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# Online Monitoring of Dyskinesia in Patients with Parkinson's Disease

*Utilizing Wearable Movement Sensors to Successfully Detect and Assess Severity of Parkinsonian Symptoms in Daily Life*

Quantitative assessment of human motor control and movement disorders has been a topic of large interest for decades. Since the 1960s, advanced equipment has become available that provided many laboratories with powerful tools to measure human motor performance in great detail and with great accuracy. The results of these studies have greatly contributed to our present understanding of the basic principles, which underlie human motor behavior. The advanced equipment has also been used for studying various pathologies of motor performance. However, sophisticated equipment alone is not a guarantee for success in the detection and analysis of motor disorders. In many situations, deficiencies in motor performance are not always prevalent and motor disorders may occur only in very specific situations, which are hard to imitate or to reproduce in a laboratory. A good example is stumbling in elderly people. In general, elderly people do not have a specific motor disorder. Rather, they tend to fall more easily than normal subjects in complex situations because of the limited information-processing capability of elderly people [1], [2], [3].

Another example relates to patients with medication, like Parkinson patients who take levodopa to eliminate the typical symptoms of Parkinson's disease. Parkinson's disease is a good example of a disease with a variety of motor disorders like tremor, hypokinesia, bradykinesia, and rigidity [4]. Usually, levodopa, which has been the most successful medication in reducing Parkinsonian symptoms, is prescribed to these patients. However, chronic levodopa therapy for several years has several side effects, one of them being that it introduces dyskinesias [5]. Many of these patients start to fluctuate between the "off" state (re-emergence of Parkinson's disease symptoms because the effect of levodopa wears off a few hours after levodopa intake) and the "on" state, in which levodopa is active and improves the patients' motor performance. But in the "on" state, patients can suffer from dyskinesia. The presence of dyskinesia is a side effect of levodopa therapy and therefore referred to as levodopa-induced dyskinesia (see Figure 1) [4], [6], [7]. The actual emergence of dyskinesias throughout the day depends mainly on the timing and quantity of each individual dose of levodopa and depends also on stress, food, and many other factors, be it to a lesser extent [6]-[8]. In these cases, patients will greatly benefit from quantitative objective assessment of their motor

state in daily life in relation to the dosing schedule [9]. The need for a quantitative objective assessment has become even more important because of the growing number of pharmacological and surgical interventions, which have become available as a last resort for patients with very severe dyskinesias or Parkinsonian symptoms [10]-[12].

New developments in microelectronics have led to the development of a new generation of movement sensors, which are smaller, cheaper, more robust, and more accurate than before. Triggered by these new developments, several studies have started to use small accelerometers and gyroscopes to monitor movements in a laboratory setting [3], [13]-[17]. Moreover, these sensors are extremely useful for measurements in daily life and, therefore, have been used as an activity monitor [18]-[22]. However, the use of movement sensors for online monitoring of human motor control or motor disorders is still in its infancy.

The purpose of this article is to describe the present state-of-the-art of online monitoring of motor behavior in patients with Parkinson's disease in daily life. We will focus on modern monitoring equipment and on new analysis tools, which allow a quantitative detection and assessment of dyskinesias throughout the day, by an objective, unsupervised rating of dyskinesias using clinical rating scores.

## Acquisition of Human Movement Signals

### Optical Motion Analysis Systems

The most commonly used and most accurate technique to monitor human movements in a research setting is by using optical motion analysis systems. These systems are extremely precise and have a resolution better than 0.2 mm within a range of about 2 m<sup>3</sup>. Some of these systems use active markers (for example, Optotrak, see, e.g., <http://www.ndigital.com/medical.html>) and have the advantage that a large number of markers can be used and that the system can unambiguously identify each of the markers for long periods of time. Other systems, like the VICON system (see <http://www.vicon.com/main/mocap/index.html>), use passive markers. This has the advantage that the subject is not connected by any wires to the measurement equipment and, therefore, is most convenient for studies on patients. However, for complex movements it is sometimes difficult and time consuming to identify the various markers. The main disadvantages of optical motion analy-

sis systems are that they are expensive and can only measure movements in a restricted space. Therefore, they cannot be used for observation of patients in daily life settings.

