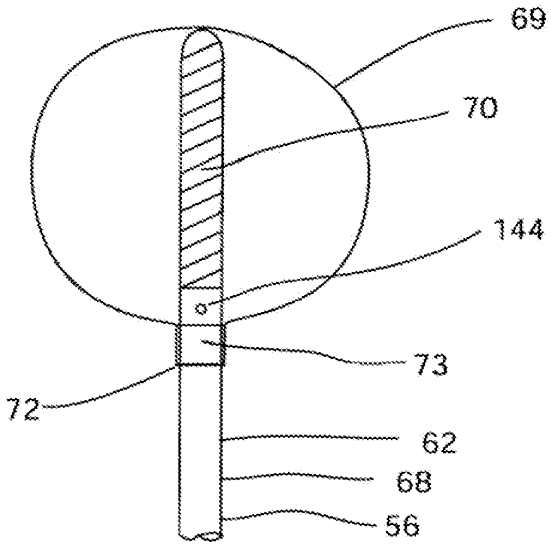


Figure 5B



View A-A

Figure 5C



View B-B

Figure 5D

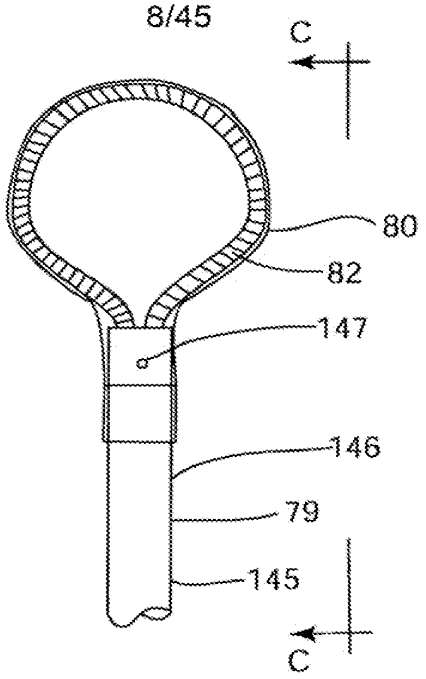


Figure 6A

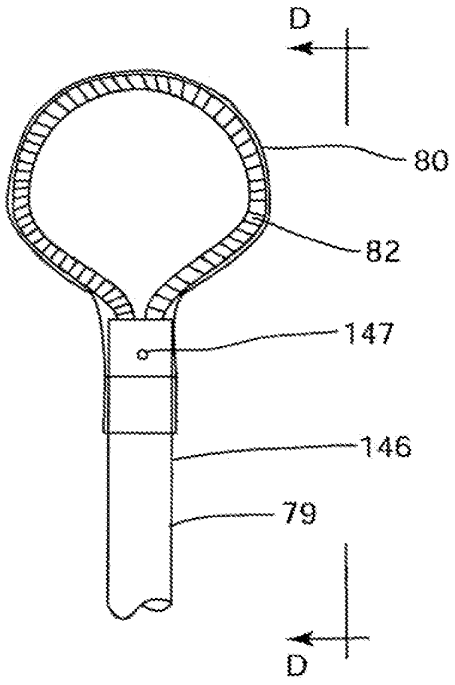
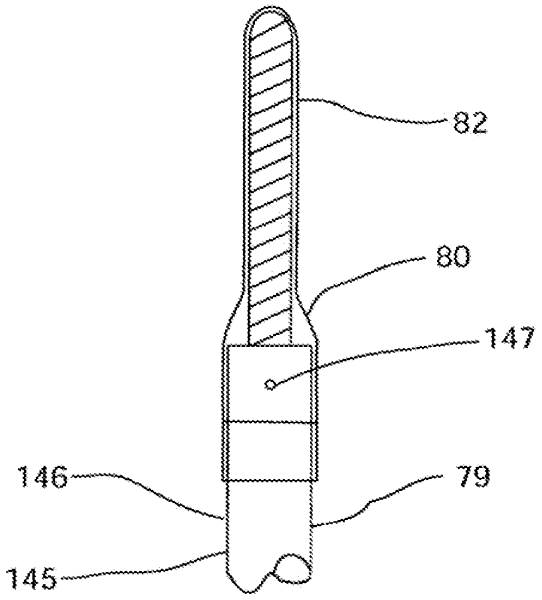
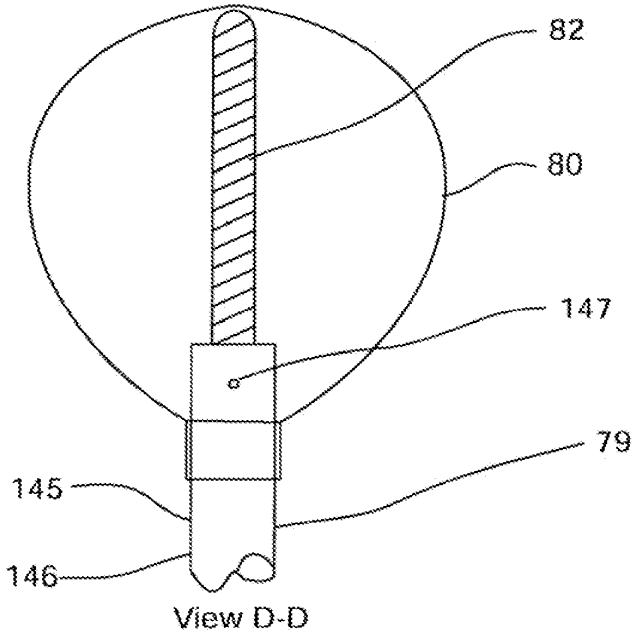


Figure 6B



View C-C

Figure 6C



View D-D

Figure 6D

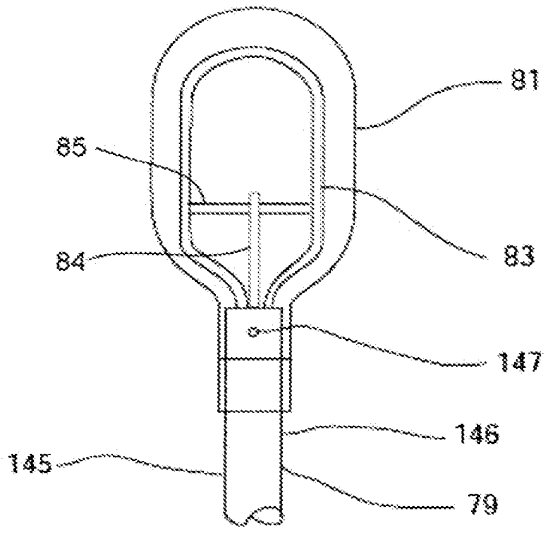


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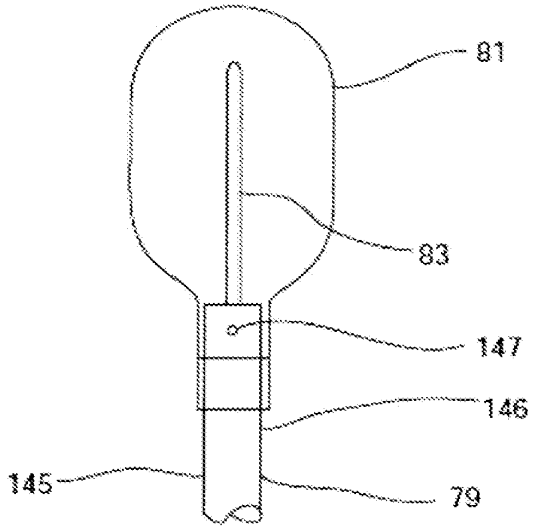


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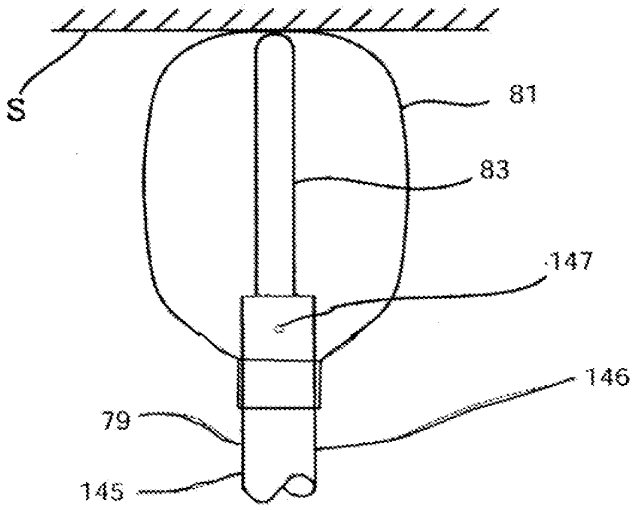


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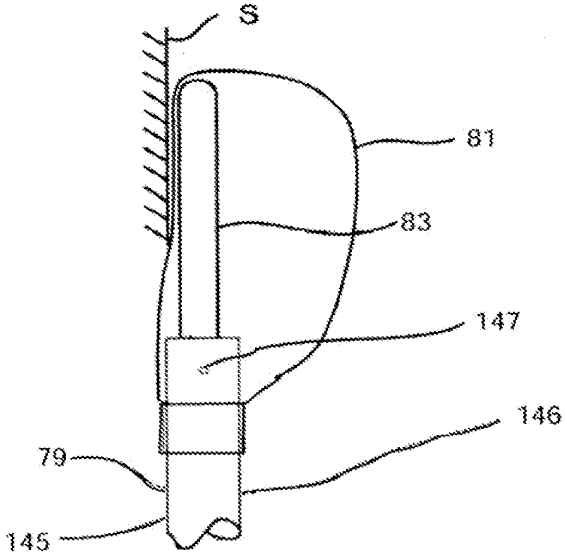


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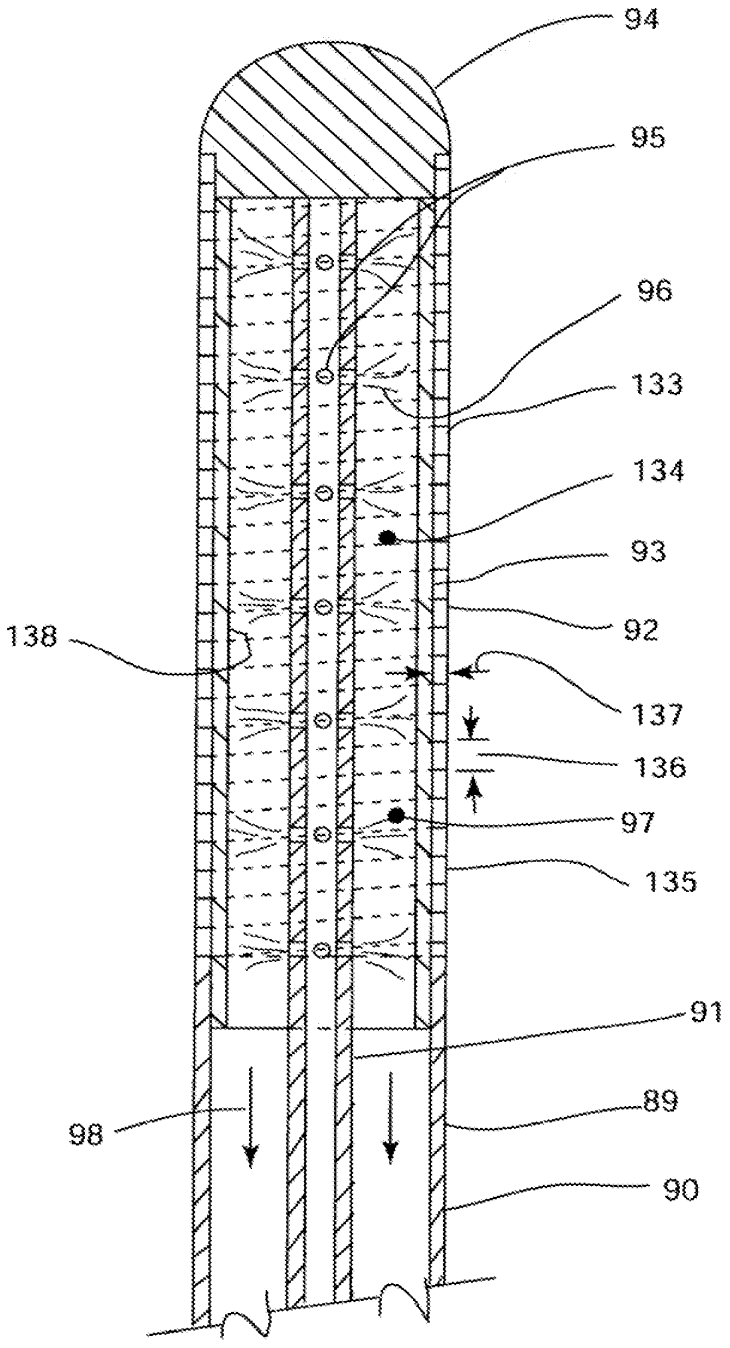


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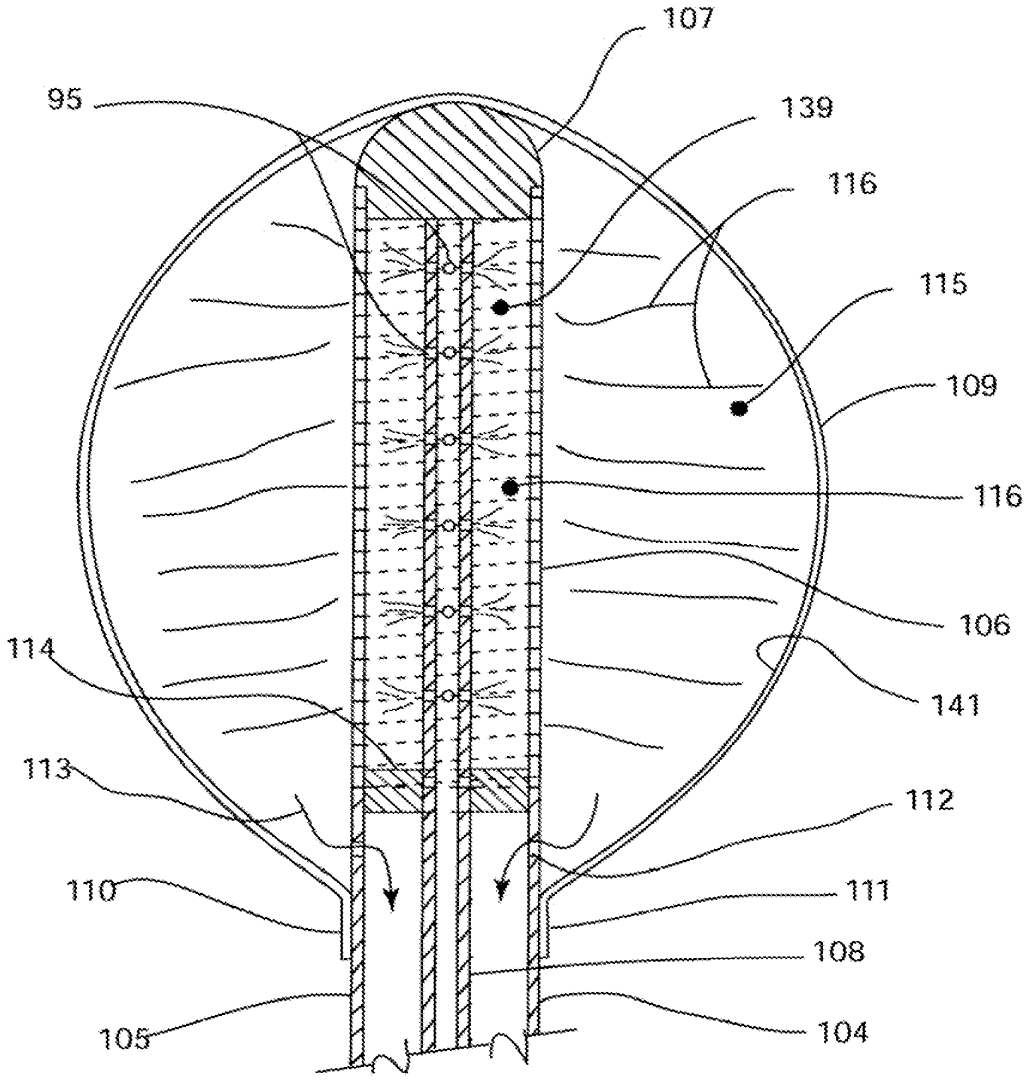

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Figure 8

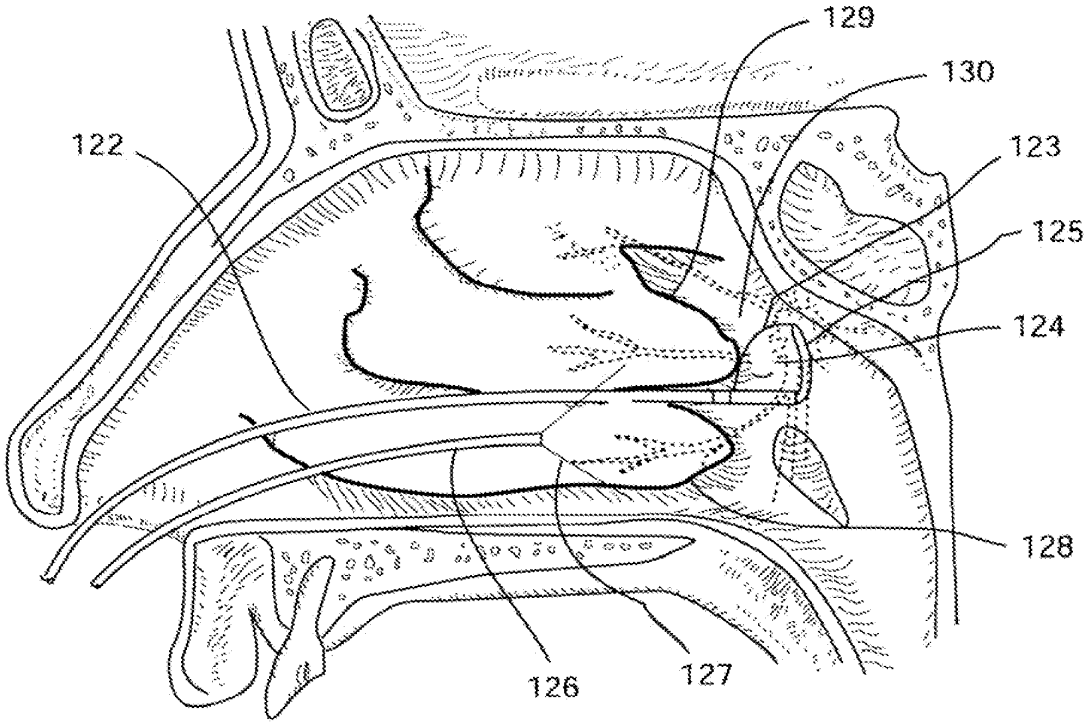


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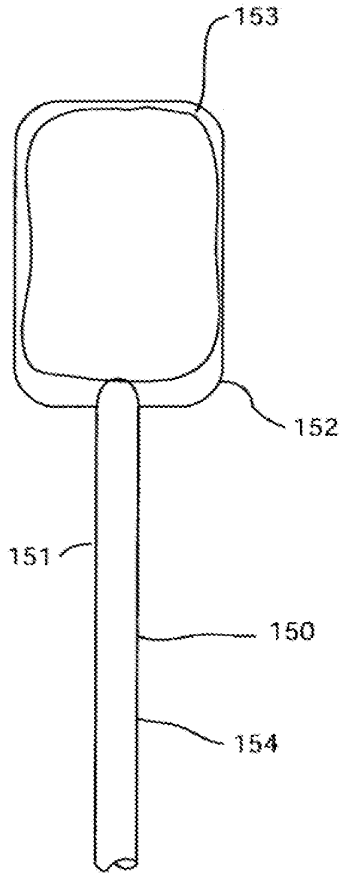


Figure 10A

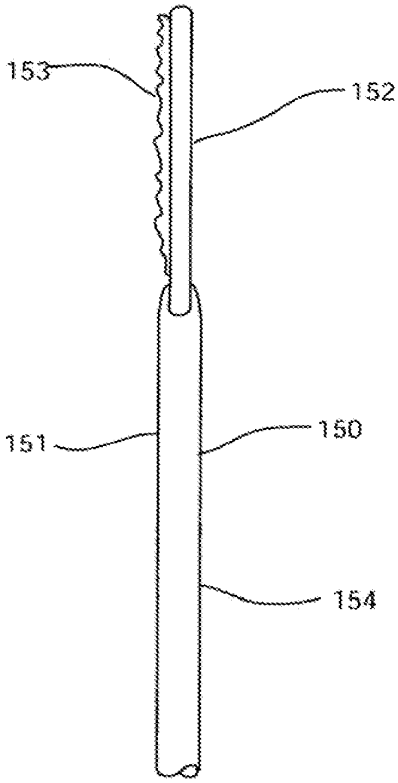


Figure 10B

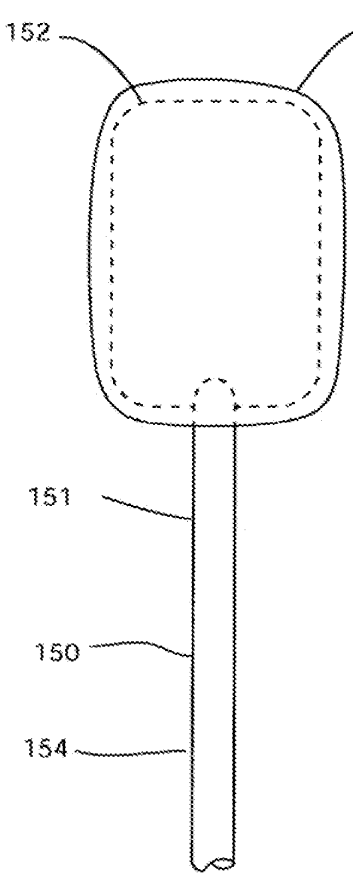


Figure 10C

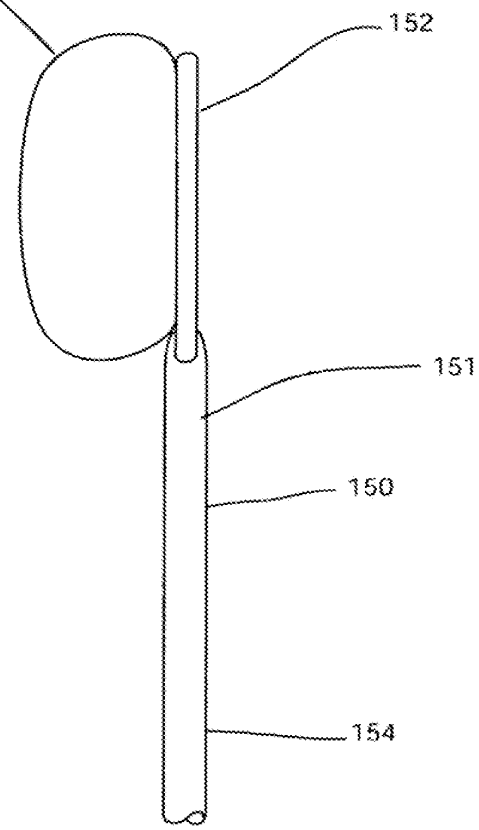


Figure 10D

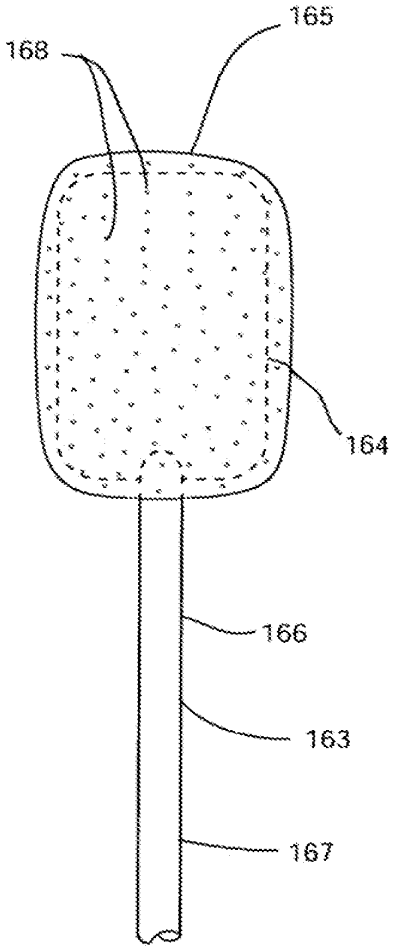


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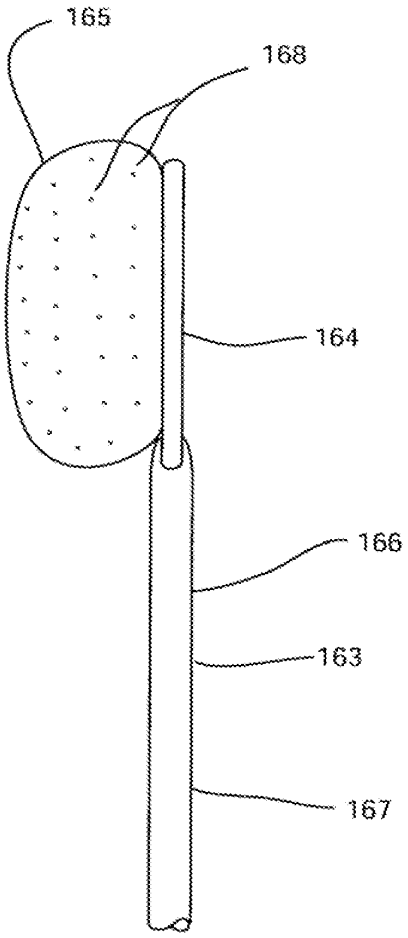


Figure 11B

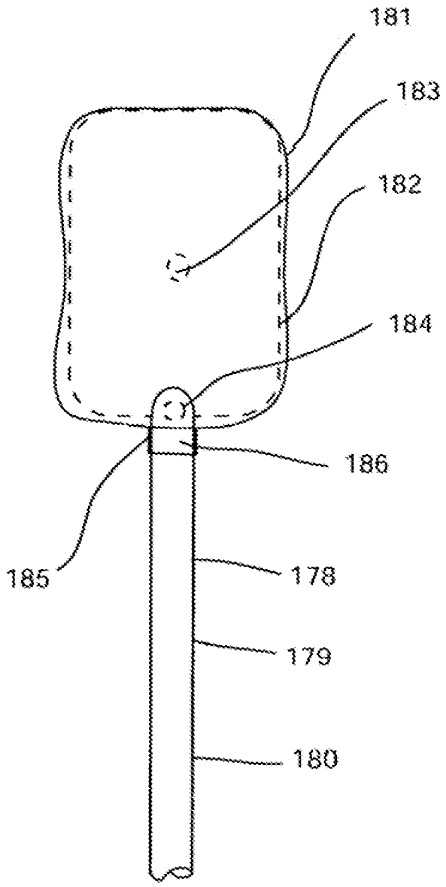


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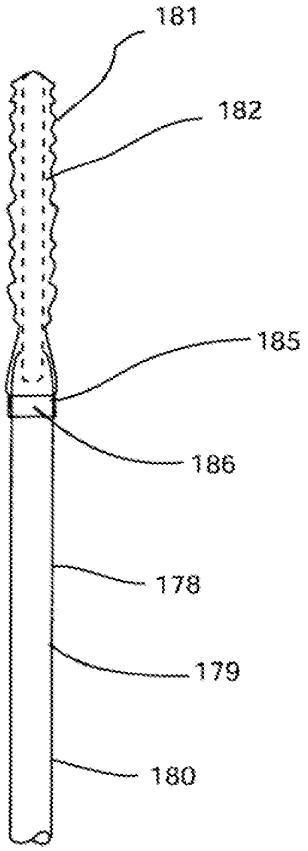


Figure 12B

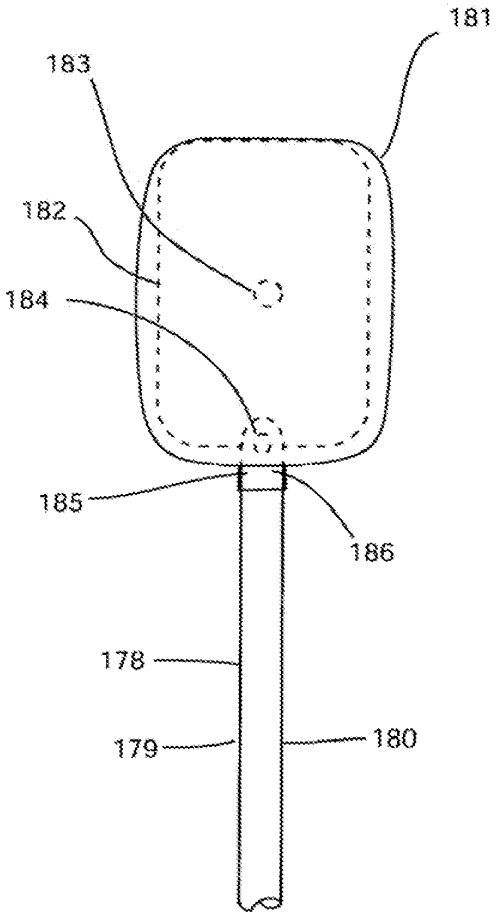


Figure 12C

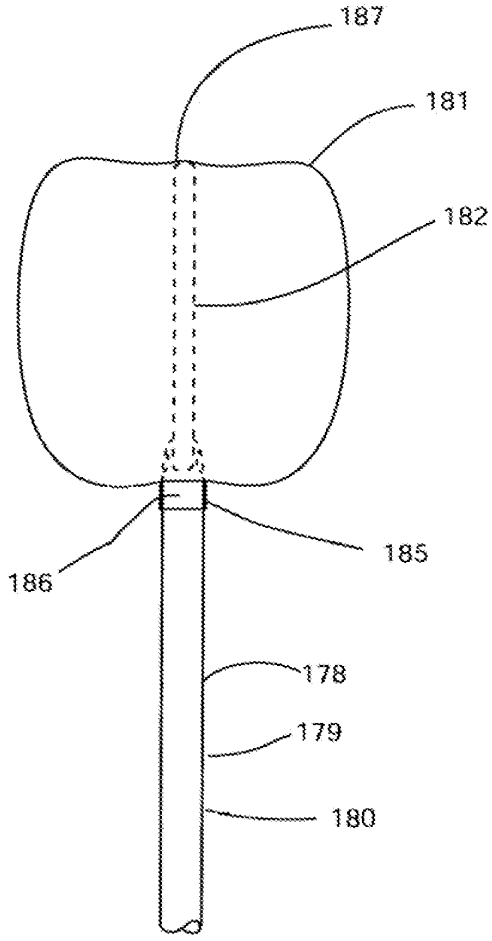


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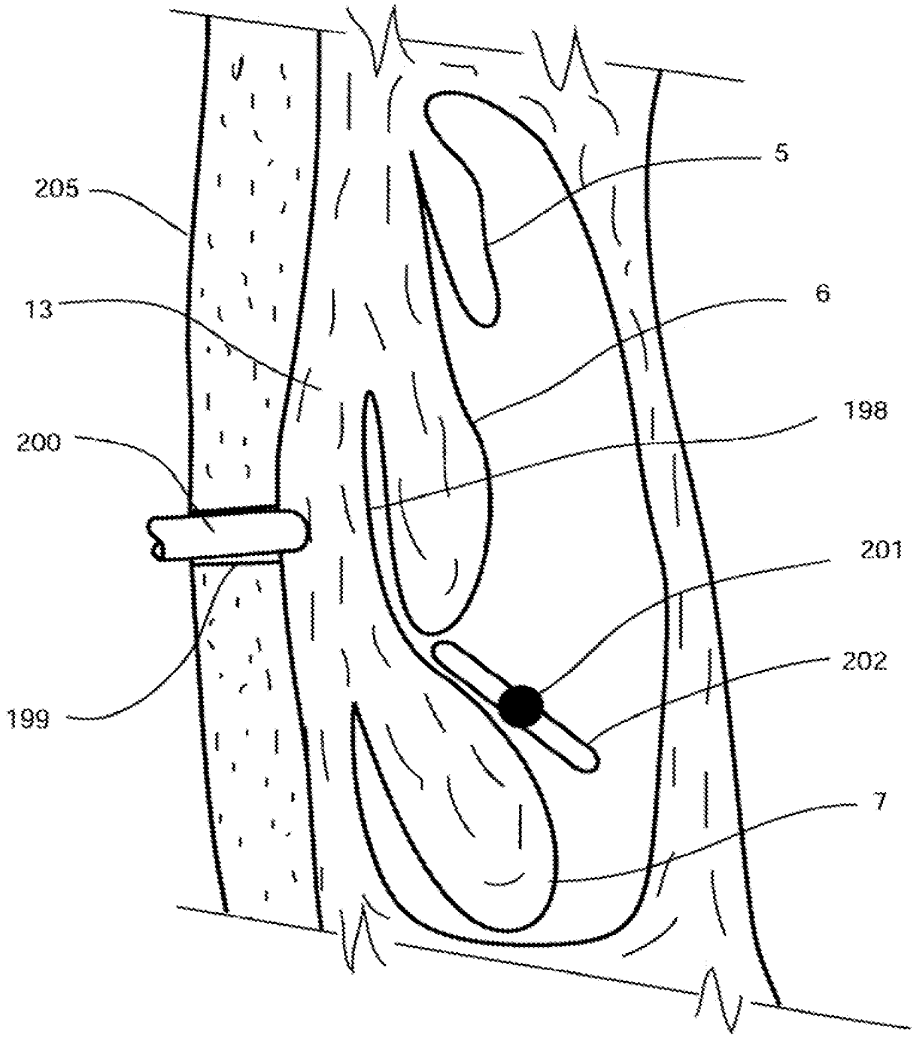


Figure 13A

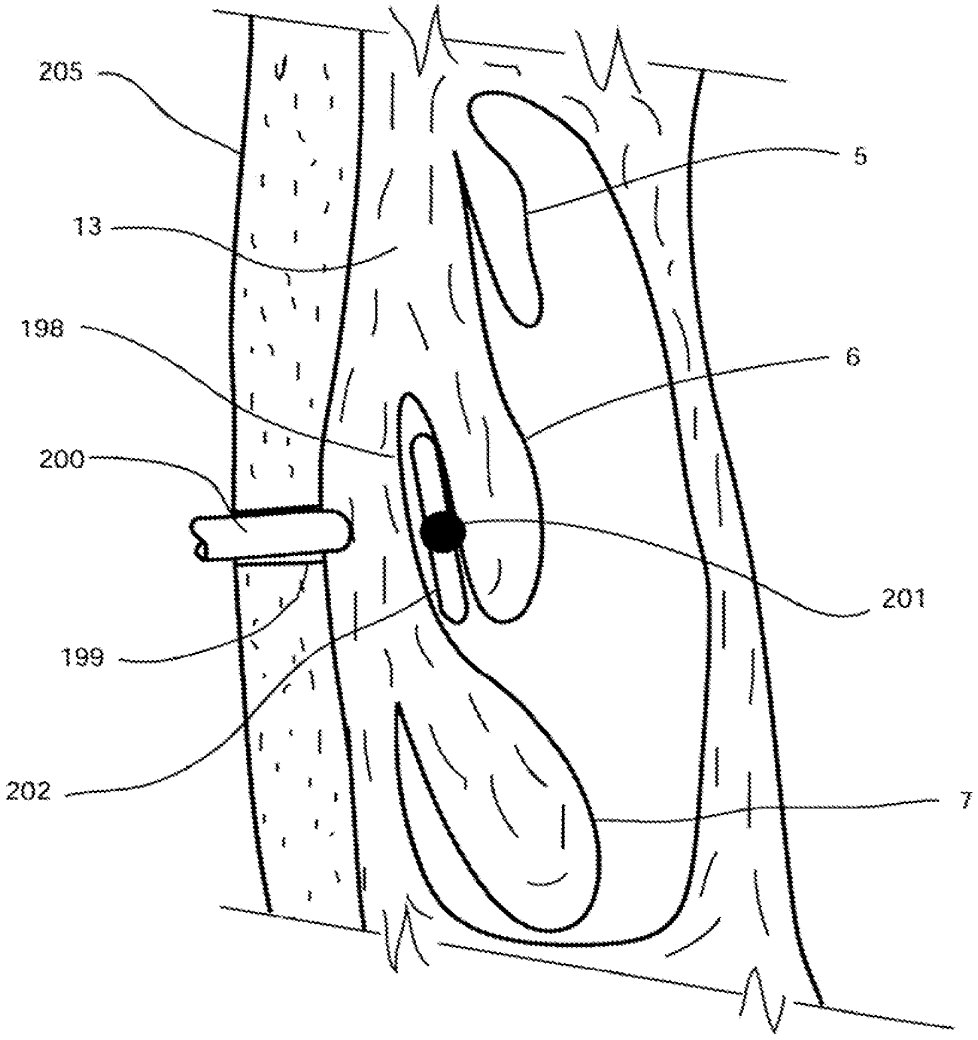


Figure 13B

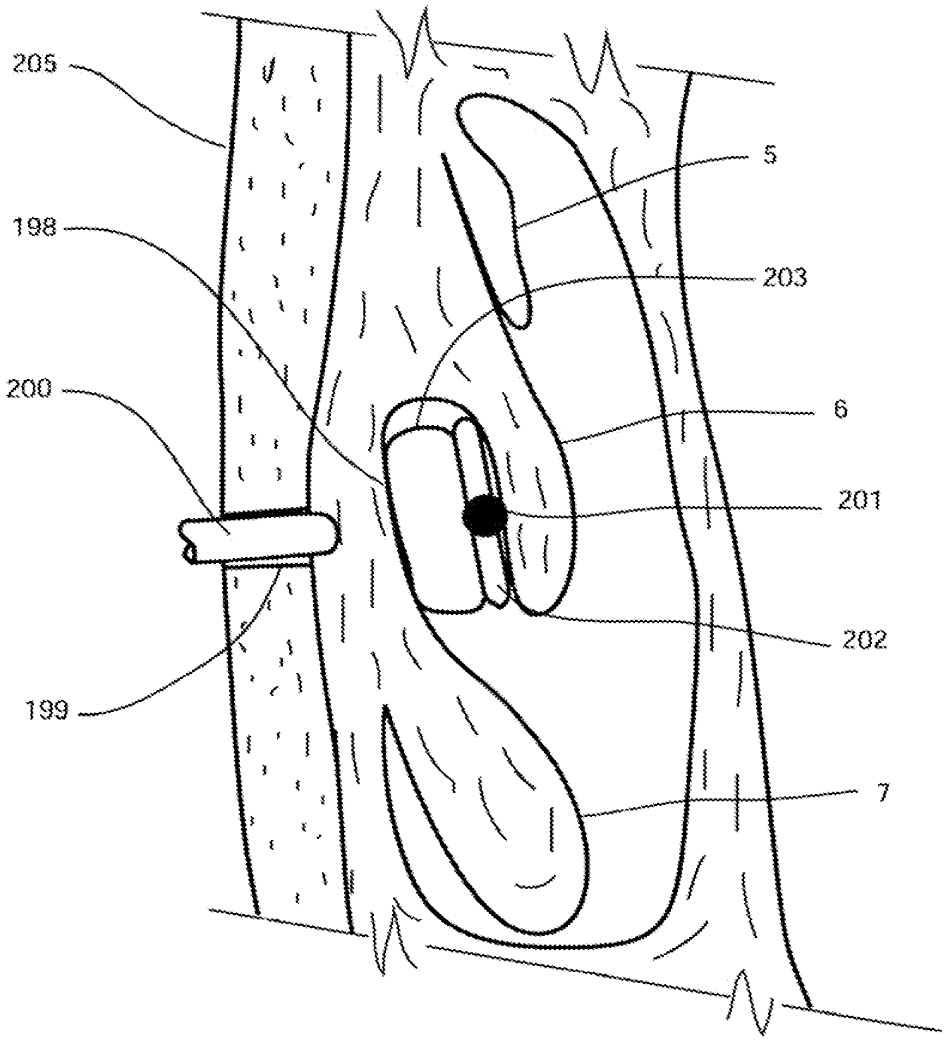


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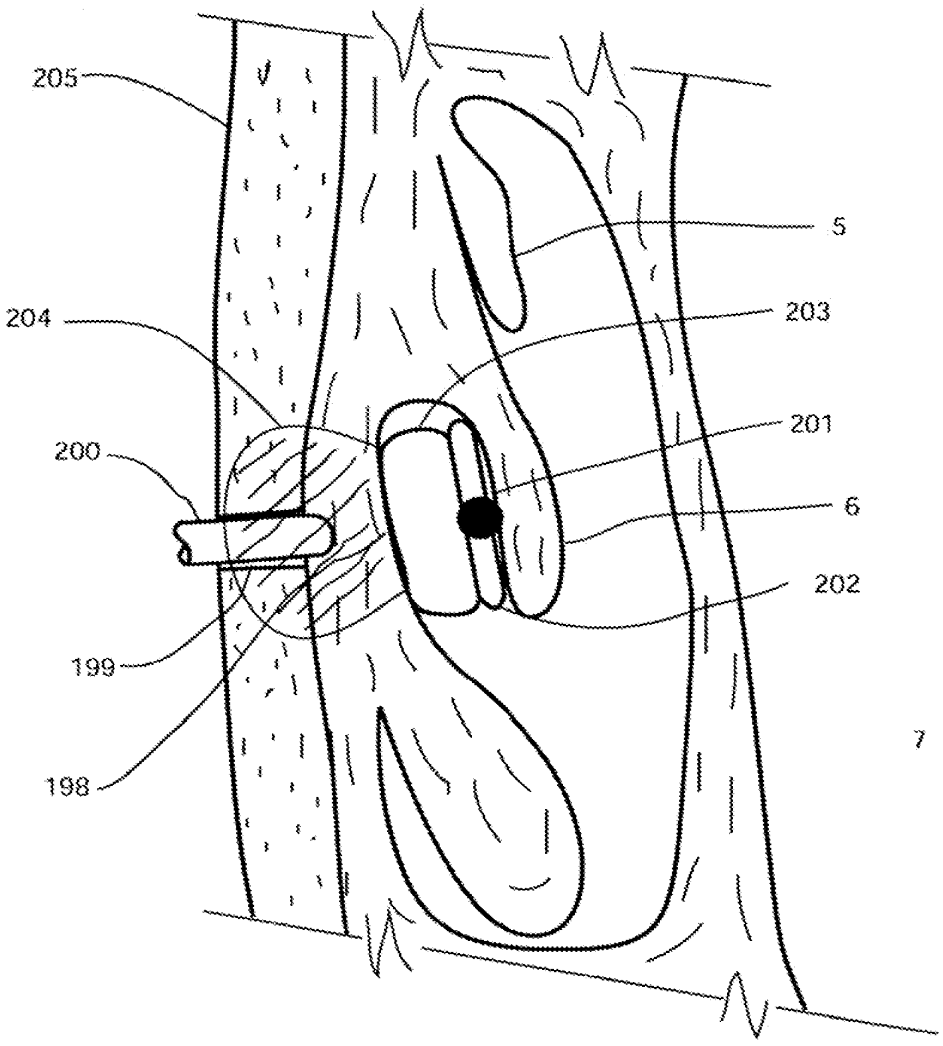