### Body-Mounted Sensors

More recently, body-mounted sensors like accelerometers, gyroscopes, goniometers, and earth-magnetic field sensors have been used to obtain data about kinematic parameters [13]-[18], [23], [24]. These sensors have become small, cheap, robust, and accurate in the last couple of years. For these reasons, movement sensors have become very useful for scientific applications and in daily life settings. In ambulatory devices that measure posture and kinematics, accelerometers and to a lesser extent also gyroscopes have been used [18]-[22].

A piezo-resistive accelerometer consists of a mass, connected to a frame by beams, which can be represented by a damped spring (see Figure 2). An accelerometer carries two signals: a signal related to the acceleration of movements and a gravity-related signal, which is related to the position of the accelerometer relative to gravity (see Figure 2). Gyroscopes measure the angular velocity based on the Coriolis principle. Accelerometers have an accuracy of about  $\pm 0.05$  g, while gyroscopes show more noise and have a drift of about  $9^\circ/\text{s}$ . Accelerometers placed on the trunk and the upper legs provide enough information to measure activities in daily life like walking, standing, and sitting [18]-[22]. The success of these activity monitors in assessing postures is a result of the fact that the accelerometer signal accurately reflects the component related to the orientation of the accelerometer with respect to gravity when there is no movement. However, when there is movement, both the orientation component and the acceleration component will change and these two components cannot be distinguished from each other. Because movement induces changes in the accelerometer signal, changes in the accelerometer signal can be used as a measure of the amount of movement. In contrast to accelerometers, gyroscopes measure one single component: the angular velocity. Integration of the gyroscope signal attached to a body segment will lead to the orientation of the body segment as a function of time. However, gyroscopes show some drift, resulting in large errors for orientation after simply integrating the gyroscope signal over time. For this reason, systems combining the advantage of accelerometers (orientation during absence of movement) and gyroscopes (angular velocity) were developed to assess movements and the position of limb segments in ambulatory conditions [15], [25]. These combined systems appear to be very accurate in assessing the orientation of a segment and tend to approach the performance obtained by camera systems (errors smaller than 7% for angle, angular velocity, and angular acceleration) [15]. Adding earth-magnetic field sensors to the combined system of gyroscopes and accelerometers will even increase the performance (accuracy of better than 1% RMS for position) (Xsens, <http://www.xsens.com/>).

### Storage of Body-Mounted Sensors

The signals of movement sensors in ambulatory conditions are usually stored on digital portable recorders like Dynaport and Vitaport. These recorders contain small A/D converters (small with respect to size and weight) and are able to record up to about 24 signals with a sample frequency of up to 1,000

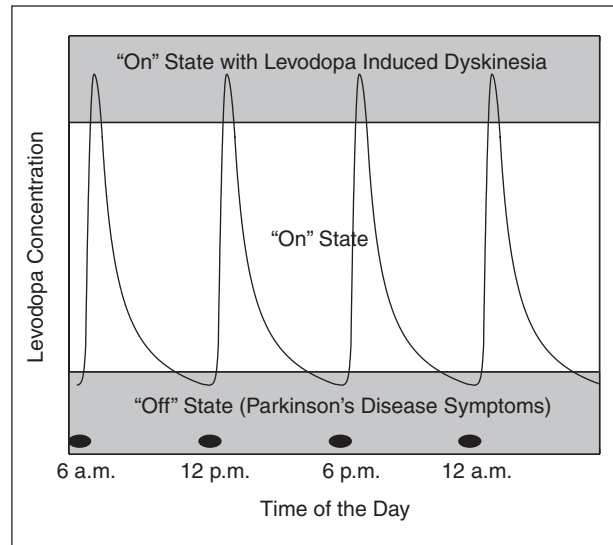


**Fig. 1.** Schematic view of the levodopa fluctuations in patients with Parkinson's disease. Patients fluctuate between "off" state (re-emergence of Parkinson's disease symptoms because the effect of levodopa wears off a few hours after levodopa intake) and the "on" state, in which levodopa is active and improves the patients' motor performance. In the "on" state we also distinguish two states, one state without and one state with dyskinesia. The presence of dyskinesia is a side effect of levodopa therapy.