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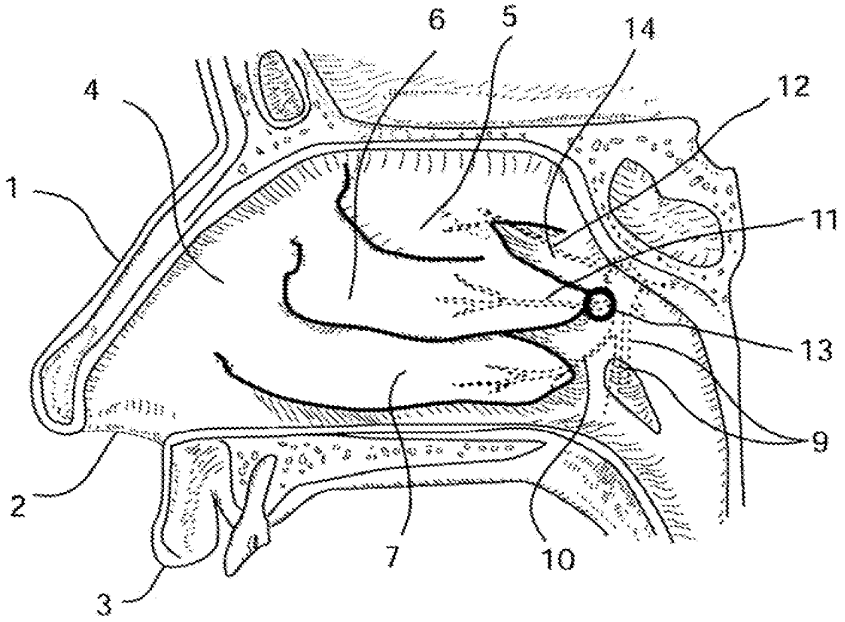


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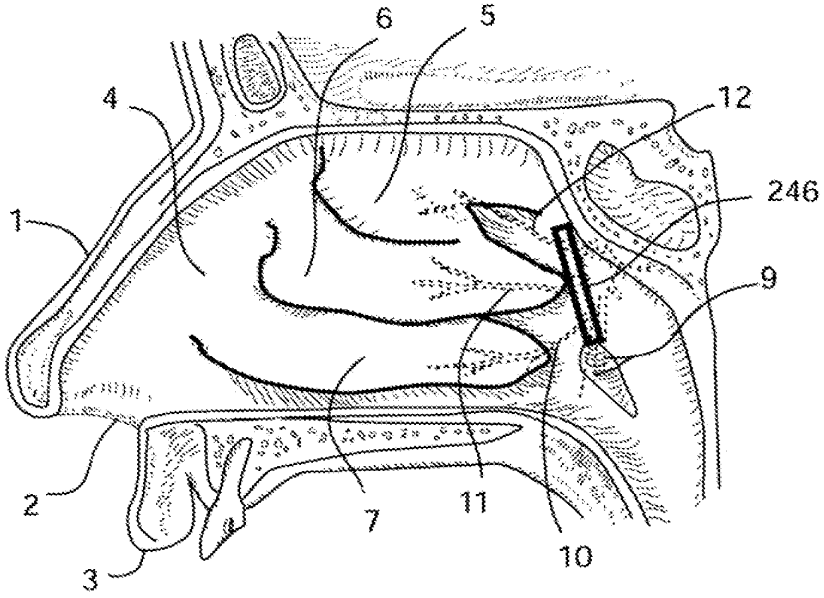


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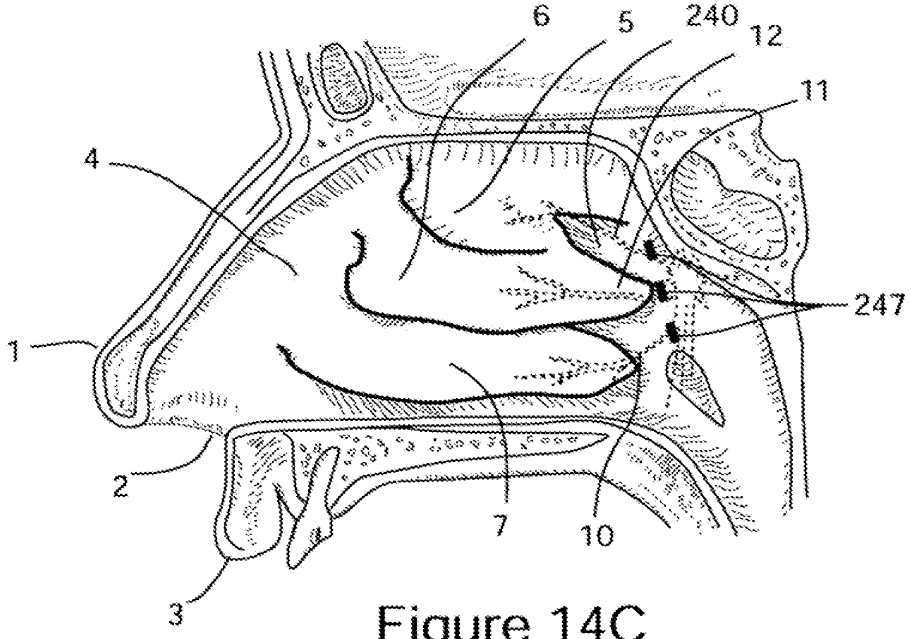


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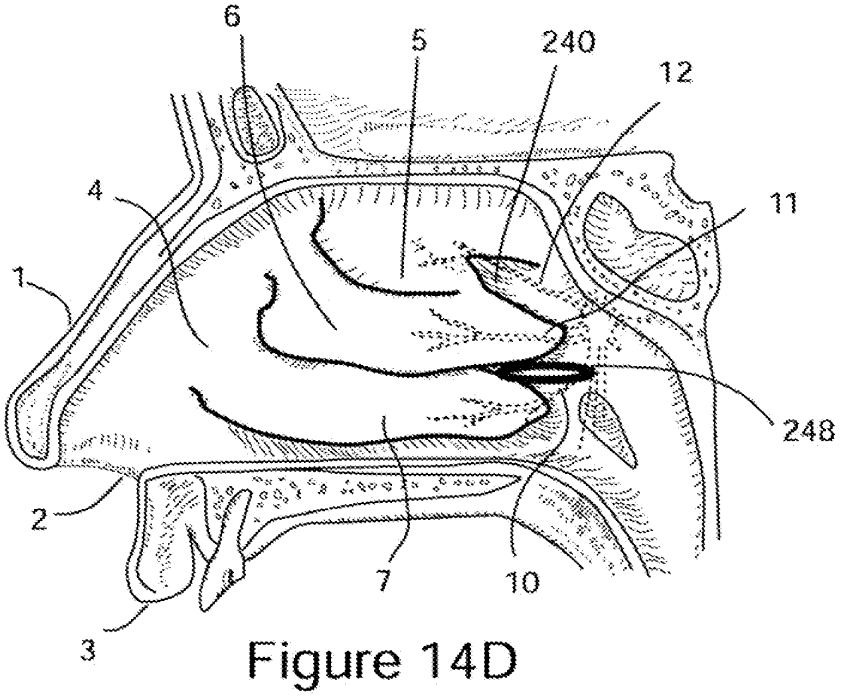


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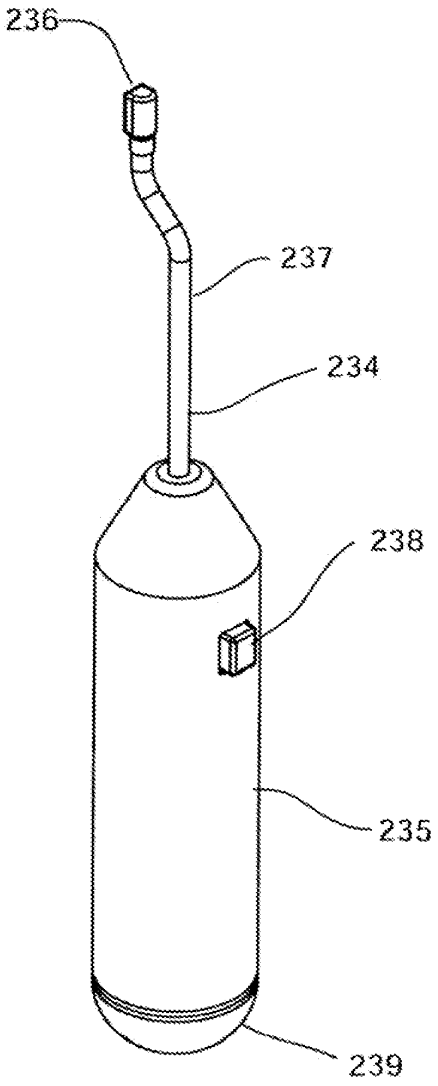


Figure 15A

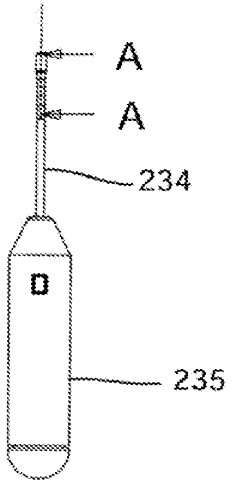
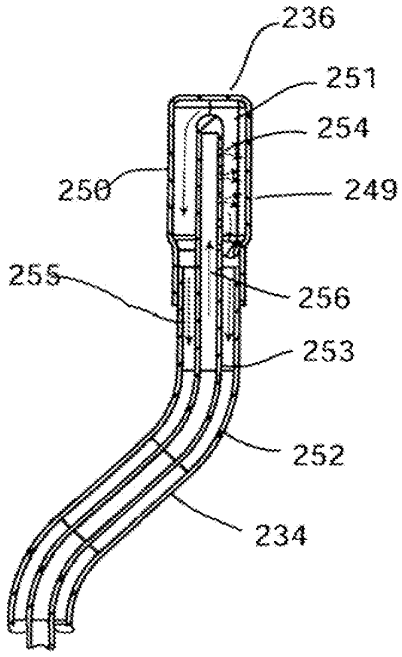