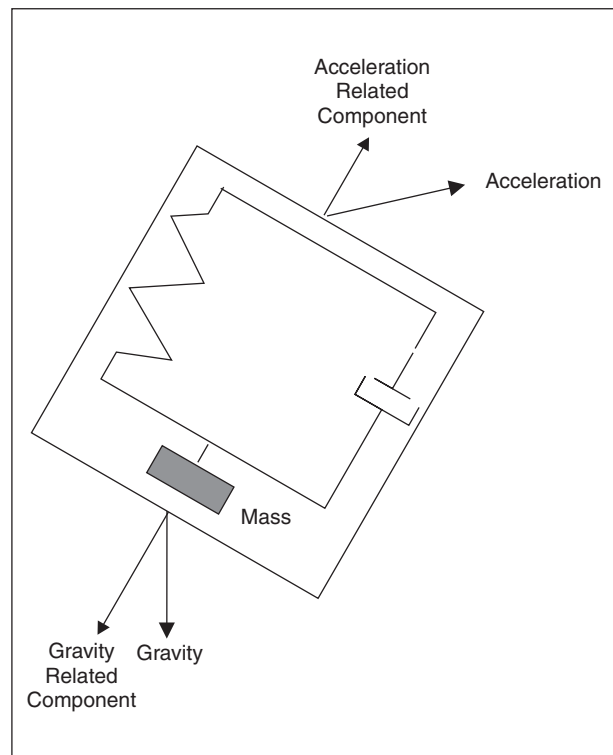


**Fig. 2.** A single-axis accelerometer consists of a mass, connected to a frame by beams, which can be represented by a damped spring. The accelerometer measures a contribution of gravity related to the orientation of the accelerometer and a contribution related to linear acceleration of the accelerometer.

Hz. The signals can be stored on a small flashdisk with a capacity larger than 2 Gb, which means that data from about 24 signals can be stored for periods of several days at a frequency of 100 Hz. A disadvantage of these kinds of devices is that they are tethered and, therefore, will lead to discomfort to the subject, especially when a large number of sensors are used. In this perspective, sensors with high storage capacity or the ability of transmitting signals telemetrically to an external recording system would be highly desirable. Devices for recording EEG, ECG, and EMG signals that can handle up to 32 signals telemetrically have become quite common. However, these devices are not yet in advantage compared to a portable recorder, since transmissions of the signals from the sensors to the telemetric system are still tethered. To reduce the discomfort due to wires, an alternative is to attach a sender to each set of sensors at a certain segment. Bluetooth wireless technology, which allows short-range radio link between two points, seems to offer a solution for such a device. However, this technology is not yet reliable enough due to its lack of robustness to interference signals from other electronic devices, especially if the signal has to be sent over distances of more than a few meters.

### Analysis of Sensor Signals in Parkinson's Disease

An important issue in the development of quantitative devices is to test their validity. So far, quantitative methods to detect and assess the severity of symptoms for motor disorders in Parkinson's disease are scarce. At present, the only gold standard of assessing the severity of these symptoms is

the assessment by a well-trained physician using standard clinical rating scales; for example, the Unified Parkinson's Disease Rating Scale (UPDRS) [26] and various dyskinesia rating scales (for review see Goetz [27]). Many doctors, however, are not familiar with such rating scales. Furthermore, these scales may be too time consuming to administer and they can hardly be applied for continuous registration procedures.

In Parkinson's disease, an automatic ambulatory assessment has to be able to distinguish between various motor states. At present, several studies have focused on the assessment of a single motor state or a particular symptom of Parkinson's disease in daily life. However, no study so far could successfully assess all three motor states and distinguish among them in daily life. The main reason for this failure is the inability to discriminate between voluntary movements and levodopa-induced dyskinesia during the "on" state on the one hand, and the inability to discriminate between voluntary refraining from moving and Parkinsonian hypokinesia on the other hand. For these reasons, it is necessary to find specific parameters and classification techniques, which can provide physicians an objective characterization of these symptoms. This means that these techniques have to distinguish between various motor disorders and be able to distinguish between normal and pathological movements.