Figure 15B



Section A-A

Figure 15C

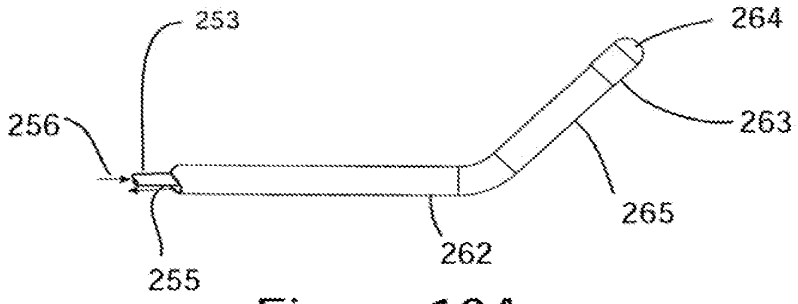


Figure 16A

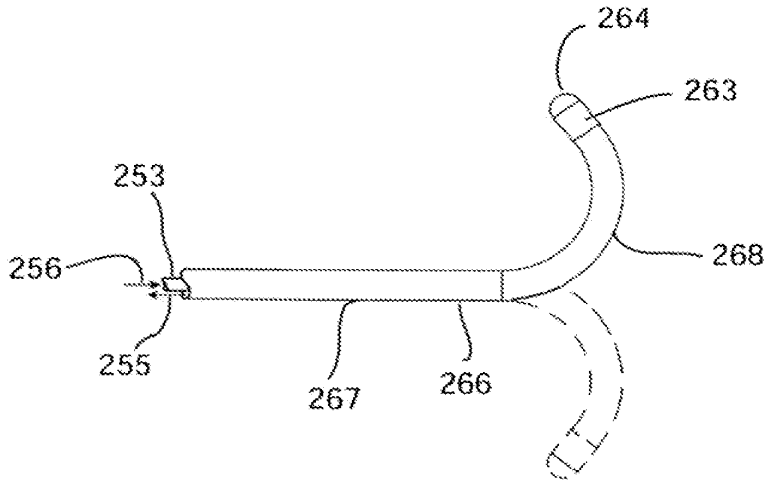


Figure 16B

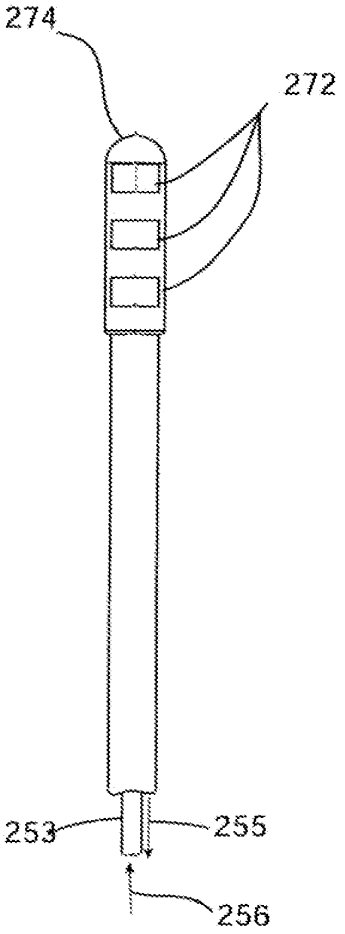


Figure 16C

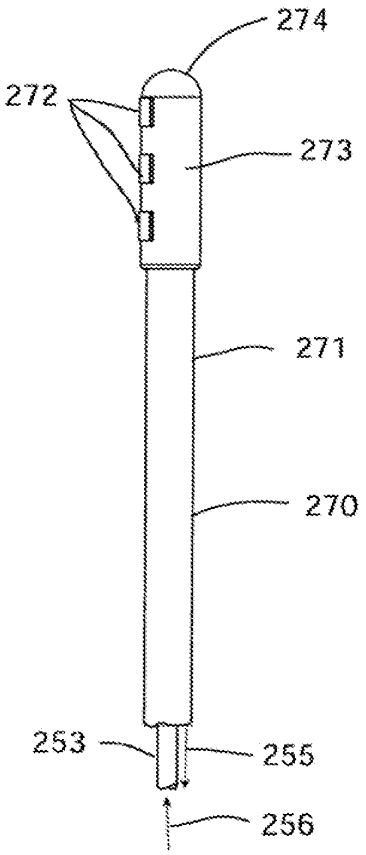


Figure 16D

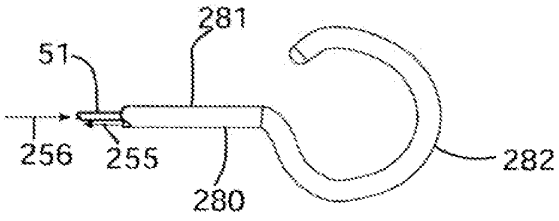


Figure 17A

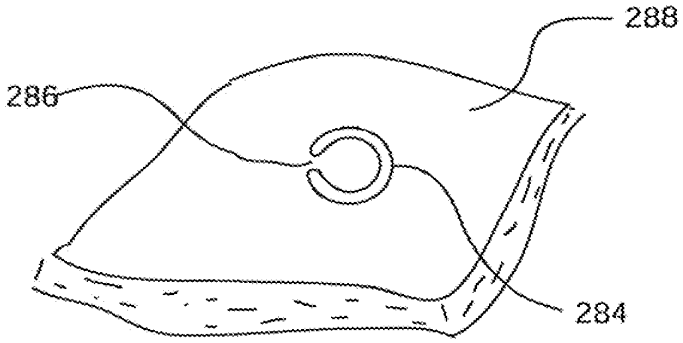


Figure 17B

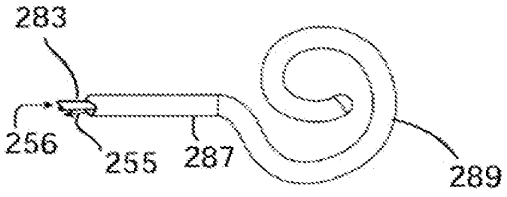


Figure 17C

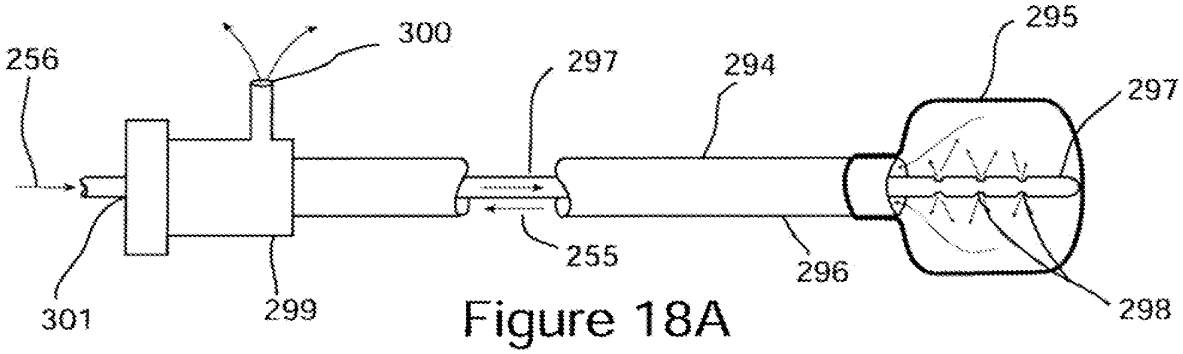


Figure 18A

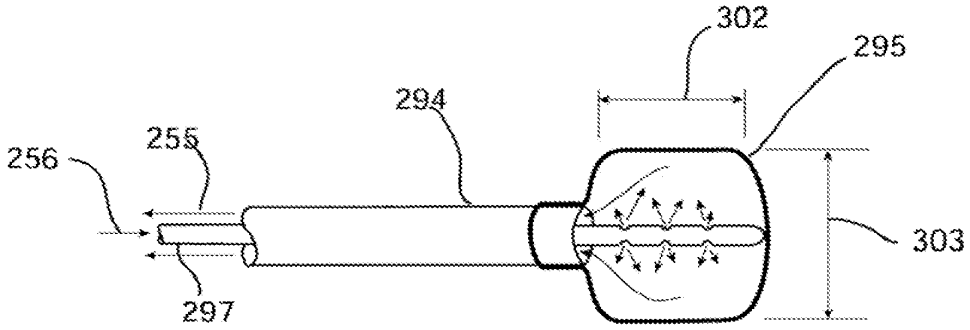


Figure 18B

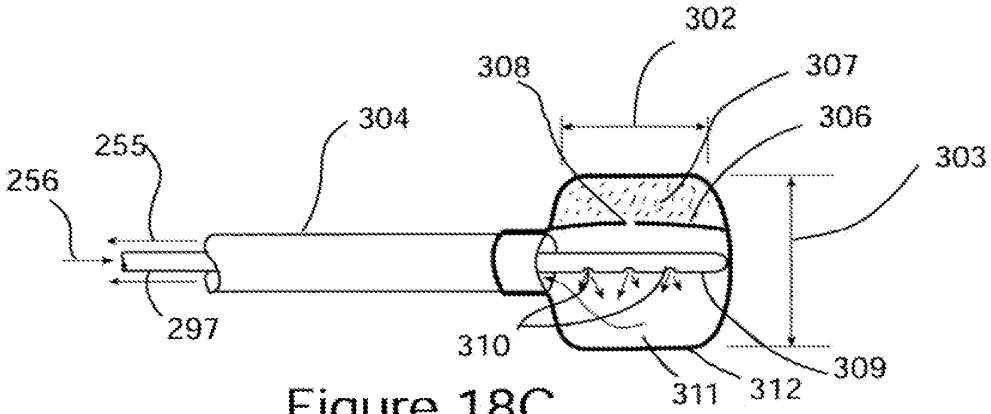


Figure 18C

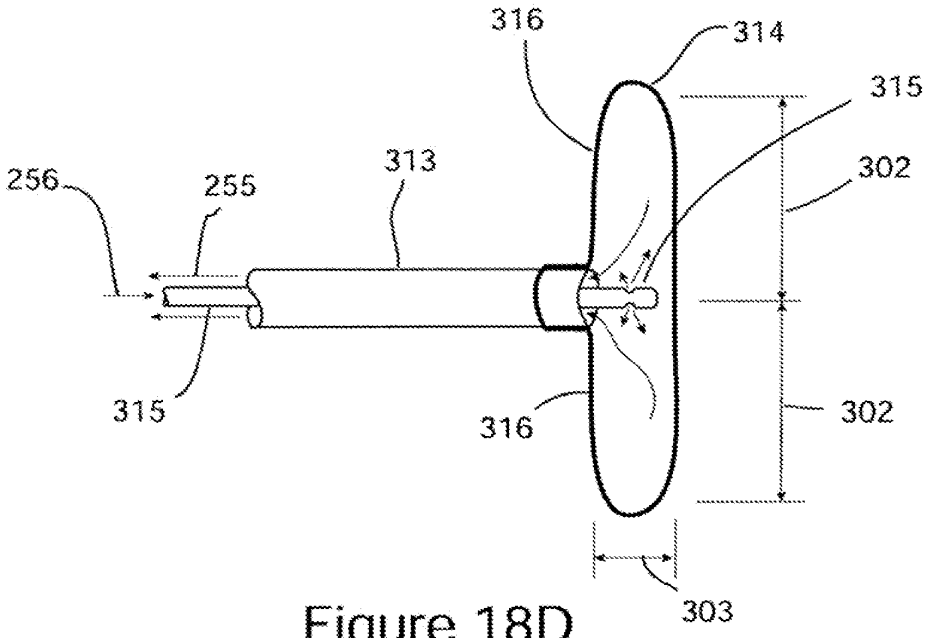


Figure 18D

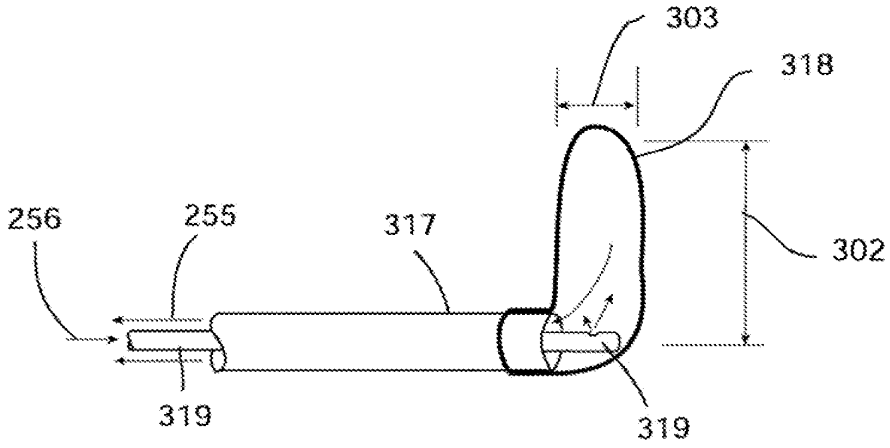


Figure 18E

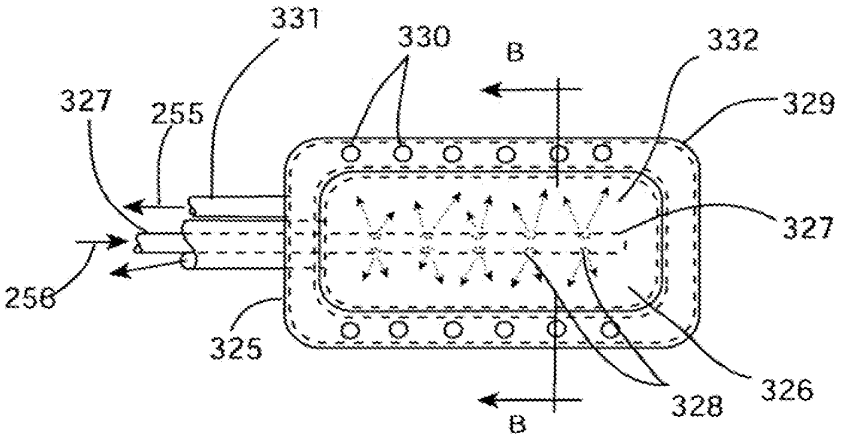
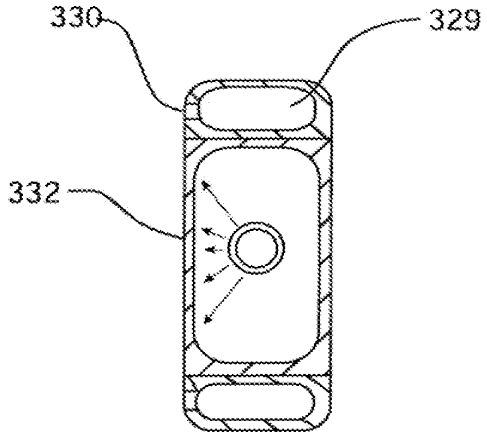


Figure 19A



Section B-B

Figure 19B

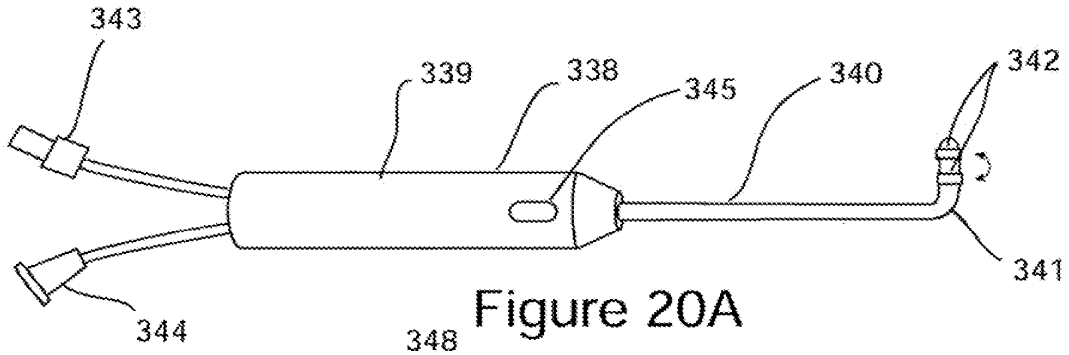


Figure 20A

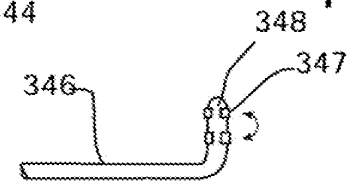


Figure 20B

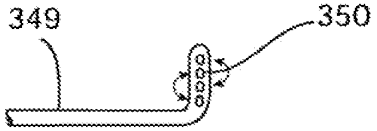


Figure 20C

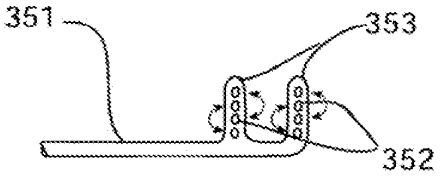


Figure 20D

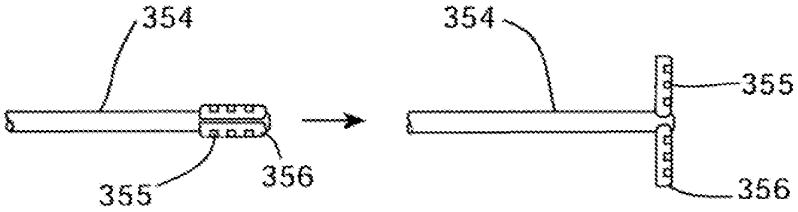


Figure 20E

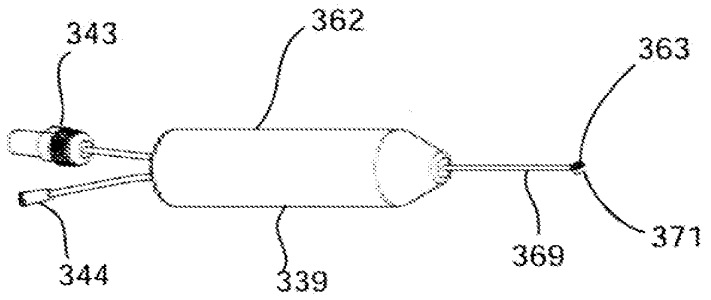


Figure 21A

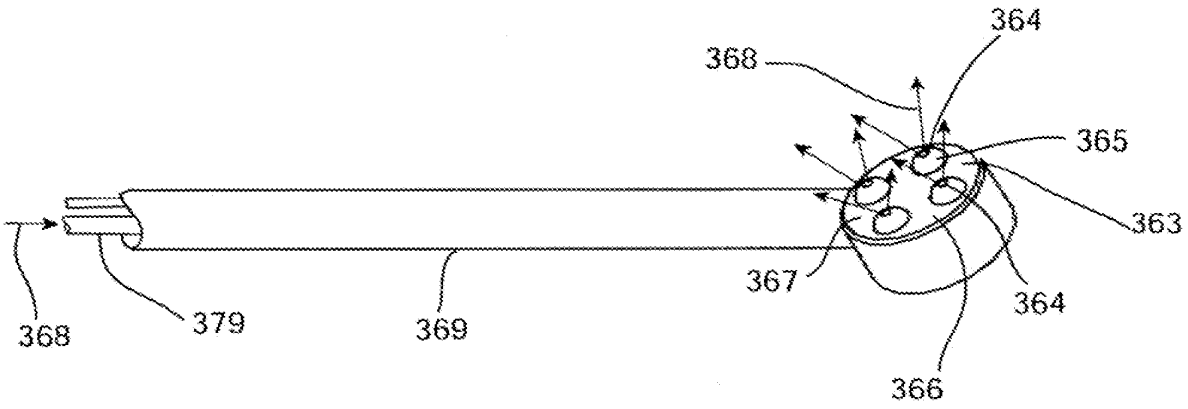


Figure 21B

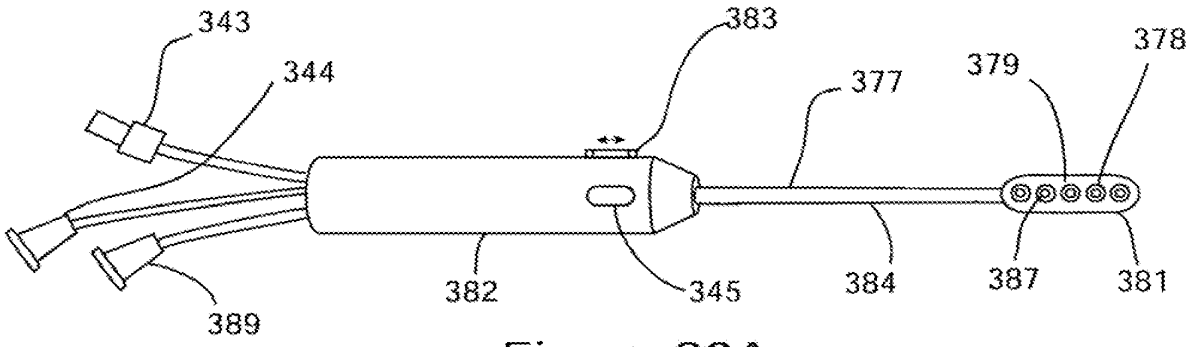


Figure 22A

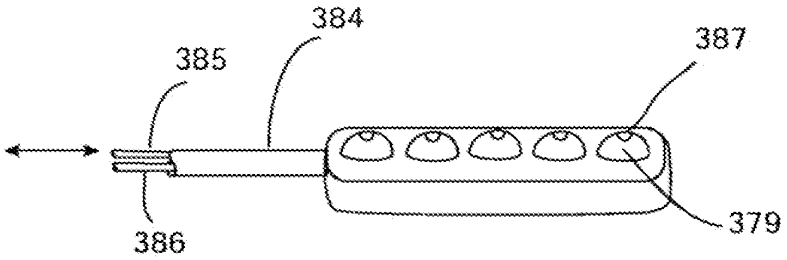


Figure 22B

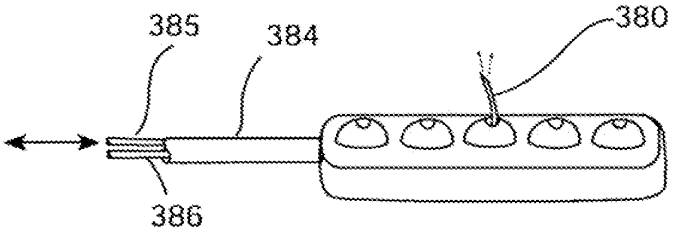


Figure 22C

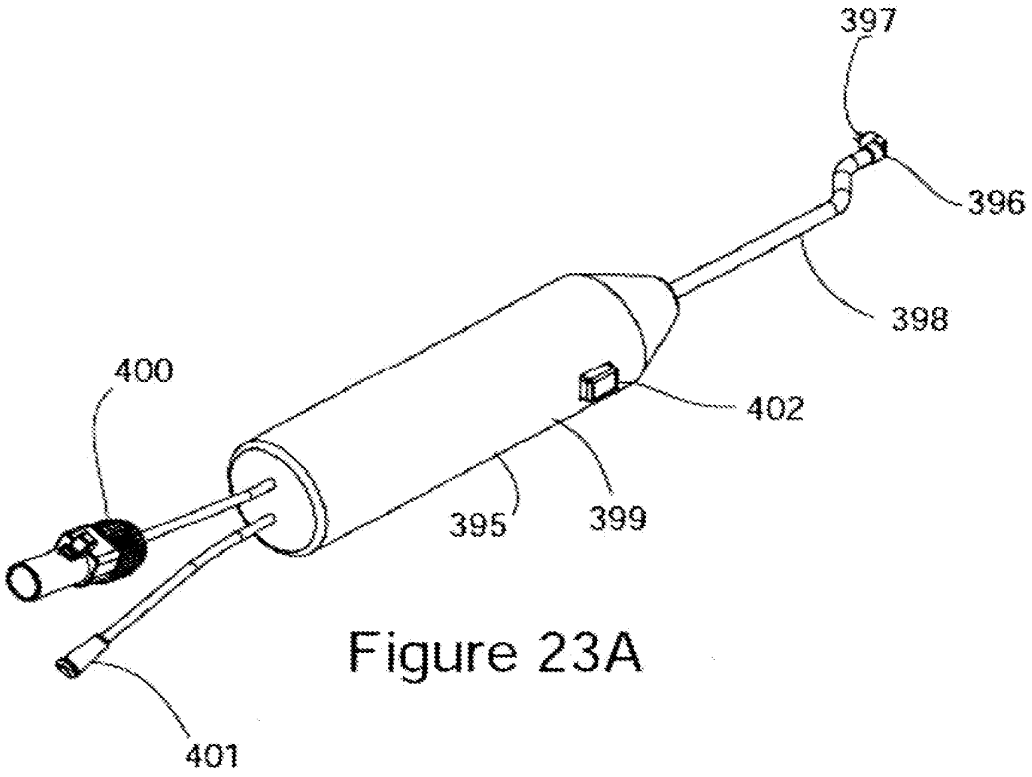


Figure 23A

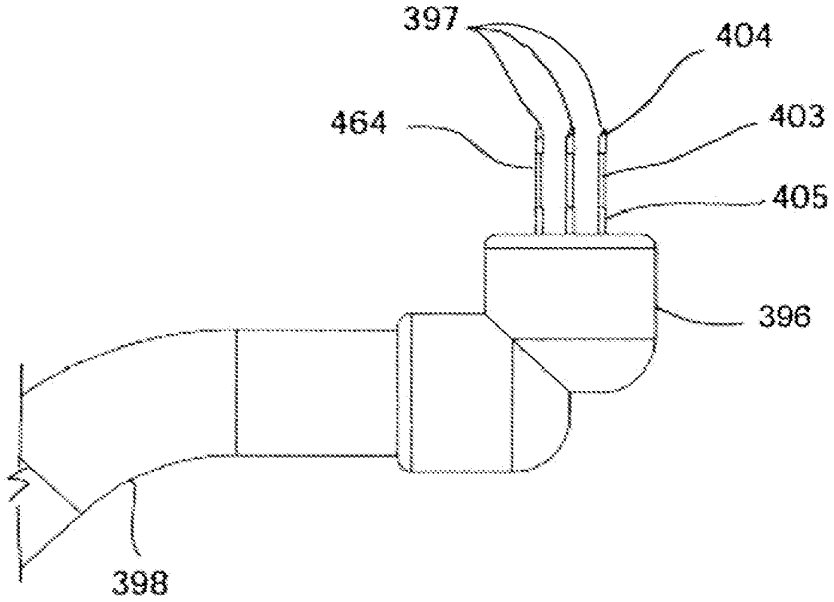


Figure 23B

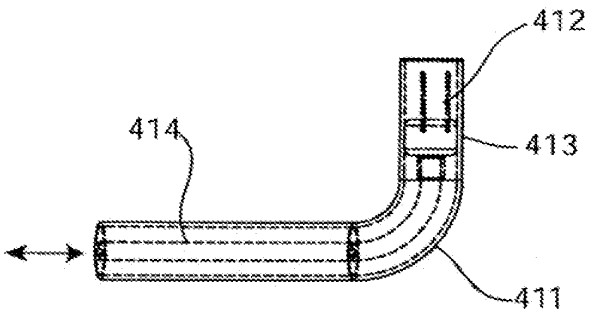


Figure 24A

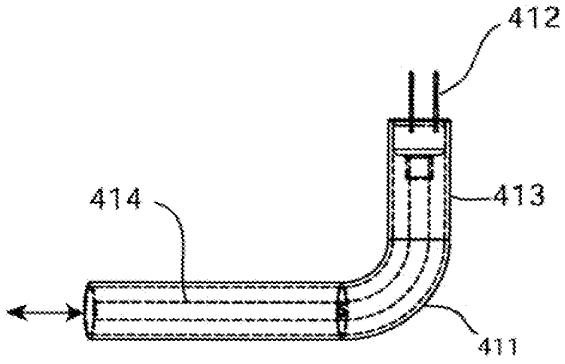


Figure 24B

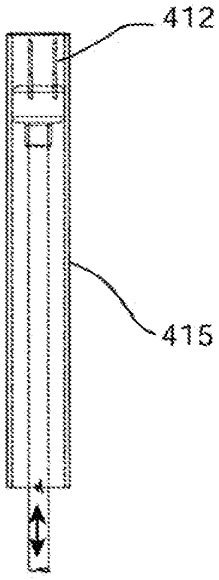


Figure 24C

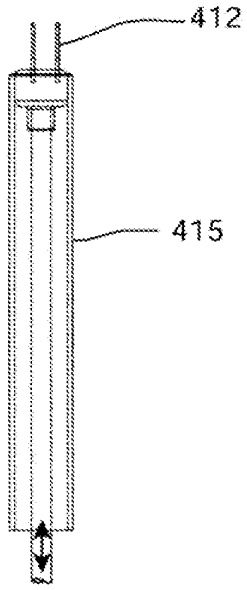


Figure 24D

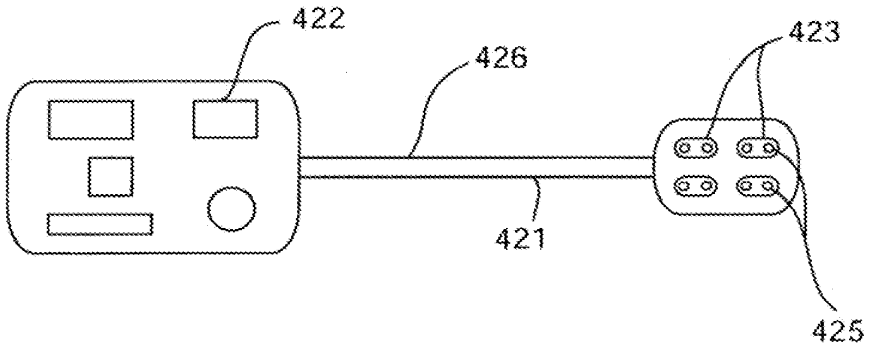


Figure 25A

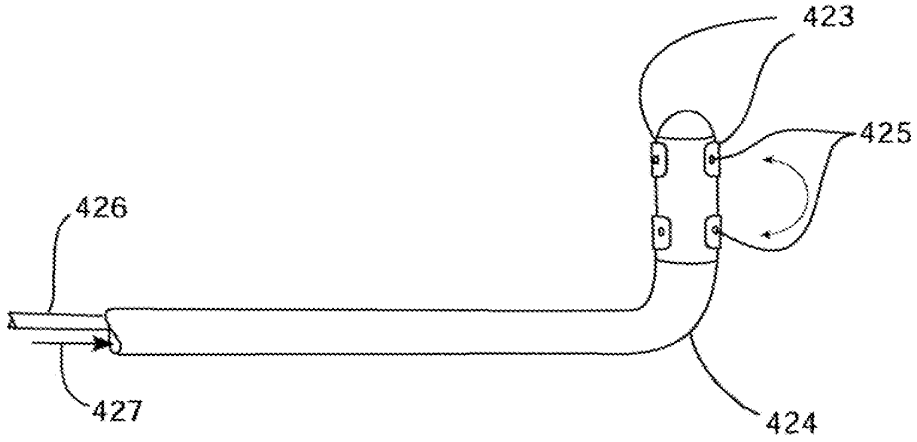


Figure 25B

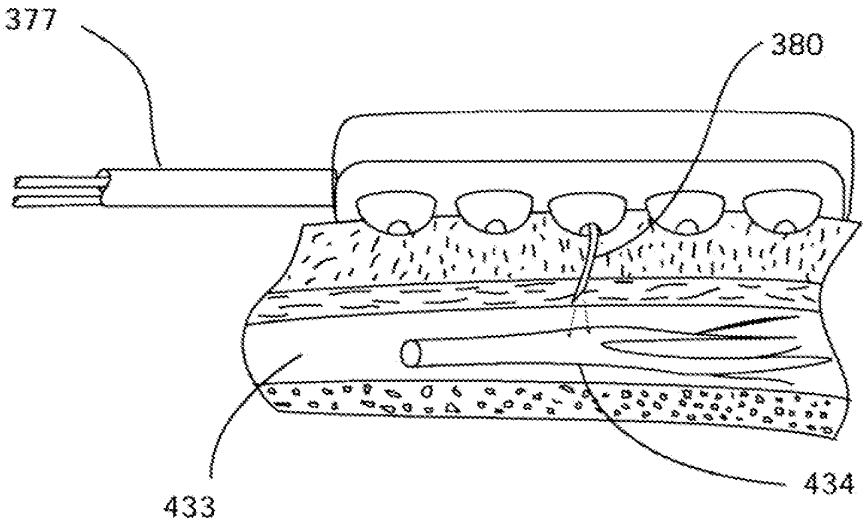


Figure 26A

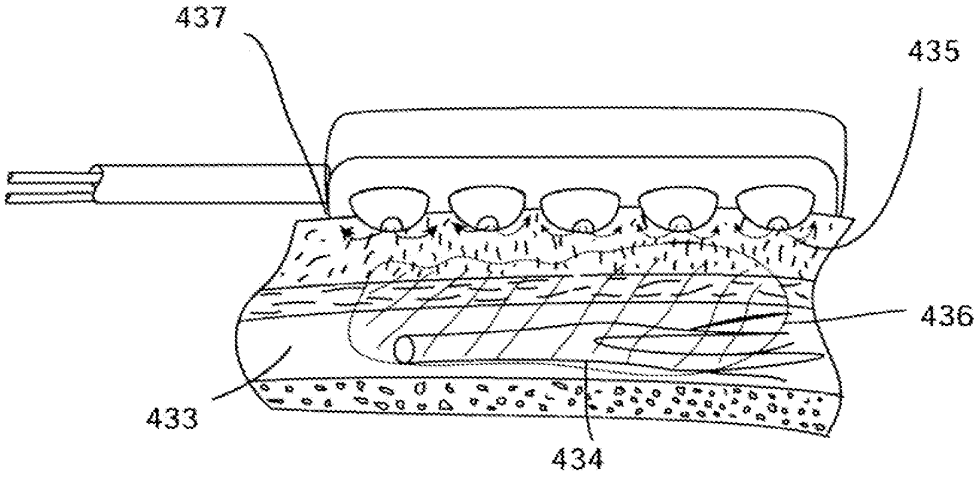


Figure 26B

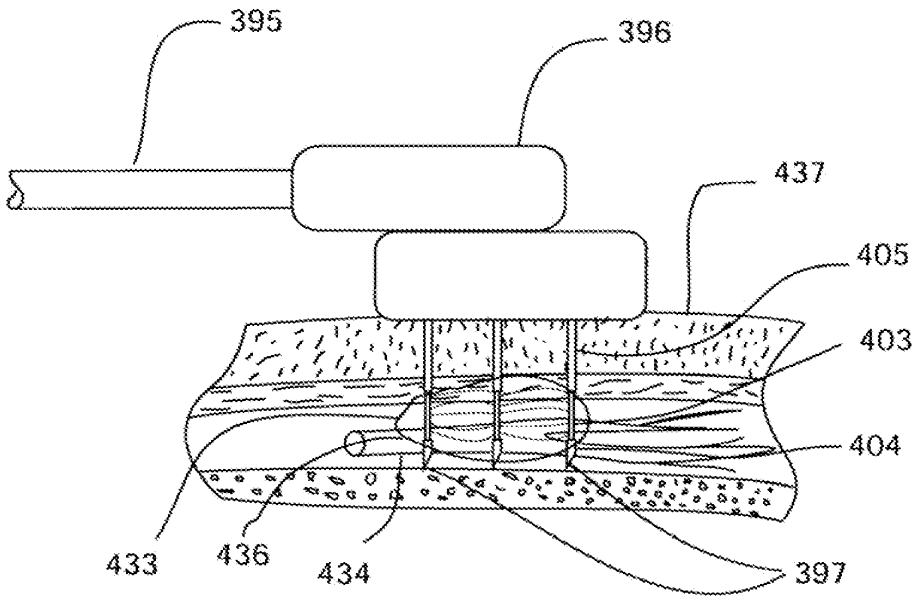


Figure 27

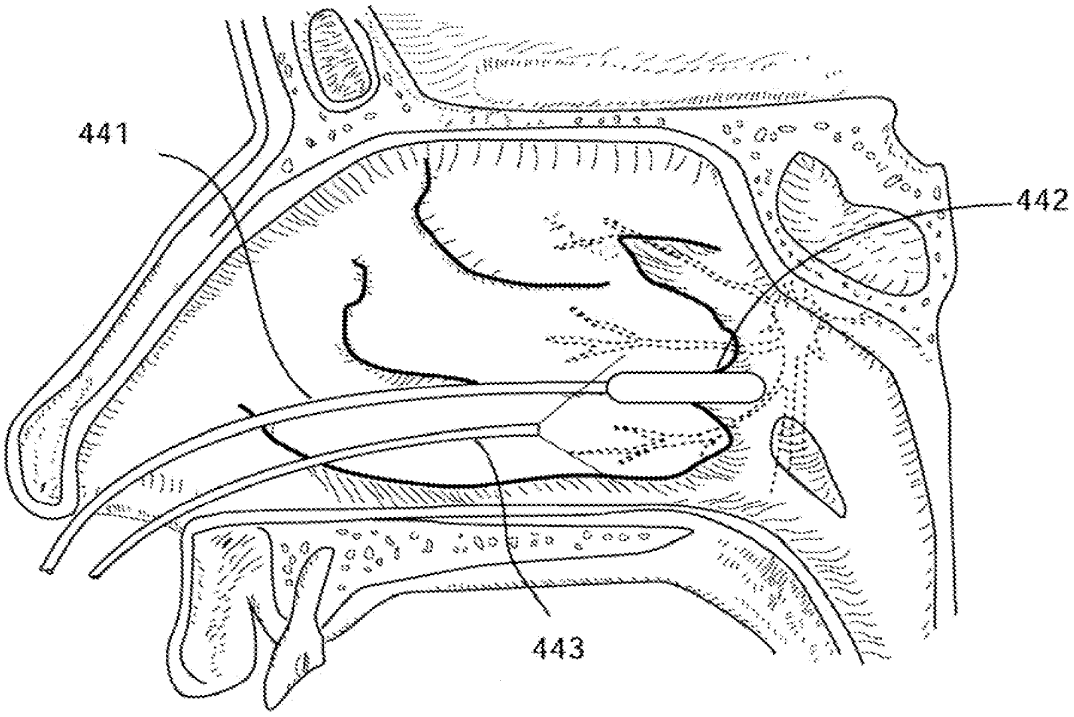


Figure 28

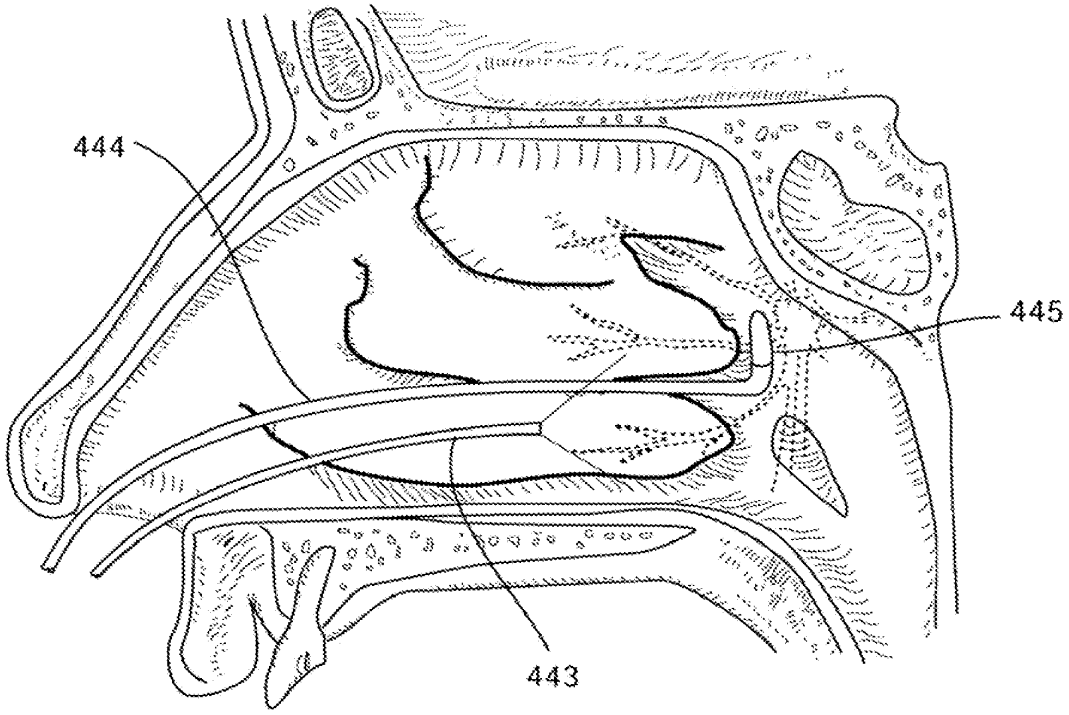


Figure 29

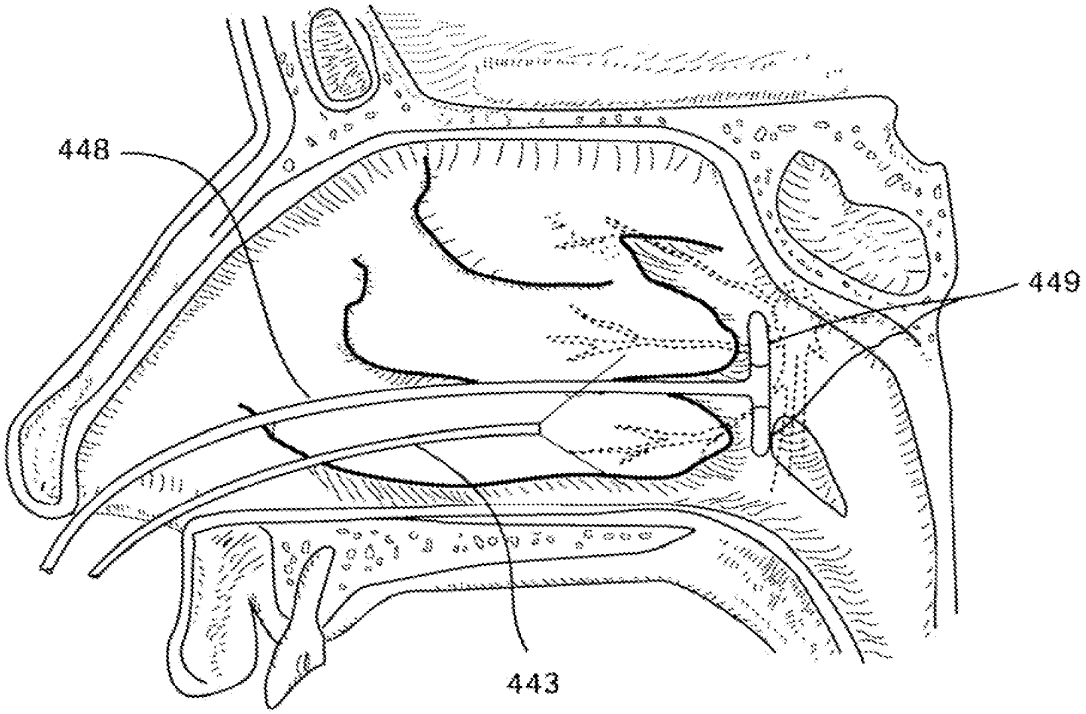


Figure 30

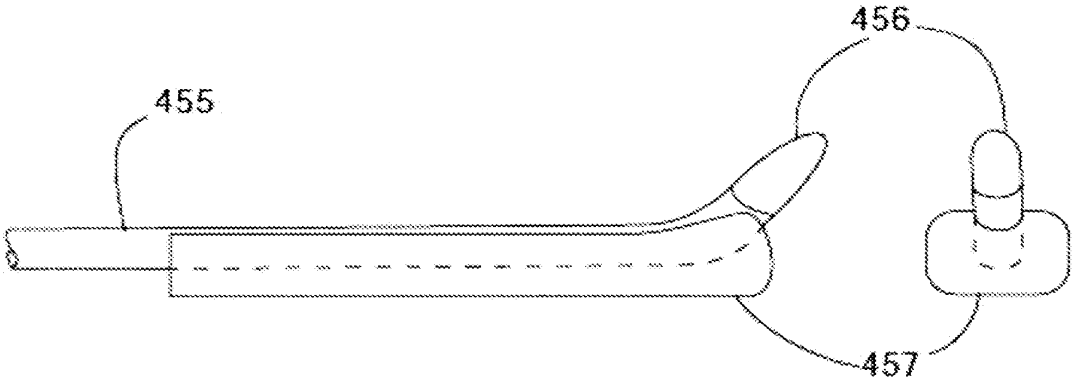


Figure 31A

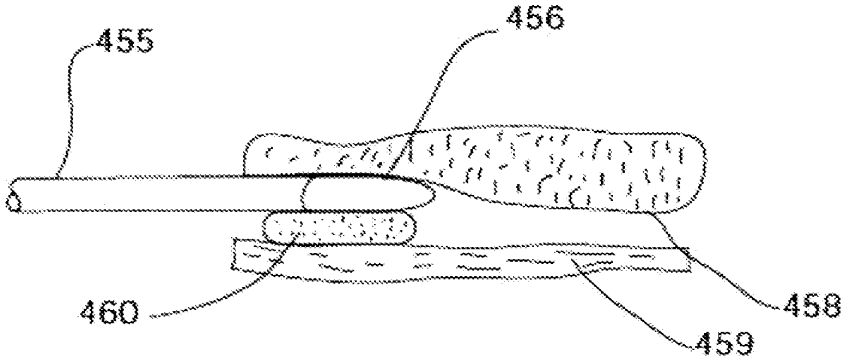


Figure 31B

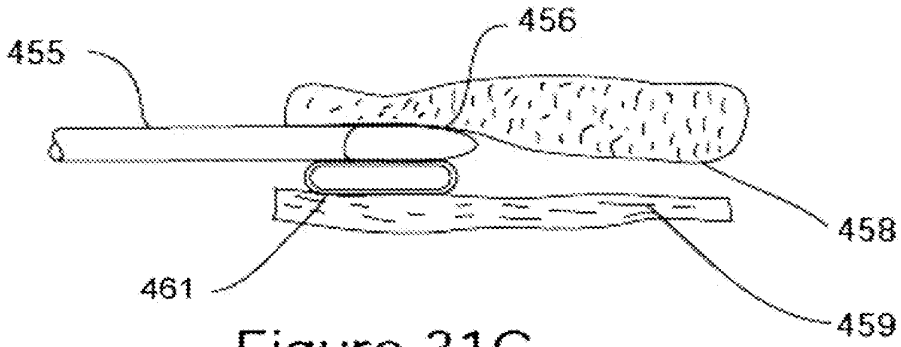


Figure 31C

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

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)

To:
Schoen, Adam M.
BROWN RUDNICK LLP
One Financial Center
Boston, MA 02111
ETATS-UNIS D'AMERIQUE

Date of mailing *(day/month/year)*	2 February 2022 (02-02-2022)
Applicant's or agent's file reference NEURE-017/01WO 35242/92	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/IB2021/000667	International filing date *(day/month/year)* 5 October 2021 (05-10-2021)
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	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040 Fax: (+31-70) 340-3016	MUSSON, Frédérique Tel: +31 (0)70 340-2490

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-017/01WO 35242/92		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/IB2021/000667	5 October 2021 (05-10-2021)	5 October 2020 (05-10-2020)
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 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. 1b
      [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

Aerin Exhibit 1011, Page 1491 of 2183
Aerin Medical Inc. v. Neurent Medical Ltd.
IPR2025-01125

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2021/000667

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.: 1-14
because they relate to subject matter not required to be searched by this Authority, namely:
Refer to the search opinion.

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.

Aerin Exhibit 1011, Page 1492 of 2183
Aerin Medical Inc. v. Neurent Medical Ltd.
IPR2025-01125

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2021/000667

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61B18/14 A61B5/00
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)
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

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 paragraph [0031]; figure 3a paragraph [0036] - paragraph [0038] paragraph [0079] paragraph [0054] - paragraph [0068]; figure 7	15-28
E	WO 2021/260435 A1 (NEURENT MEDICAL LTD [IE]) 30 December 2021 (2021-12-30) page 50, line 10 - page 53, line 9; figure 10 page 15, line 26 - page 19, line 15; figures 1a-2 page 47, line 21 - line 31; figure 9c	15-23, 25-28

-/--

[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
26 January 2022	02/02/2022

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	Ekstrand, Vilhelm

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Form PCT/ISA/210 (second sheet) (April 2005)

Aerin Exhibit 1011, Page 1493 of 2183
Aerin Medical Inc. v. Neurent Medical Ltd.
IPR2025-01125

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2021/000667

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 2021/205231 A1 (NEURENT MEDICAL LTD [IE]) 14 October 2021 (2021-10-14) page 14, line 815 - page 15, line 30; figures 1,2 page 38, line 21 - page 45, line 5; figure 9a page 45, line 6 - page 51, line 16; figure 9b page 51, line 17 - page 54, line 15; figure 9c page 55, line 4 - line 13	15-23, 25-28
A	US 2017/215952 A1 (NAIR ANUJA [US]) 3 August 2017 (2017-08-03) paragraph [0093]; figure 3	21
A	US 2015/112321 A1 (CADOURI HADAR [US]) 23 April 2015 (2015-04-23) paragraph [0008] - paragraph [0009] paragraph [0059] paragraph [0082] - paragraph [0084]	22,24

2

Form PCT/ISA/210 (continuation of second sheet) (April 2005)

Aerin Exhibit 1011, Page 1494 of 2183
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IPR2025-01125

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2021/000667

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 2021260435 A1	30-12-2021	NONE	
WO 2021205231 A1	14-10-2021	US 2021315638 A1	14-10-2021
		WO 2021205231 A1	14-10-2021
US 2017215952 A1	03-08-2017	US 2014180273 A1	26-06-2014
		US 2017215952 A1	03-08-2017
US 2015112321 A1	23-04-2015	EP 3060150 A1	31-08-2016
		US 2015112321 A1	23-04-2015
		US 2020030029 A1	30-01-2020
		WO 2015061478 A1	30-04-2015

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/IB2021/000667

TITLE: SYSTEMS AND METHODS FOR THERAPEUTIC NASAL TREATMENT

APPLICANT: NEURENT MEDICAL LIMITED

IPC CLASSIFICATION: A61B18/14, A61B5/00

EXAMINER: Ekstrand, Vilhelm

CONSULTED DATABASES: PRESEARCH, TXT, OMBI

CLASSIFICATION SYMBOLS DEFINING EXTENT OF THE SEARCH:

IPC:

CPC: A61B2018/00327, A61B18/12, A61B2018/00577, A61B2018/00267, A61B2018/00434, A61B2018/00702, A61B2018/00761, A61B2034/101, A61B2018/0016, A61B2090/062, A61B2018/00773, A61B2018/00791, A61B2018/00875, A61B2018/1475, A61B2018/00946, A61B5/40, A61B2018/00839, A61B2018/00779, A61B2018/00714, A61B2017/00154, A61B2018/0072

FI/F-TERMS:

KEYWORDS OR OTHER ELEMENTS FEATURING THE INVENTION:
nose, nasal, sinus, cavty, nero-modulation, collateral, energy level, duration, current density.