Linear classification techniques have been most commonly used to evaluate the validity of a new quantitative measurement. Linear classification techniques are often sufficient in controlled settings when only characteristics of a single motor disorder are involved. Additional motor disorders and voluntary movements often show characteristics that interfere with characteristics of the movement disorder of interest. In addition, relations between clinical rating and various movement parameters are usually not known and these relations can be highly nonlinear. Therefore, linear classification techniques are often not sufficient for a proper detection and assessment of motor disorders. In this context, neural networks have proven to be very successful since they can be trained to detect and assess the severity of dyskinesia even when no explicit rules and relationships are available for proper classification, and as long as data are available to train them [28], [29]. Neural networks can be more accurate than linear statistical methods because they learn to recognize the critical nonlinear interactions among variables and then weigh these interactions to predict a given outcome. Figure 3 shows a schematic overview of the neural network approach in assessing the severity of dyskinesia by Keijsers et al. [30], [31]. Figure 3 shows a neural network with an input layer with six units, a hidden layer with three units and an output layer with one unit. Each unit is connected to all units in the next layer. Each connection has a certain weight, and this weight illustrates the influence of the unit to the response of the unit in the subsequent layer. Training the network implies that the weights between units of subsequent layers are adjusted in order to minimize the error between the desired network output (e.g., score by physician) and the neural network output for each set of input variables (e.g., parameters from accelerometer signals). Each pass through the data increases the model's accuracy as the actual outcome is compared with the predicted outcome. So the system learns by trial and error.

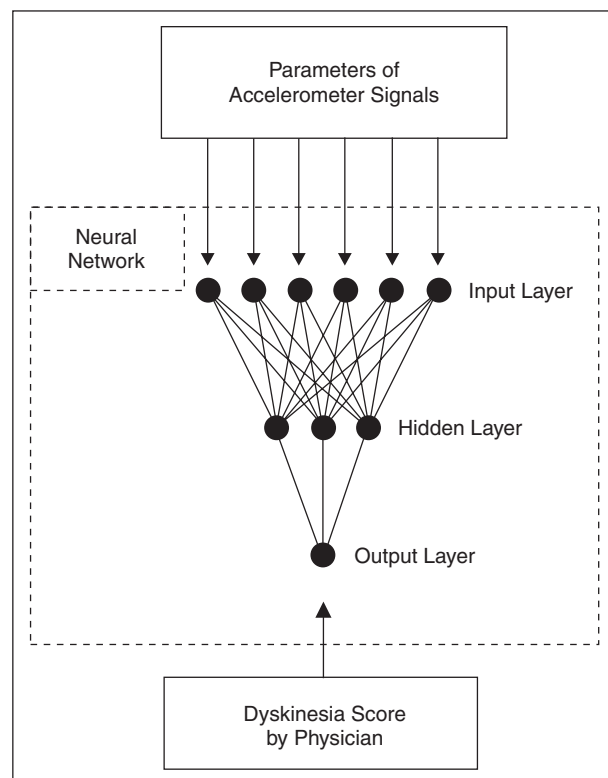


**Fig. 3.** Schematic overview of the neural network approach in assessing the severity of dyskinesia by Keijsers et al. The neural network maps the parameters of the accelerometer signal (input) to the rating by the neurologist (output) by adjusting the connection between units in subsequent layers.

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### Results in Assessing Symptoms of Parkinson's Disease

#### Assessing Symptoms of the "Off" State

A well-known symptom of Parkinson's disease in the "off" state is tremor, which has been studied by many research groups [32]-[36]. Tremor is most commonly present in the hands. The rhythmic pattern of tremor can be detected by using two axes accelerometers attached on the hand or the wrist. Fourier analysis of accelerometer signals is the method most commonly applied for tremor analysis. Dominant frequency and amplitude of tremor are typically derived to evaluate tremor in controlled laboratory settings. However, Fourier analysis will not be sufficient for long time monitoring since voluntary movements or dyskinesias will interfere with and/or resolve the Parkinson tremor. Therefore, more advanced algorithms, which are able to detect tremor in a time period of only a few seconds, are needed for ambulatory assessment. Studies that evaluated tremor detection algorithms for long-term assessment, used extra parameters of the accelerometer signal together with Fourier analysis [23], [32], [36]. Hoff and coworkers [36] found high sensitivity (0.82, true positive detection) and specificity (0.93, true negative detection) for their algorithm [36]. They also found increased objective values for duration and intensity of tremor for patients with high clinical tremor severity. Van Someren and colleagues found a false positive error rate of 4% for their tremor detection algorithm and found the method successful in discriminating tremor from other movements [23], [32].