EPO FORM P04A42

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/IB2021/000667	05.10.2021	05.10.2020

International Patent Classification (IPC) or both national classification and IPC
INV. A61B18/14 A61B5/00

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 P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Fax: +31 70 340 - 3016	see form PCT/ISA/210	Ekstrand, Vilhelm Telephone No. +31 70 340-0

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. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

   see separate sheet

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. 1-14

because:

☒ the said international application, or the said claims Nos. 1-14 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. 1-14

☐ 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	21, 24
	No:	Claims	15-20, 22, 23, 25-28
Inventive step (IS)	Yes:	Claims	
	No:	Claims	15-28
Industrial applicability (IA)	Yes:	Claims	15-28
	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

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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 2021/260435 A1 (NEURENT MEDICAL LTD [IE]) 30 December 2021 (2021-12-30)

D3 WO 2021/205231 A1 (NEURENT MEDICAL LTD [IE]) 14 October 2021 (2021-10-14)

D4 US 2017/215952 A1 (NAIR ANUJA [US]) 3 August 2017 (2017-08-03)

D5 US 2015/112321 A1 (CADOURI HADAR [US]) 23 April 2015 (2015-04-23)

1 **Re Item II**

The validity of the priority claim cannot be assessed since the search authority does not have the priority document in its possession.

2 **Re Item III**

Claim 1 refer to treating a condition and includes the step of "delivering treatment energy" which in at least some embodiments is performed on the human body. Thus, claims 1-14 refer to methods of treating the human body by therapy and surgery. According to Rule 39.1 (iv) PCT and to Art 43bis.1 PCT as well as Rule 67.1 PCT, neither a search nor an international preliminary examination is required to be carried out on these claims.

3 **Re Item V**

3.1 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 15 is not new in the sense of Article 33(2) PCT. D1 discloses:

> A system for treating a condition within a sino-nasal cavity of a patient *(paragraph [0031]; figure 3a)*, the system comprising:
>
> a treatment device including an end effector comprising one or more electrodes *(308),(344)*; and

a controller operably associated with the treatment device and configured to control delivery of treatment energy from the one or more electrodes to one or more tissues at one or more target sites within a sino-nasal cavity of the patient at a level and for a period of time sufficient to ablate and/or modulate targeted neural tissue for the treatment of a nasal condition while minimizing or preventing collateral damage to surface tissue at the one or more target sites *(paragraph [0036] - paragraph [0038]: the claim does not specify what parameters are controlled)*

3.2 The dependent claims 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 novelty and/or inventive step, refer to the following passages:

claims 16-20: D1, paragraph [0064] - paragraph [0067]; figure 7: Tissue types and their location are identified from stimulation measurements. It is implicit that the different types of tissues have predefined characterisation data associated with them in order to be able to perform a characterisation. Paragraph [0079] discloses that the selection of the ablation pattern can be done autonomously.

claim 21: D1: automating the development of the characterisation thresholds for the different tissues cannot be considered to be inventive. Refer also to D4, paragraph [0093]; figure 3.

claim 22-24: D1, [68]: The treatment pattern could be a constant power for a predetermined period. It is thus implicit that these parameters are fed back to enable this protocol. Referring to the "predetermined current density threshold", using an impedance threshold instead of the claimed current density to detect treatment completion is considered to be a non-inventive equivalent, especially if the voltage is controlled. Refer also to D5, paragraph [0008] - paragraph [0009]; paragraph [0059]; paragraph [0082]

claims, 24 25: D1, [68]: if temperature, duration or impedance is used to control treatment completion, the act of turning off power can be a digital indicator of efficacy. Moreover, to make a ratio of the target vs current parameter values cannot be considered to be inventive. To measure and control the current density is straight forward when controlling output power and current ([68]).

claims 26-28: D1 the device is suitable for this.

4 **Re Item VI**

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Aerin Medical Inc. v. Neurent Medical Ltd.
IPR2025-01125

Certain documents cited

4.1 D2
Application: WO2021260435 A1

Publication date: 2021-12-30

Filing date: 2021-06-25

Priority date: 2020-06-26 (US202063044904P)

D2 discloses all features of claims 15-23,25-28, refer to the cited passages of the search report.

4.2 D3
Application: WO2021205231A1

Publication date: 2021-10-14

Filing date: 2021-04-08

Priority date: 2020-04-09 (US202063007639P)

D3 discloses all features of claims 15-23,25-28 refer to the cited passages of the search report.

5 **Re Item VII**

5.1 The independent claim(s) is/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 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).

5.2 The features of the claims are not provided with reference signs placed in parentheses (Rule 6.2(b) PCT).

5.3 Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in prior art is not mentioned in the description, nor are these documents identified therein.

6 **Re Item VIII**

Certain observations on the international application

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Aerin Medical Inc. v. Neurent Medical Ltd.
IPR2025-01125

6.1 The application does not meet the requirements of Articles 5,6 PCT, because claims 15,22,26-28 are not clear.

claim 15

The claims are formulated in terms of a result to be achieved. A treatment effect with low collateral damage can only be achieved if a plan is made and executed or if damage is detected online in both the target and sensitive tissue. These features are considered to be essential to achieve the claimed effect. Moreover, it is not clear how the treatment pattern is used during treatment. Thus, the feed-back loop must be properly described, i.e. what parameters are varied and what parameters are controlled.

claim 22

It is unclear if the "predetermined current density threshold" of the treatment pattern refers to a completion parameter or if a high/low restriction during treatment.

claims 26-28

The claims refer to use of the device or refer to planner features. However, a planner is not claimed per se.

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Aerin Medical Inc. v. Neurent Medical Ltd.
IPR2025-01125

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).

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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IPR2025-01125

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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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:

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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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.

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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IPR2025-01125

Espacenet

Bibliographic data: JP2001526077 (A) — 2001-12-18

APPARATUS FOR REDUCING TISSUE VOLUMES BY THE USE OF ENERGY

Inventor(s):

Applicant(s):

Classification: **- international:** ***A61B17/24; A61B18/00; A61B18/12; A61B18/14; A61B18/18; A61B18/20;*** (IPC1-7): A61B17/24; A61B18/00; A61B18/12; A61B18/18; A61B18/20

- cooperative: **A61B18/1485 (EP);** A61B2018/00011 (EP); A61B2018/00666 (EP); A61B2018/00678 (EP); A61B2018/00702 (EP); A61B2018/00708 (EP); A61B2018/00744 (EP); A61B2018/00791 (EP); A61B2018/00875 (EP); A61B2018/1425 (EP); A61B2018/1472 (EP)

Application number: JP20000525039 19981208

Priority number(s): US19970997224 19971223 ; WO1998US26144 19981208

Also published as: AU1720199 (A) CA2315842 (A1) EP1049413 (A1) WO9932041 (A1)

Abstract not available for JP2001526077 (A)
Abstract of corresponding document: WO9932041 (A1)

A cell necrosis is used to reduce a volume of a selected site of an anatomical structure. An energy delivery device is coupled to a distal portion of a handpiece. The energy delivery device has a tissue piercing distal end. A pressure plate is positioned at an exterior of the energy delivery device to prevent excessive penetration of the energy delivery device into the tissue.

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Espacenet

Description: JP2001526077 (A) — 2001-12-18

APPARATUS FOR REDUCING TISSUE VOLUMES BY THE USE OF ENERGY

Description not available for JP2001526077 (A)
Description of corresponding document: WO9932041 (A1)

A high quality text as facsimile in your desired language may be available amongst the following family members:

CA2315842 (A1) WO9932041 (A1)

The EPO does not accept any responsibility for the accuracy of data and information originating from other authorities than the EPO; in particular, the EPO does not guarantee that they are complete, up-to-date or fit for specific purposes.

APPARATUS FOR REDUCING TISSUE VOLUMES BY THE USE OF ENERGY
BACKGROUND OF THE INVENTION
Cross-Reference to Related Applications
This application is a continuation in part of U.S. Patent Application No. 08/905,991, filed August 5, 1997, which is a continuation-in-part of U.S. Patent Application No. 08/642,327, filed May 3, 1996, entitled "Method for Treatment of Airway Obstructions", which is in turn a continuation-in-part application of U.S. Patent Application No. 08/606,195, filed February 23, 1996, entitled "Method for Treatment of Airway Obstructions", which cross-references U.S. Patent Application No. 08/516,781, filed August 18, 1995, entitled "Ablation Apparatus and System for Removal of Soft Palate Tissue", having named inventors Stuart D. Edwards, Edward J. Gough and David L. Douglass, which is a continuation-in-part of U.S. Application No. 08/239,658, filed May 9, 1994 entitled "Method for Reducing Snoring by RF Ablation of the Uvula." This application is also related to an Application Serial No. 08/642,053, filed 5/3/96, entitled "Method and Apparatus for Treatment of Air Way Obstructions", all incorporated by reference herein.

Field of the Invention
This invention relates to an apparatus for the treatment of air way obstructions, and more particularly to an apparatus for creating selective cell necrosis in interior sections of selected head and neck anatomical structures of the human body without damaging vital structures.

Description of Related Art
Sleep-apnea syndrome is a medical condition characterized by daytime

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Aerin Medical Inc. v. Neurent Medical Ltd.
IPR2025-01125

hypersomnomulence, morning arm aches, intellectual deterioration, cardiac arrhythmias, snoring and thrashing during sleep. It is caused by frequent episodes of apnea during the patient's sleep. The syndrome is classically subdivided into two types. One type, termed "central sleep apnea syndrome", is characterized by repeated loss of respiratory effort. The second type, termed obstructive sleep apnea syndrome, is characterized by repeated apneic episodes during sleep resulting from obstruction of the patient's upper airway or that portion of the patient's respiratory tract which is cephalad to, and does not include, the larynx.

Treatment thus far includes various medical, surgical and physical measures.

Medical measures include the use of medications such as protriptyline, medroxyprogesterone, acetazolamide, theophyl line, nicotine and other medications in addition to avoidance of central nervous system depressants such as sedatives or alcohol.

The medical measures above are sometimes helpful but are rarely completely effective.

Further, the medications frequently have undesirable side effects and may be contraindicated for some patients.

Surgical interventions have included uvulopalatopharyngoplasty, tonsillectomy, surgery to correct severe retrognathia and tracheostomy. In one type of surgical intervention a standard LeFort I osteotomy is combined with a sagittal split ramus osteotomy to advance the maxilla, mandible and chin. Such a procedure may be effective but the risk of surgery (e.g. morbidity and mortality) in these patients can be prohibitive and the procedures are often unacceptable to the patients.

Physical measures have included weight loss, nasopharyngeal airways, nasal CPAP and various tongue retaining devices used nocturnally. These measures may be partially effective but are cumbersome, uncomfortable and patients often will not continue to use these for prolonged periods of time. Weight loss may be effective but is rarely achieved by these patients.

In patients with central sleep apnea syndrome, phrenic nerve or diaphragmatic pacing has been used. Phrenic nerve or diaphragmatic pacing includes the use of electrical stimulation to regulate and control the patient's diaphragm which is innervated bilaterally by the phrenic nerves to assist or support ventilation. This pacing is disclosed in Direct Diaphragm Stimulation by J. Mugica et al. PACE vol. 10 Jan-Feb, 1987, Part II; Preliminary Test of a Muscular Diaphragm Pacing System on Human Patients by J. Mugica et al. from Neurostimulation: An Overview 1985, pp. 263-279; and, Electrical Activation ofRespiration by Nochomovitez IEEE Eng. in Medicine and Biology, June, 1993.

However, it was found that many of these patients also have some degree of obstructive sleep apnea which worsens when the inspiratory force is augmented by the pacer. The ventilation induced by the activation of the diaphragm also collapses the upper airway upon inspiration and draws the patient's tongue inferiorly down the throat choking the patient. These patients then require tracheostomies for adequate treatment.

A physiological laryngeal pacemaker as described in Physiological Laryngeal

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Pacemaker by F. Kaneko et al. from Trans Am Soc Artif Intern Organs, 1985, pp. 293296 senses volume displaced by the lungs and stimulates the appropriate nerve to open the patient's glottis to treat dyspnea. This apparatus is not effective for treatment of sleep apnea. The apparatus produces a signal proportional in the displaced air volume of the lungs and thereby the signal produced is too late to be used as an indicator for the treatment of sleep apnea. Also, there is often no displaced air volume in sleep apnea due to obstruction.

There are other surgical methods for the treatment of obstructive sleep apnea but they also have medical drawbacks. Tracheostomy, while effective, carries considerable morbidity and is aesthetically unacceptable to many patients. Another surgical procedure involves a standard Le Fort I osteotomy in combination with a sagittal split ramus osteotomy. However, this is a major surgical intervention that requires the advancement of the maxilla, mandible and chin.

Generally, there are two types of snoring. They are distinguished, depending on the localization of their origin. The first type of snoring, velar, is produced by the vibration of all of the structures of the soft palate including the velum, the interior and posterior arches of the tonsils and the uvula. Velar snoring results from a vibration of the soft palate created by the inspiratory flow of air, both nasal and oral, which makes the soft palate wave like a flag. The sound intensity of these vibrations is accentuated by the opening of the buccal cavity which acts as a sound box.

The second type, pharyngeal snoring, is a kind of rattle, including even horn whistling. It is caused by the partial obstruction of the oropharyngeal isthmus by the base of the tongue with, now and again, its total exclusion by the tongue base becoming jammed against the posterior wall of the pharynx. This results in a sensation of breathing, apnea, which constitutes the sleep apnea syndrome. These two types of snoring may easily be combined in the same individual.

For some years there have been surgical techniques for correcting apnea.

However, maxillary surgery to cure pharyngeal snoring requires major surgery, with the operation lasting several hours, and the uvula-palatopharnygoplasty procedure to correct velar snoring is not without draw backs. This explains the popularity of prosthesis and other preventive devices.

More recently, portions of the soft palate have been removed by laser ablation; however, there are several limitations to this procedure. First, if too much tissue is removed, severe consequences result. Also, the degree of laser ablation is difficult to control and multiple treatments are usually required. Finally, patients have a high degree of soreness in their throats for many weeks.

U.S. Patent No. 4,423,812 discloses a loop electrode design characterized by a bare active wire portion suspended between wire supports on an electrode shaft. Tissue striping is performed with a bare wire, that is connected to an electrode shaft insulated to prevent accidental burns to the patient. This allows the physician to use these insulated parts to help position and guide the active wire portion during the surgical procedure. However, this requires that the physician shave off, during multiple procedures, successive thin superficial layers of the obstructing tissues to avoid gross resection and its adverse affects.

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U.S. Patent No. 5,046,512 discloses a method for the treatment of snoring and apnea. The method regulates air flow to the user to an extent comparable to the volume of air which flows through the users nasal passages. An associated apparatus provides a device having a body portion sufficiently wide to separate the users teeth. It includes an air passage comparable in area to the area of the user's nasal passages.

The use of oral cavity appliances has been proposed frequently for the treatment of sleep disorders. It has been recognized that movement of the mandible forward relative to the maxilla can eliminate or reduce sleep apnea and snoring symptoms by causing the pharyngeal air passage to remain open. Several intra-oral dental appliances have been developed which the user wears at night to fix the mandible in an anterior protruded position. Such dental appliances essentially consist of acrylic or elastomeric bit blocks, similar to orthodontic retainers or athletic mouth guards, which are custom
fitted to a user's upper and lower teeth. The device may be adjusted to vary the degree of anterior protrusion.

U.S. Patent 4,901,737 discloses an intra-oral appliance while reducing snoring which repositions the mandible in an inferior, open, and anterior, protrusive, position as compared to the normally closed position of the jaw. Once the dentist or physician determines the operative snoring reduction position for a particular patient, an appropriate mold is taken for the maxillary dentition and of the mandibular dentition to form an appliance template. This device includes a pair of V-shaped spacer members formed from dental acrylic which extend between the maxillary and mandibular dentition to form a unitary mouthpiece.

While such dental appliances have proven effective in maintaining the mandible in a protruded position to improve airway patency, they often result in undesirable side effects. One of the most common side effects is aggravation of the tempromandibular joint and related jaw muscles and ligaments, especially in individuals who have a tendency to grind their teeth during sleep. Aggravation of the tempromandibularjoint has be associated with a wide variety of physical ailments, including migraine headaches. Accordingly, many individuals suffering from sleep apnea and snoring disorders are not able to tolerate existing anti-snoring dental appliances for long periods of time.

Opening of obstructed nasal airways by reducing the size of the turbinates has been performed using surgical and pharmaceutical treatments. Examples of surgical procedures include anterior and posterior ethmoidectomy, such as those described in "Endoscopic Paranasal Sinus Surgery" by D. Rice and S. Schaefer, Raven Press, 1988; the writings of M. Wigand, Messerklinger and Stamberger; and, U.S. Patent No.

5,094,233. The Wigand procedure, described in U.S. Patent No. 5,094,233, involves the transection of the middle turbinate, beginning with the posterior aspect, visualization of the sphenoid ostium and opening of the posterior ethmoid cells for subsequent surgery. In the sphenoidectomy step, the ostium of the sphenoid is identified and the anterior wall of the sinus removed. Following this step, the posterior ethmoid cells may be entered at their junction with the sphenoid and the fovea ethmoidalis can be identified as an anatomical landmark for further dissection. In anterior ethmoidectomy, the exenteration of the ethmoids is carried anteriorly to the frontal recess.

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Complications, such as hemorrhage, infection, perforation of the fovea ethmoidalis or lamina papyracea, and scarring or adhesion of the middle turbinate, have been reported in connection with these procedures.

One of the problems encountered as a result of these procedures is postoperative adhesion occurring between the turbinates and adjacent nasal areas, such as medial adhesion to the septum and lateral adhesion to the lateral nasal wall in the area of the ethmoid sinuses. Otherwise successful surgical procedures may have poor results in these cases. Some surgeons have proposed amputation of a portion of the turbinate at the conclusion of surgery to avoid this complication, resulting in protracted morbidity (crust formation and nasal hygiene problems). The turbinate adhesion problem detracts from these endoscopic surgical procedures. Efforts have been made to reduce the complications associated with the surgical treatment of turbinate tissue, for example by the use of a turbinate sheath device. U.S. Patent No. 5,094,233.

U.S. Patent No. 3,901,241 teaches a cryosurgical instrument which is said to be useful for shrinking nasal turbinates. U.S. Patent No. 3,901,241.

Pharmaceuticals have also been developed for reducing the size of the turbinates. However, pharmaceuticals are not always efficacious and generally do not provide a permanent reduction in turbinate size. Additionally, pharmaceuticals can have adverse side effects and are contraindicated for some patients.

Clearly, a medical need exists for a method and device for clearing obstructed nasal passageways. It is preferred that the method and device be performable with minimal surgical intervention or post operative complications. It is also preferred that the method and device reduce the size of the turbinate structure without involving surgical cutting or the physical removal of tissue. It is also preferred that the method and device provide a reduction in turbinate structure size to increase air flow in the nasal passageway sufficiently impairing blood flow to the optic nerve and/or retina and create a permanent impairment of vision by the ablation.

It would be desirable to provide an ablation apparatus which eliminates the need for dental appliances for the treatment of snoring and sleep apnea disorders. It would also be desirable to provide a treatment device which is not an intra-oral dental appliance, and which can effectively and safely remove selected portions of the soft palate without providing the patient with undesirable side effects. Further, it would be desirable to provide a tissue ablation device which creates localized pressure at an electrode introduction tissue site to make it easier for electrode introduction into tissue.

It would yet further desirable to provide an ablation apparatus with a safety stop that reduces surface ablation at an electrode introduction tissue site.

SUMMARY OF THE INVENTION

Accordingly, an object of the invention is to provide an apparatus for the treatment of obstructed nasal and upper respiratory passage ways through the use of selective cell necrosis at a selected site of different head and neck anatomical structures.

Another object of the invention is to provide an apparatus to treat airway obstructions.

Yet another object of the invention is to provide an ablation apparatus that provides controlled cell necrosis of upper airway anatomical structures.

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A further object of the invention is to provide an ablation apparatus that applies localized force at an electrode tissue introduction site.

Still another object of the invention is to provide an ablation apparatus that minimizes surface cell necrosis at an energy delivery device tissue introduction site.

These and other objects of the invention are achieved in a cell necrosis apparatus to reduce the volume of a selected site of an anatomical structure. An energy delivery device is coupled to a distal portion of a handpiece. The energy delivery device has a tissue piercing distal end. A pressure plate is positioned at an exterior of the energy delivery device and a cable is coupled to the energy delivery device.

In another embodiment, a cell necrosis apparatus includes a handpiece and an energy delivery device coupled to a distal portion of the handpiece. A safety stop is positioned at an exterior of the energy delivery device. A cable is coupled to the energy delivery device.

In yet another embodiment, An apparatus to reduce a volume of a selected site in an interior of an anatomical structure includes an introducer. An energy delivery device is at least partially positionable in the interior of the introducer. A pressure plate is positioned at an exterior of the introducer and a cable is coupled to the energy delivery device.

In still a further embodiment, an advancement member is coupled to the energy delivery device.

In still yet another embodiment, an infusion lumen in the energy delivery device is coupled to medicinal solutions, irrigating solutions electrolyte solutions, contrast media and disinfectants via a disinfectant medium introduction member.

BRIEF DESCRIPTION OF THE FIGURES

Figures 1A-B illustrate lateral view of the oral cavity and the positioning of the cell necrosis apparatus of the present invention in the oral cavity.

Figure 1C depicts a lateral view of the oral cavity illustrating the repositioning of the tongue following treatment.

Figures 2A-B illustrate front and side perspective views of the pressure plate shown in Figures IA-C.

Figures 3A-3B illustrate the creation of various cell necrosis zones.