In contrast to tremor, other Parkinson's disease symptoms in the "off" state such as bradykinesia, hypokinesia, rigidity, and akinesia have been studied much less in a quantitative way during daily life. Hypokinesia (lack of movement) and bradykinesia (slowness of movement) are symptoms that almost always occur in the "off" state of Parkinson patients. Bradykinesia has often been studied in highly controlled settings or during clinical visits using timed motor tasks like tapping, writing and Peg-board [37]-[39]. Studies that evaluated hypokinesia and bradykinesia in long-term recordings mostly used a wrist-worn activity monitor. These activity monitors consist of an accelerometer combined with a storage capacity attached to the wrist. Katayama (2001) found this activity monitor a reliable method to study the effect of drugs on hypokinesia and to determine hypokinetic periods during a day [40]. Van Hilten and coworkers have studied these wrist-worn activity monitors by patients with Parkinson's disease in several studies [20], [41]-[44]. In 1997, Dunnewold et al. mounted a triaxial accelerometer to the wrist and found that the mean acceleration in a 30-s interval correlated well (0.87 and -0.78 for tap rate and movement time, respectively) with a commonly used test procedure in the assessment of slowness of movement [44]. The main problem of these wrist-worn activity monitors is

that they only measure movements of the wrist without any knowledge of other limb movements. An activity monitor with accelerometers placed on various body parts could be helpful to detect certain postures and motor activities like sitting, lying, and walking. So far, only Dunnewold and coworkers (1998) reported results of such an activity monitor in patients with Parkinson's disease [20]. They were able to reliably identify body postures such as sitting, standing, and lying by using an accelerometer mounted on the trunk and an accelerometer mounted on the upper dominant leg [20]. They also attached two accelerometers to the arm and evaluated these accelerometer signals in assessing bradykinesia and hypokinesia. The mean value of the vectorial sum of the accelerometer signals for each pair of sensors was used as a measure of bradykinesia. The mean duration of immobility periods (defined as a period of time with acceleration below an amplitude threshold of 0.08 g in the frequency range of 1.0-3.5 Hz) was used as a measure for hypokinesia. Patients with Parkinson's disease showed significantly smaller bradykinesia and larger hypokinesia values than controls. However, the objective measures of bradykinesia and hypokinesia showed only a modest or no relation at all to the Unified Parkinson's Disease Rating Scale (UPDRS) [26]. These authors did not investigate whether the wrist signals in combination with the body positions resulted in an increase in the performance of assessing hypokinesia and bradykinesia.

#### Assessing Dyskinesia

Recently, pharmacological and surgical interventions to improve dyskinesia have been evaluated [10]-[12]. Due to a need for objective evaluation of these interventions, the interest in assessing dyskinesia in a quantitative way has increased [9], [30], [31], [45]-[47]. All dyskinesia studies used accelerometers except for the study of Burkhard and associates, who used gyroscopes [45]. The accelerometer studies differed in the body segments, from which movements were measured, and the number of accelerometers per segment. The major challenge in automatically assessing dyskinesia is that the method has to be able to distinguish dyskinesias from voluntary movements. Most studies that tried to detect dyskinesia focused on the frequency domains of the signals from the movement sensors [45]-[47]. These studies correlated features in the frequency domain (mean power and maximal power in various parts of the frequency domain) with the physicians' score to evaluate their validity. Only in the studies by Keijsers et al. were more advanced methods and a large number of parameters calculated from the accelerometer signals used to detect and to assess the severity of dyskinesia [30], [31]. So far, the optimal number and placement of accelerometers, the most important parameters, and the various nonlinear classification techniques to assess dyskinesia are not known. For this reason, we will give a detailed overview of the studies that

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focused on quantitative ambulatory assessment of dyskinesia in patients with Parkinson's disease.