Figure 4 illustrates the introduction of fluids into the necrosis zone using a multi aperture hollow energy delivery device.

Figure 5 illustrates the introduction of boluses solution to tissue.

Figure 6A illustrates a perspective view of the cell necrosis apparatus of the present invention coupled to an energy source.

Figure 6B illustrates a close up cross-sectional view of a hollow energy delivery device

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of the invention utilized to create a cell necrosis zone below a tissue surface.

Figure 7 illustrates a cross-sectional view of the distal end of the energy delivery device of Figure 6B.

Figure 8 illustrates a cross-sectional view of the hollow energy delivery device with a sealing plug to control fluid flow.

Figure 9 illustrates the creation of cell necrosis zones in the uvula and the repositioning of the uvula in the oral cavity.

Figure 10 illustrates the creation of cell necrosis zones in the turbinates and the repositioning of the turbinates in the nasal cavity.

Figure ii illustrates a cross-sectional view of the arteries of the nasal cavity.

Figure 12 depicts a cross-sectional view of the head illustrating the arteries of the nasal cavity.

Figure 13 depicts a cross-sectional view of the head taken laterally through the nasal cavity illustrating a shrinkage of the turbinates following treatment with the cell necrosis apparatus of the present invention.

Figure 14 depicts a close up cross-sectional view of Figure 13.

Figure 15 depicts a cross-sectional view of the head illustrating the creation of cell necrosis zones in the soft palate structure.

Figure 16 depicts a cross-sectional view of the soft palate structure of Figure 15 illustrating the repositioning of the soft palate structure following creation of the cell necrosis zones.

Figure 1 7A is a perspective view of an embodiment of the present invention with the pressure plate positioned at an exterior of an introducer.

Figure 17B depicts a perspective and cross sectional view of the distal tip of the introducer.

Figure 17C is an enlarged view of the distal tip of the energy delivery device.

Figure 1 7D depicts the flow path between the cell necrosis apparatus and the infusion fluid reservoir.

Figure 18 depicts a block diagram of the feed back control system that can be used with the cell necrosis apparatus as shown in Figures IA-C.

Figure 19 depicts a block diagram of an analog amplifier, analog multiplexer and microprocessor used with the feedback control system of Figure 19.

Figure 20 depicts a block diagram of the operations performed in the feedback control system depicted in Figure 18.

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DETAILED DESCRIPTION

Referring now to Figures IA-C, a cell necrosis apparatus 10 is used to reduce the volume of a selected site in an interior of a head and neck structure, and more particularly to a structure that is associated with an airway passage. Suitable anatomical structures include but are not limited to the tongue, uvula, soft palate tissue, tonsils, adenoids, turbinate structures and the like. In Figures IA-C, cell necrosis apparatus 10 is shown as including a handpiece 12 coupled to an energy delivery device 14.

It will be appreciated that although the term "energy delivery device" in includes but is not limited to a device for the delivery of electromagnetic energy such as RF, microwave and optical energy; a device for the delivery of acoustical energy such as ultrasonic energy; a device for the delivery of a thermal liquid jet; and, a device for performing resistance heating. The preferred energy source is an RF source and electrode 14 is an RF electrode operated in either bipolar or monopolar mode with a ground pad electrode. In a monopolar mode of delivering RF energy, a single electrode 14 is used in combination with an indifferent electrode patch that is applied to the body to form the other contact and complete an electrical circuit. Bipolar operation is possible when two or more electrodes 14 are used. Multiple electrodes 14 may be used.

When the energy source is RF, an RF energy source may have multiple channels, delivering separately modulated power to each electrode 14. This reduces preferential heating that occurs when more energy is delivered to a zone of greater conductivity and less heating occurs around electrodes 14 which are placed into less conductive tissue. If the tissue hydration or blood infusion in the tissue is uniform, a single channel RF energy source may be used to provide power for the treatment of cell necrosis zones relatively uniform in size.

Handpiece 12 can be a proximal portion of energy delivery device 14 that is suitably configured to enable placement and removal of cell necrosis apparatus to and from a selected anatomical structure and may include, in one embodiment, a proximal portion of energy delivery device 14 that is insulated. A pressure plate 15 can be positioned on an exterior surface of energy delivery device 14. Pressure plate 15 includes a tissue interface surface 1 7 which can include all of a portion of the indicated surface depending on the amount of contact between the anatomical structure surface and tissue interface surface 17 which may be dependent on the amount of force applied to the surface of the anatomical structure.

Handpiece 12 and energy delivery device 14 are sized and of a suitable geometry to be maneuverable in an oral cavity 16, pierce a tongue surface 18 and advance into an interior 20 of a tongue 22 a sufficient distance 24 to a tissue site 26.

Another embodiment of pressure plate 15 is as a safety stop such that depth of tissue penetration of energy delivery device 14 is controlled by pressure plate 15.

Electromagnetic energy is delivered to tissue site 26 to create cell necrosis at zone 28 without damaging a main branch of the hypoglossal nerve. A cable 30 is coupled to energy delivery device 14. For purposes of this disclosure, the main branches of the hypoglossal nerve are those branches which if damaged create an impairment, either partial or full, of speech or swallowing capabilities. As shown in Figure 1 C, the treated structure of tongue 22 is repositioned in oral cavity 16. With this cell necrosis, the back of the tongue 22 moves in a forward direction (as indicated by the arrow) away from the

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air passageway. The result is an increase in the cross-sectional diameter of the air passageway.

Handle 14 is preferably made of an electrical and thermal insulating material.

When energy delivery device 14 is an electrode, the electrode can be made of a conductive material such as stainless or a shaped memory metal, such as Nitinol (a nickel titanium alloy), commercially available from Raychem Corporation (Menlo Park, California) as well as numerous other companies. In one embodiment, only a distal end of electrode 14 is made of the shaped memory metal in order to effect a desired deflection.

Cell necrosis apparatus 10 can include visualization capability including but not limited to a viewing scope, an expanded eyepiece, fiber optics, video imaging, and the like.

Energy delivery device 14 can include an insulator 32 which can be adjustable in length and in a surrounding relationship to an exterior surface of energy delivery device 14. Insulator 32 serves as a barrier to thermal or RF energy flow. Insulator 32 can be in the form of an sleeve that may be adjustably positioned at the exterior of energy delivery device 14. in one embodiment insulator can be made of a polyamide material and be a 0.002 inch shrink wrap. The polyamide insulating layer is semi-rigid.

That portion of energy delivery device 14 which is not insulated is an energy delivery surface 33.

Handpiece 12 can have a reduced diameter at a distal portion 34 to facilitate positioning, maneuverability, provide easier access to smaller openings and improve the visibility in the area where energy delivery device 14 is to penetrate.

To use cell necrosis apparatus 10 in oral cavity 16, a topical and then a local anesthetic is applied to tongue 22. After a suitable period for the anesthesia to take effect, the physician may grasp the body of tongue 22 near the apex, using a gauze pad for a better grip. Tongue 22 is then drawn forward, bringing the body and the root of tongue 22 further forward for improved accessibility. Grasping handpiece 12, the physician positions a distal portion of energy delivery device 14 at tongue surface 18.

The position of energy delivery device 14 in Figures I A-C illustrates cell necrosis zone 28 below a mucosal surface 36 providing a protected zone 38. An insulated portion 40 of energy delivery device 14 prevents delivery of energy to a main branch of a hypoglossal nerve and/or to mucosal surface 36.

Energy delivery device 14 can have an angle 42 at a bend zone 44 which is lateral to a longitudinal axis of handpiece 12. Energy delivery device 14 can be malleable to create different bend zones, depending on the anatomical structure and the insertion position of the anatomical structure. With the use of a bending fixture, not shown, the arc of angle 42 can be adjusted by the physician as needed at the time of treatment.

One or more sensors 46 can be included and positioned at a distal end of energy delivery device 14, at a distal end of insulator 32, as well as at other positions of cell necrosis apparatus 10. Sensor 46 is of conventional design, including but not limited to thermistors, thermocouples, resistive wires, and the like. Suitable sensors that may be used for sensor 46 include: thermocouples, fiber optics, resistive wires, thermocouple

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IR detectors, and the like. Suitable thermocouples for sensor 46 include: T type with copper constantene, J type, E type and K types.

Energy delivery device 14 can experience a steep temperature gradient as current moves outward through the energy delivery device 14. This causes the tissue that is immediately adjacent to energy delivery device 14 to reach temperatures of 100 degrees C or more while tissue only 5 to 10 mm away may be at or near body temperature. Because of this temperature gradient, it is often necessary to position energy delivery device 14 several times at the intended insertion site or use a plurality of energy delivery devices 14 to create a cell necrosis zone 28 of the desired volume.

Because of the aggressive heating immediately proximal of energy delivery device 14 desiccation of tissue adjacent to energy delivery device 14 may result. When the fluid within the tissue is desiccated, no electrical current flows through the tissue and the heating is then terminated. This problem can be solved by using lower energy delivery rates (e.g. power) to energy delivery device 14, in turn reducing the rate of temperature increase in adjacent tissue. This solution requires extended treatment periods.

Referring now to Figures 2A and 2B, pressure plate 15 has an exterior geometry section selected from a planar surface, a curved surface, a concave surface, a convex surface and combinations thereof. One embodiment is a convex curved shape, including hemispherical in order to minimize trauma to tissue adjacent to the tissue insertion site. Pressure plate 15 will also have an aperture for the advancement and retraction of electrode 14. The preferred planar geometry of pressure plate 15 is circular. The preferred tissue contact surface area of pressure plate 15 is between 0.005 to 0.250 inches. Pressure plate 15 will also be made of an electrically non-conductive material in order to electrically isolate tissue insertion site from all sources of electrical current other than that delivered by energy delivery device 14. Tissue interface surface
17 applies a force to energy delivery device insertion site of the anatomical structure.

This force can compress and/or immobilize the tissue at the energy delivery device insertion site to facilitate a penetration ofth tissue. When a highly conductive fluid is infused into tissue, the electrical resistance is reduced and the electrical conductivity of the infused tissue is increased. With this condition there will be little tendency for tissue surrounding energy delivery device 14 to desiccate and the result is a large increase in the capacity of the tissue to carry RF energy. A zone of tissue which has been heavily infused with a concentrated electrolytic solution can then become so conductive as to actually act as an electrode. The effect of the larger (fluid) electrode is that greater amounts of current can be conducted, making it possible to heat a much greater volume of tissue in a given time period.

In addition to the larger electrode area that results from infusion of an electrolytic solution it is then possible to inject one or more boluses 50 of electrolytic solution as shown in Figure 5. RF current 52 can then flow through the infused tissue surrounding electrode 14 and follow the course of least electrical resistance into the infused tissue of the neighboring bolus.

By placing the injections of electrolytic solution according to the need for thermal tissue damage, a single electrode 14 may deliver heating to a large volume of tissue and the shape of cell necrosis zone 28 created may be placed to create cell necrosis in exactly the area desired. This simplifies the control of cell necrosis zone 28 generation and

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allows the physician to produce larger lesions in a brief session.

Additionally, the conductivity of the injected electrolytic solution can be decreased. While the advantages of avoiding desiccation adjacent to electrode 14 are maintained, higher electrical resistance is encountered in the infused tissue. This results in greater heating in the tissue closer to electrode 14. Varying the electrical conductivity of the infused tissue can be used to adjust the size of cell necrosis zone 28 and control the extent of thermal damage.

Disinfectant mediums can also be introduced through energy delivery device 14. Suitable disinfectant mediums include but are not limited to Peridex, an oral rinse containing 0.12% chlorhexidine glucinate (1, 1 '-hexanethylenebis[S-(p-chlorophenyl) biganide) di-D-gluconate in a base containing water, 11.6% alcohol, glycerin, PEG 40 sorbitan arisoterate, flavor, dosium saccharin, and FD & C Blue No. 1. The disinfectant medium can be introduced prior to, during and after cell necrosis.

Referring now to Figures 6 through 8, energy delivery device 14 may include hollow lumen 48 that is in fluid communication with a control unit 54 which controls the delivery of the fluid via a conduit 56 configured to receive a cooling or heating solution. All of only a portion of a distal portion 14' of energy delivery device 14 is cooled or heating.

The introduction of a cooling fluid reduces cell necrosis of surface layers without the use of insulator 32. This preserves surface mucosal and/or epidermal layers as well as protects a tissue site in the vicinity or in cell necrosis zone 28 from receiving sufficient energy to cause cell necrosis. For instance, it may be desirable to insert energy delivery device 14 into an organ in a position which is adjacent to, or even within, some feature that must be preserved while treating other areas including but not limited to blood vessels, nerve bundles, glands and the like. The use of cooling permits the delivery of thermal energy in a predetermined pattern while avoiding heating critical structures.

A sealing plug 58 may be positioned in hollow energy delivery device 14 and used to determine the length of energy delivery device 14 that receives the cooling fluid.

Sealing plug 58 can include one or more sealing wipers 60 positioned on an outer diameter of sealing plug 50. A fluid tube 62 is coupled to a proximal portion of sealing plug 58 and positioned adjacent to the proximal surface of sealing plug 58. A plurality of fluid distribution ports 64 are formed in fluid tube 62. Cooling fluid, which may be a saline solution or other biologically compatible fluid, is fed from control unit 54 through a small diameter dual lumen tube positioned in conduit 56. Cooling fluid flows through fluid tube 62 to the most distal end where it exits through fluid distribution ports 64 arranged about the outer diameter of fluid tube 62. Cooling fluid then flows within hollow lumen 48 and is in direct contact with the wall structure of energy delivery device 14, which is typically metallic and provides a highly efficient heat transfer.

Cooling fluid flows to the proximal end of energy delivery device protected a 14 and through the second lumen of the fluid tube 62, then to control unit 54 which includes both a supply reservoir and a return reservoir to catch and retain the used cooling fluid.

Energy delivery device 14 may have one or more sensors 46 for sensing the temperature of the tissue. This data is fed back to control unit 54 and through an algorithm is stored within a microprocessor memory of control unit 54. Instructions are

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sent to an electronically controlled micropump (not shown) to deliver fluid through the fluid lines at the appropriate flow rate and duration to provide control of tissue temperature.

The reservoir of control unit 54 may have the ability to control the temperature of the cooling fluid by either cooling the fluid or heating the fluid. Alternatively, a fluid reservoir of sufficient size may be used in which the cooling fluid is introduced at a temperature at or near that of the normal body temperature. Using a thermally insulated reservoir, adequate control of the tissue temperature may be accomplished without need of refrigeration or heating of the cooling fluid.

Cooling zone 66 is adjustable in size and location by moving sealing plug 58 using a stylet 68 which is controlled by a slider 70 position at handpiece 12. In this manner, the position of cooling zone 66 can be moved along the length of energy delivery device 14 and the area which is cooled is then proximal of sealing plug 58. In the event it is desirable to have cooling zone 66 within a length of energy delivery device 14 then a second sealing plug 58 can be positioned at a distance proximal of the first or distal sealing plug 58 and the cooling fluid then re-enters the second lumen of fluid tube 62 at proximal sealing plug 58. The distance between the two sealing plugs 58 determines the length of cooling zone 66. In this example, the distal and proximal sealing plugs 58 move together when activated by stylet 68, re-positioning cooling zone 66.

In another embodiment, the distal and proximal sealing plugs 58 are adjusted individually. This provides the ability to both change the position and length of cooling zone 66.

In typical use, cooling zone 66 is positioned so that a predetermined thickness of mucosal or epidermal tissue 72 on the surface of the tissue to be treated 74 is protected as indicated at 75 while the desired cell necrosis zone 28 is formed.

An alternative feature is the ability to indicate to the physician the amount of energy delivery device 14 length that is inserted into the tissue and the depth of protected area 32. To accomplish this, a portion of cell necrosis apparatus 10 comes in contact with mucosal or epidermal surface 72. This can be achieved with a contact collar 76 or with a larger surface that is contoured to fit against the organ or anatomical feature to be treated. The dimensional relationship between contact collar 76 and handpiece 12 is maintained by a sleeve 78 through which energy delivery device 14, fluid tube 62 and stylet 68 all pass. With this dimensional relationship maintained, it is then possible to indicate with indexing pointers on handpiece 12 the distance of energy delivery device 14 distal of contact collar 76 or the surface of cell necrosis apparatus 10.

The distance of cooling zone 66 is then positioned distal of contact collar 76 or the surface cell necrosis apparatus 10. Because all cooling is within energy delivery device 14 and external insulator 32 is not used, energy delivery device 14 penetrates easily through the tissue without drag or resistance that is present when insulator 32 is present.

In another embodiment, sealing plugs 58 and direct flow of cooling fluid are replaced with a slidable inner cooling plug which may be constructed of a material with efficient heat transfer characteristics. Suitable cooling plug materials include but are not limited to copper, beryllium copper, silver and aluminum alloys. Cooling plug is sized to fit intimately against the inner surface of needle 14. This allows transfer of heat from

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energy delivery device 14 to cooling the plug. In this embodiment, cooling plug has interior passageways through which cooling fluid passes. This draws heat from the cooling plug.

Although this embodiment does not provide the highly efficient cooling available by having the cooling fluid in direct contact with the inner surface of energy delivery device 14, a more thorough isolation of the cooling fluid from the body is provided. This results from reducing the possibility of experiencing some leakage past sealing plug 58 of the other embodiment.

In yet another embodiment of cooling, heat pipe technology is used. A sealed compartment contains a mixture of gases which have the ability to rapidly vaporize and condense at temperatures which facilitate the transfer of heat with high efficiency. In this embodiment, a cooling module within handpiece 12 cools the proximal end of the tubular heat pipe and heat is conducted from cooling zone 66 to the cooling module.

Cell necrosis apparatus 10 can be used to create cell necrosis in other structures that affect airway passages including but not limited to the uvula, turbinate structures, soft palate structures and tonsils.

As shown in Figure 9, cell necrosis apparatus 10 is used to create one or more cell necrosis zones 28 in uvula 80. Energy delivery device 14 is configured to be maneuverable in oral cavity 16, pierce an uvula exterior surface, advance into an interior of the uvula a sufficient distance 84 to a tissue site, deliver electromagnetic energy to the tissue site and create controlled cell necrosis. The creation of cell necrosis zones 28 repositions the treated uvula 80 in oral cavity 16 (as indicated by the arrows) while substantially preserving an uvula mucosal layer 82 at an exterior of uvula 80. Cell necrosis zones 28 are created in uvula 80 without creating an ulceration line at a tip 86 of uvula 80. Controlled cell necrosis tightens and reshapes uvula 80.

In creating uvula 80, energy delivery device 12 can have a variety of geometric configurations and may include a curved distal end. The different cell necrosis zones 28 can be stacked in one or more treatment sessions. This permits the physician to control the amount of tissue treated and to assess the results of each session before proceeding with additional procedures. Because exterior mucosal tissue is spared, the patient experiences little pain or discomfort.

Referring now to Figure 10, cell necrosis apparatus 10 is used to create cell necrosis zones 28 in a turbinate structure 88, which can include the interior nasal concha, the middle nasal concha, the superior nasal concha, and combinations thereof.

Energy delivery device 14 is configured to be maneuverable in a nostril, pierce a turbinate structure surface 90 advance into an interior of turbinate structure 88 a sufficient distance to a tissue site, deliver electromagnetic energy to the tissue site and create controlled cell necrosis of turbinate structure 88 to increase the size of a nasal passageway 90.

Sufficient electromagnetic energy is delivered to the tissue site to create controlled cell necrosis of the turbinate structure without sufficiently limiting blood flow to the optic nerve and/or the retina (Figure 11). As shown in Figure 12 disruption of the blood flow to the optic nerve and/or retina can sufficiently damage the optic nerve and/or retina and create a permanent impairment of vision.

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Referring to Figure 10, energy delivery device 14 creates cell necrosis zones 28 to reduce the size turbinate structure 88 by removing only so much of turbinate structure 88 to increase the size of the nasal passageway but insufficient to create a permanent, (i) dysosmic state, (ii) dry nose condition, (iii) atrophic rhinitis state, (iv) a loss of ciliary function or (v) damage to the nerves of nasal cavity creating a permanent loss of nasal and facial structure activity. The creation of the ablation zones in turbinate structure 88 repositions turbinate structure 88. In one embodiment, no more than 33% of the mucosal layer of the lower turbinate is removed. Further removal may create the dysosmic state, a permanent dry nose condition and/or a loss of ciliary function.

As illustrated in Figures 13 and 14, cell necrosis apparatus 10 provides controlled ablation of turbinate structures 88 and the resulting turbinate structure is repositioned in the nasal cavity, and can "open up" the nasal cavity for allergy sufferers and the like. Pressure plate 15 is positioned against desired turbinate to facilitate entry of energy delivery device into tissue to reach necrosis site 92.

In another embodiment, cell necrosis apparatus 10 reduces a volume of a selected site in an interior of a soft palate structure 94 (refer to Figures 15 and 16).

Energy delivery device 14 is configured to be maneuverable in oral cavity 16, pierce a soft palate structure surface 96, advance a sufficient distance to a tissue site, deliver electromagnetic energy to the tissue site, create controlled cell necrosis zones 28 and reposition soft palate structure 94 in oral cavity 16 with reduced necrosis of an exterior mucosal surface 98 of soft palate structure 94. The creation of cell necrosis zones 28 repositions soft palate structure 94 and tightens the interior tissue of soft palate structure as illustrated by the arrows.

Referring now to Figures 17A, 17B, 17C, and 17D an embodiment of cell necrosis apparatus 100 is illustrated where energy delivery device 114 is at least partially positionable in an introducer 102 coupled to handpiece 112 and pressure plate 115 is positionable on an exterior surface of introducer 102. Pressure plate 115 includes a tissue interface surface 117.

One or more energy delivery devices 114 can extend from different ports formed along an exterior surface of introducer 102. Introducer 102 can also be the same as handpiece 112. An energy delivery device advancement device 104 may be provided, although in various embodiments with introducer 102 one is not necessary.

Energy delivery device advancement device 104 can include guide tracks or tubes 106 positioned in the interior of introducer 102. Energy delivery devices 114 may be positioned in guide tracks 106 and advanced from the guide tracks 106 into the interior of the anatomical structure. Cabling is coupled to energy delivery devices 114.

Introducer 102 and handpiece 112 may be one device. Pressure plate 115 can also be positioned at a distal portion of the introducer 102. A second energy delivery device 114 can be coupled to a second introducer 102 coupled to the handpiece. Similarly a second pressure 115 can be positioned at an exterior of the second introducer 102.

A disinfectant medium introduction member 108 can be coupled to cell necrosis apparatus 100 either in an interior or at an exterior. Disinfectant medium introduction member 108 may be slidably positioned in introducer 102 or at its exterior.

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Alternatively, disinfectant medium introduction member 108 can be an optical fiber coupled to a light energy source. Disinfection medium introduction member can be coupled to infusion fluid reservoir 111 (see figure 17D).

Energy delivery devices 114 are at least partially positioned in an interior of introducer 102. Each energy delivery device 114 can be advanced and retracted through a port 109 formed at a distal end or along a side of introducer 102. Energy delivery devices 114 can be hollow to receive a variety of different infusion fluids, including medicinal solutions, electrolyte solutions, irrigation solutions and contrast media. This is accomplished by coupling energy delivery device 114 to infusion fluid reservoir 111 through energy delivery device advancement device 104 (see figure 17D).

Introducer 102 includes a temperature control medium conduit 111 that can extend through an interior of introducer 102. The depth of tissue penetration of energy delivery device 114 is controlled by pressure plate 115.

An energy delivery surface 133 of energy delivery device 114 can be adjusted by inclusion of an adjustable or non-adjustable insulation sleeve 132. Insulation sleeve 132 can be advanced and retracted along the exterior surface of energy delivery device 114 in order to increase or decrease the length of energy delivery surface 133.

Introducer 102 can be malleable. A soft metal member may be enclosed or encapsulated within a flexible outer housing to form a malleable introducer 102.

In another embodiment, handpiece 112 is conformable or deflectable. This can be achieved mechanically or with the use of shape memory metals. A steering wire, or other mechanical structure, can be attached to either the exterior or interior of a distal end of introducer 102. In one embodiment, a deflection knob (not shown) located on handpiece 112 is activated by the physician causing a steering wire to tighten (not shown). This imparts a retraction of the distal end of introducer 102. It will be appreciated that other mechanical devices can be used in place of the steering wire. The deflection may be desirable for tissue sites with difficult access.

Energy delivery devices 114 can be spring loaded. When energy delivery device advancement device 104 is moved back, springs cause selected energy delivery devices 114 to advance out of introducer 102.

One or more sensors 146 may be used to measure temperatures. One or more sensors 146 may be positioned on an interior or exterior surface of energy delivery device 114, insulation sleeve 132, or be independently inserted into the interior ofthe anatomical structure.

Cell necrosis apparatus 100 can include visualization capability including but not limited to a viewing scope, ultrasound, an expanded eyepiece, fiber optics, video imaging, and the like.

Additionally, an ultrasound transducer 116 can determine the size and position of the created lesion. In one embodiment, two ultrasound transducers 116 are positioned on opposite sides of introducer 102 to create an image depicting the lesion in the anatomical structure. Each ultrasound transducer 116 is coupled to an ultrasound source (not shown).

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In one embodiment, cell necrosis apparatus 100 is coupled to an open or closed loop feedback system. Referring now to Figure 18, an open or closed loop feedback system couples sensor 346 to energy source 392. In this embodiment, energy delivery device 314 is one or more RF electrodes 314.

The temperature of the tissue, or of RF electrode 314 is monitored, and the output power of energy source 392 adjusted accordingly. Additionally, the level of disinfection in the oral cavity can be monitored. The physician can, if desired, override the closed or open loop system. A microprocessor can be included and incorporated in the closed or open loop system to switch power on and off, as well as modulate the power. The closed loop system utilizes a microprocessor 394 to serve as a controller, monitor the temperature, adjust the RF power, analyze at the result, refeed the result, and then modulate the power.

With the use of sensor 346 and the feedback control system a tissue adjacent to RF electrode 314 can be maintained at a desired temperature for a selected period of time without impeding out. Each RF electrode 314 is connected to resources which generate an independent output. The output maintains a selected energy at RF electrode 314 for a selected length of time.

Current delivered through RF electrode 314 is measured by current sensor 396.

Voltage is measured by voltage sensor 398. Impedance and power are then calculated at power and impedance calculation device 400. These values can then be displayed at user interface and display 402. Signals representative of power and impedance values are received by a controller 404.

A control signal is generated by controller 404 that is proportional to the difference between an actual measured value, and a desired value. The control signal is used by power circuits 406 to adjust the power output in an appropriate amount in order to maintain the desired power delivered at respective RF electrodes 314.

In a similar manner, temperatures detected at sensor 346 provide feedback for maintaining a selected power. Temperature at sensor 346 is used as a safety means to interrupt the delivery of energy when maximum pre-set temperatures are exceeded. The actual temperatures are measured at temperature measurement device 408, and the temperatures are displayed at user interface and display 402. A control signal is generated by controller 404 that is proportional to the difference between an actual measured temperature and a desired temperature. The control signal is used by power circuits 406 to adjust the power output in an appropriate amount in order to maintain the desired temperature delivered at the sensor 346. A multiplexer can be included to measure current, voltage and temperature, at the sensor 346, and energy can be delivered to RF electrode 314 in monopolar or bipolar fashion.

Controller 404 can be a digital or analog controller, or a computer with software. When controller 404 is a computer it can include a CPU coupled through a system bus. On this system can be a keyboard, a disk drive, or other non-volatile memory systems, a display, and other peripherals, as are known in the art. Also coupled to the bus is a program memory and a data memory.

User interface and display 402 includes operator controls and a display.

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Controller 404 can be coupled to imaging systems, including but not limited to ultrasound, CT scanners, X-ray, MRI, mammographic X-ray and the like. Further, direct visualization and tactile imaging can be utilized.

The output of current sensor 396 and voltage sensor 398 is used by controller 404 to maintain a selected power level at RF electrode 314. The amount of RE energy delivered controls the amount of power. A profile of power delivered can be incorporated in controller 404 and a preset amount of energy to be delivered may also be profiled.

Circuitry, software and feedback to controller 404 result in process control, and the maintenance of the selected power setting that is independent of changes in voltage or current, and used to change, (i) the selected power setting, (ii) the duty cycle (on-off time), (iii) bipolar or monopolar energy delivery and (iv) fluid delivery, including flow rate and pressure. These process variables are controlled and varied, while maintaining the desired delivery of power independent of changes in voltage or current, based on temperatures monitored at sensor 346.

Referring to Figure 19, current sensor 396 and voltage sensor 398 are connected to the input of an analog amplifier 410. Analog amplifier 410 can be a conventional differential amplifier circuit for use with sensor 346. The output of analog amplifier 410 is sequentially connected by an analog multiplexer 406 to the input of A/D converter 408. The output of analog amplifier 410 is a voltage which represents the respective sensed temperatures. Digitized amplifier output voltages are supplied by A/D converter 408 to microprocessor 394. Microprocessor 394 may be a type 68HCII available from Motorola. However, it will be appreciated that any suitable microprocessor or general purpose digital or analog computer can be used to calculate impedance or temperature.

Microprocessor 394 sequentially receives and stores digital representations of impedance and temperature. Each digital value received by microprocessor 394 corresponds to different temperatures and impedances.

Calculated power and impedance values can be indicated on user interface and display 402. Alternatively, or in addition to the numerical indication of power or impedance, calculated impedance and power values can be compared by microprocessor 394 with power and impedance limits. When the values exceed predetermined power or impedance values, a warning can be given on user interface and display 402, and additionally, the delivery of RF energy can be reduced, modified or interrupted. A control signal from microprocessor 394 can modify the power level supplied by energy source 392.

Figure 20 illustrates a block diagram of a temperature/impedance feedback system that can be used to control temperature control fluid flow rate through introducer 102. Energy is delivered to RF electrode 314 by energy source 392, and applied to tissue site 424. A monitor 416 ascertains tissue impedance, based on the energy delivered to tissue, and compares the measured impedance value to a set value. If the measured impedance exceeds the set value, a disabling signal 412 is transmitted to energy source 392, ceasing further delivery of energy to electrode 314. If measured impedance is within acceptable limits, energy continues to be applied to the tissue.

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During the application of energy sensor 346 measures the temperature of tissue and/or electrode 314. A comparator 420 receives a signal representative of the measured temperature and compares this value to a pre-set signal representative of the desired temperature. Comparator 420 sends a signal to a flow regulator 422 representing a need for a higher temperature control fluid flow rate, if the tissue temperature is too high, or to maintain the flow rate if the temperature has not exceeded the desired temperature.

The foregoing description of a preferred embodiment of the invention has been presented for purposes of illustration and description. It is not intended to be exhaustive or to limit the invention to the precise forms disclosed. Obviously, many modifications and variations will be apparent to practitioners skilled in this art. It is intended that the scope of the invention be defined by the following claims and their equivalents.

What is claimed is:

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Espacenet

Claims: JP2001526077 (A) — 2001-12-18

APPARATUS FOR REDUCING TISSUE VOLUMES BY THE USE OF ENERGY

Claims not available for JP2001526077 (A)
Claims of corresponding document: WO9932041 (A1)

A high quality text as facsimile in your desired language may be available amongst the following family members:

CA2315842 (A1) WO9932041 (A1)

- Original claims
- Claims tree

The EPO does not accept any responsibility for the accuracy of data and information originating from other authorities than the EPO; in particular, the EPO does not guarantee that they are complete, up-to-date or fit for specific purposes.

CLAIMS

1. A cell necrosis apparatus to treat a selected site of an anatomical structure, comprising:
a handpiece;
an energy delivery device coupled to a distal portion of the handpiece including a tissue piercing distal end;
a pressure plate positioned at an exterior of the energy delivery device; and
a cable coupled to the energy delivery device.

2. The apparatus of claim 1, wherein the apparatus reduces a volume of the selected site of the anatomical structure.

3. The apparatus of claim 1, wherein the apparatus alters a shape of the anatomical structure.

4. The apparatus of claim 1, wherein the energy delivery device is an RF electrode.

5. The apparatus of claim 4, further comprising:
an RF energy source coupled to the RF electrode.

6. The apparatus of claim 1, wherein the energy delivery device is a microwave antenna.

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7. The apparatus of claim 6, further comprising:
a microwave energy source coupled to the microwave antenna.

8. The apparatus of claim 1, wherein the energy delivery device is a waveguide.

9. The apparatus of claim 8, further comprising:
a light source coupled to the waveguide.

10. The apparatus of claim 9, wherein the light source is a laser.

11. The apparatus of claim 1, wherein the energy delivery device is an acoustical transducer.

12. The apparatus of claim 11, further comprising:
an acoustical energy source coupled to the acoustical transducer.

13. The apparatus of claim 1, wherein the energy delivery device is a resistive heating device.

14. The apparatus of claim 13, further comprising:
an electrical current source coupled to the resistive heating device.

15. The apparatus of claim 1, further comprising:
a second energy delivery device coupled to the handpiece.

16. The apparatus of claim 15, further comprising: a second pressure plate positioned at an exterior of the second energy delivery device.

17. The apparatus of claim 1, wherein the energy delivery device includes an infusion lumen.

18. The apparatus of claim 17, wherein the infusion lumen is coupled to a medication source.

19. The apparatus of claim 17, wherein the infusion lumen is coupled to a contrast medium source.

20. The apparatus of claim 17, wherein the infusion lumen is coupled to a electrolytic solution source.

21. The apparatus of claim 17, wherein the infusion lumen is coupled to a disinfectant source.

22. The apparatus of claim 1, further comprising:
a cooling device coupled to the energy delivery device.

23. The apparatus of claim 1, further comprising:
an insulator positioned at an exterior of the energy delivery device.

24. The apparatus of claim 1, further comprising:
a sensor coupled to the energy delivery device.

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25. The apparatus of claim 24, wherein the sensor is positioned at a distal portion of the energy delivery device.

26. The apparatus of claim 1, further comprising:
a feedback control system coupled to the energy delivery device, a sensor and an energy source.

27. The apparatus of claim 1, wherein the pressure plate defines a depth of penetration of the energy delivery device in the anatomical structure.

28. The apparatus of claim 1, wherein the pressure plate defines an area of an energy delivery surface of the energy delivery device.

29. The apparatus of claim 1, wherein the pressure plate includes a tissue interface surface.

30. The apparatus of claim 1, wherein the pressure plate has a an exterior geometry section selected from a planar surface, a curved surface, a concave surface, a convex surface and combinations thereof.

31. The apparatus of claim 29, wherein the tissue interface surface applies a force to an energy delivery device insertion site of the anatomical structure.

32. The apparatus of claim 31, wherein the force immobilizes the tissue at the energy delivery device insertion site to facilitate a penetration of the energy delivery device into the anatomical structure.

33. The apparatus of claim 31, wherein the force creates a compression of the energy delivery device insertion site to facilitate a penetration of the energy delivery device into the anatomical structure.

34. The apparatus of claim 29, wherein an area of the tissue interface surface is in the range of 0.005 to 0.25 in2.

35. The apparatus of claim 1, wherein the pressure plate is adjustably mounted on an exterior of the energy delivery device.

36. The apparatus of claim 1, wherein the pressure plate is configured to allow the advancement and retraction of the energy delivery device.

37. The apparatus of claim 36, wherein the pressure plate includes an aperture for the advancement and retraction of the energy delivery device through the pressure plate.

38. The apparatus of claim 1, wherein the pressure plate is made of a nonconductive material.

39. The apparatus of claim 38, wherein the pressure plate provides electrical isolation at the tissue insertion site from the cell necrosis apparatus.

40. The apparatus of claim 1, wherein the anatomical structure is selected from a tongue, a turbinate, an uvula, a soft palate, and a tonsil.

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41. A cell necrosis apparatus to treat a selected site of an anatomical structure, comprising:
a handpiece;
an energy delivery device coupled to a distal portion of the handpiece including a tissue piercing distal end;
a safety stop positioned at an exterior of the energy delivery device; and
a cable coupled to the energy delivery device.

42. The apparatus of claim 41, wherein the safety stop defines a depth of penetration ofthe energy delivery device in the anatomical structure.

43. The apparatus of claim 41, wherein the safety stop defines an area of an energy delivery surface of the energy delivery device.

44. The apparatus of claim 41, wherein the safety stop includes a tissue interface surface.

45. The apparatus of claim 41, wherein the safety stop has a an exterior geometry section selected from a planar surface, a curved surface, a concave surface, a convex surface and combinations thereof.

46. The apparatus of claim 29, wherein the tissue interface surface applies a force to an energy delivery device insertion site of the anatomical structure.

47. The apparatus of claim 46, wherein the force immobilizes the tissue at the energy delivery device insertion site to facilitate a penetration of the energy delivery device into the anatomical structure.

48. The apparatus of claim 42, wherein the force creates a compression of the energy delivery device insertion site to facilitate a penetration of the energy delivery device into the anatomical structure.

49. The apparatus of claim 44, wherein an area of the tissue interface surface is in the range of 0.005 to 0.25 in2.

50. The apparatus of claim 41, wherein the safety stop is adjustably mounted on an exterior of the energy delivery device.

51. The apparatus of claim 41, wherein the safety stop is configured to allow the advancement and retraction of the energy delivery device.

52. The apparatus of claim Si, wherein the safety stop includes an aperture for the advancement and retraction of the energy delivery device through the safety stop.

53. The apparatus of claim 41, wherein the anatomical structure is selected from a tongue, a turbinate, an uvula, a soft palate, and a tonsil.

54. The apparatus of claim 41, wherein the safety stop defines an energy delivery device energy delivery surface length.

55. An apparatus to treat a selected site in an interior of an anatomical structure, comprising:

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an introducer;
an energy delivery device at least partially positionable in the interior of the introducer;
a pressure plate positioned at an exterior of the introducer; and
a cable coupled to the energy delivery device.

56. The apparatus of claim 55, wherein the pressure plate is positioned at a distal portion of the introducer.

57. The apparatus of claim 55, wherein the pressure plate is positioned at a distal end of the introducer.

58. The apparatus of claim 55, further comprising:
an advancement member coupled to the energy delivery device.

59. The apparatus of claim 55, wherein the apparatus reduces a volume of the selected site of the anatomical structure.

60. The apparatus of claim 55, wherein the apparatus alters a shape of the anatomical structure.

61. The apparatus of claim 55, wherein the energy delivery device is an RF electrode.

62. The apparatus of claim 61, further comprising:
an RF energy source coupled to the RF electrode.

63. The apparatus of claim 55, wherein the energy delivery device is a microwave antenna.

64. The apparatus of claim 63, further comprising:
a microwave energy source coupled to the microwave antenna.

65. The apparatus of claim 55, wherein the energy delivery device is a waveguide.

66. The apparatus of claim 65, further comprising:
a light source coupled to the waveguide.

67. The apparatus of claim 66, wherein the light source is a laser.

68. The apparatus of claim 55, wherein the energy delivery device is an acoustical transducer.

69. The apparatus of claim 68, further comprising:
an acoustical energy source coupled to the acoustical transducer.

70. The apparatus of claim 55, wherein the energy delivery device is a resistive heating device.

71. The apparatus of claim 70, further comprising:
an electrical current source coupled to the resistive heating device.

72. The apparatus of claim 55, further comprising:
a second energy delivery device coupled to a second introducer coupled to the

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handpiece.

73. The apparatus of claim 72, further comprising:
a second pressure plate positioned at an exterior of the second introducer.

74. The apparatus of claim 55, wherein the energy delivery device includes an infusion lumen.

75. The apparatus of claim 74, wherein the infusion lumen is coupled to a medication source.

76. The apparatus of claim 74, wherein the infusion lumen is coupled to a contrast medium source.

77. The apparatus of claim 74, wherein the infusion lumen is coupled to a electrolytic solution source.

78. The apparatus of claim 74, wherein the infusion lumen is coupled to a disinfectant source.

79. The apparatus of claim 55, further comprising:
a cooling device coupled to the energy delivery device.

80. The apparatus of claim 55, further comprising:
an insulator positioned at an exterior of the energy delivery device.

81. The apparatus of claim 55, further comprising:
a sensor coupled to the energy delivery device.

82. The apparatus of claim 81, wherein the sensor is positioned at a distal portion of the energy delivery device.

83. The apparatus of claim 55, further comprising:
a feedback control device coupled to the energy delivery device, a sensor and an energy source.

84. The apparatus of claim 55, wherein the pressure plate defines a depth of penetration of the energy delivery device in the anatomical structure.

85. The apparatus of claim 55, wherein the pressure plate defines an area of an energy delivery surface of the energy delivery device.

86. The apparatus of claim 55, wherein the pressure plate includes a tissue interface surface.

87. The apparatus of claim 55, wherein the pressure plate has an exterior geometry section selected from a planar surface, a curved surface, a concave surface, a convex surface and combinations thereof.

88. The apparatus of claim 86, wherein the tissue interface surface applies a force to an energy delivery device insertion site of the anatomical structure.

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89. The apparatus of claim 88, wherein the force immobilizes the tissue at the energy delivery device insertion site to facilitate a penetration of the energy delivery device into the anatomical structure.

90. The apparatus of claim 88, wherein the force creates a compression of the energy delivery device insertion site to facilitate a penetration of the energy delivery device into the anatomical structure.

91. The apparatus of claim 86, wherein an area of the tissue interface surface is in the range of 0.005 to 0.25 in2.

92. The apparatus of claim 55, wherein the pressure plate is adjustably mounted on an exterior of the introducer.

93. The apparatus of claim 55, wherein the pressure plate is configured to allow the advancement and retraction of the energy delivery device.

94. The apparatus of claim 93, wherein the pressure plate includes an aperture for the advancement and retraction of the energy delivery device through the pressure plate.

95. The apparatus of claim 55, wherein the anatomical structure is selected from a tongue, a turbinate, a uvula, a soft palate, and a tonsil.

96. The apparatus of claim 55, wherein the energy delivery device is sufficiently sharp to pierce an exterior surface of the anatomical member without a support device.

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