Burkhard et al. (1999) used gyroscopes on both hands and recorded data from 22 patients with dyskinesia in the arm for a period of 10 seconds while these patients were standing and counting backwards [45]. They found a correlation of 0.54 between the clinical dyskinesia score and the root mean square of the frequency power spectrum of the hand movements in a frequency bandwidth of 0-20 Hz. They also found a clear frequency peak of dyskinesia for all subjects in the range between 0.25 to 3.25 Hz (mean  $1.26 \text{ Hz} \pm 0.65$ ). In a study by Hoff et al. (2001) patients were tested in a set of seven tasks of 1-minute duration each by using four sets of two accelerometers on the trunk, the wrist, the upper arm, and the leg [47]. These authors calculated the mean amplitude of the dominant frequency in two frequency bands (1-4 Hz and 4-8 Hz) and used a linear discriminant analysis to distinguish dyskinesias from normal movements. The mean amplitude in both frequency bands of the wrist showed a significant correlation with the clinical rating score (m-AIMS) for tasks, in which patients abstained from any voluntary movements (correlation coefficients between 0.78 and 0.87). However, these authors had problems in assessing dyskinesia when voluntary movements were present, like in drinking and walking. Keijsers et al. (2000) used the same data set as used in the study by Hoff et al. (2001), but they used neural networks instead of linear discriminant analysis to assess dyskinesia [30], [47]. The neural network (using the mean segment velocity and the cross-correlation between movements of different body parts as input) approach revealed a significantly better performance than the linear classification technique used by Hoff et al [47]. However, the results of Keijsers et al. (2000) were far from optimal, indicating that considerable improvement was needed in order to obtain a reliable method, which can be used in daily life [30]. Manson et al. (2000) attached a tri-axial accelerometer to the shoulder and showed that the accelerations in the 1-3 Hz frequency band correlated well with the clinical score (AIMS scale) for various tasks except for walking [46]. Manson et al. (2000) and Keijsers et al. (2000) were both able to assess the severity of LID, even when patients made voluntary movements [30], [46]. However, a main limitation in the study by Manson et al. (2000) might have been the low specificity for mild dyskinesias.

In order to study the effect of task conditions in a group of patients with varying degrees of dyskinesia, Keijsers et al. (2002) monitored patients while performing a large variety of daily life tasks in a natural environment for a long period

of time [31]. In this study six sets of triaxial accelerometers were placed at both upper arms, at the wrist of the most affected side, at the trunk, and at both upper legs. A large number of parameters were calculated from the accelerometer signals before they were presented as input to the neural network. The optimal neural network architecture was found by using forward selection for neural networks with various numbers of hidden units [31], [48]. The optimal number of hidden units of the neural network for rating the severity of dyskinesia was one for the trunk, two for the arm, and three for the leg. The number of hidden units larger than one indicates that nonlinear interactions between movement variables are important for a proper rating of dyskinesia. The neural network correctly classified more than 95% of the data. Figure 4 shows an example of scores given by physicians and those given by the neural network for a set of 81 1-minute intervals taken out of a 2.5-hour session (periods of rest are not shown). Patients performed activities like reading a newspaper, making and serving coffee, taking off shoes, and washing hands, and each activity was divided in time intervals of 1 minute. The scores predicted by the neural network do agree well with the scores given by the physicians, and both scores change almost simultaneously in time. The neural network used a variety of variables to classify the severity of dyskinesia for a certain limb segment. Important variables to distinguish dyskinesia from normal voluntary movements appeared to be the percentage of time that a segment was moving and the cross-correlation between movements of different segments. They also found that dyskinesia is most dominant in the lower frequencies. However, the frequency range of accelerometer signals of voluntary movements is not clearly different from that of the accelerometer signals for dyskinesias.

## Discussion

The most commonly used methods to assess the severity of symptoms in patients with Parkinson's disease are clinical rating scales. However, these scales are subjective and patients are rated in a laboratory or clinical setting, where the clinician only obtains a cross-sectional view of the patient. With regard to Parkinson's disease, major progress has been made with the use of small, accurate, and robust accelerometers and gyroscopes, which made it possible to successfully detect and assess the severity of Parkinsonian symptoms. So far, this seems just the beginning of a rapid new development in ambulatory assessment. At present, tremor (specificity of 0.95) and dyskinesia (correct classification of 95%) can be detected accurately in daily life [31], [32].

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At present, the assessment of hypokinesia (lack of movement) and bradykinesia (slowness of movement) in daily life seems difficult. Relaxing periods without voluntary movements and slow voluntary movements are hard or may even be impossible to distinguish from hypokinesia and bradykinesia by using movement sensors. In this prospect, other recordings like EMG, ECG, and EEG could be helpful and can be added easily in addition to the signals from the movement sensors [49]. EMG recordings have been successfully used in long-term assessment of tremor in patients with Parkinson's disease [50], [51]. The specificity and sensitivity of these

methods were about 95%. According to these investigators, artifacts caused by movements and general activity of the patient did not materially interfere with tremor evaluation using surface EMG [50], [51]. Haapaniemi and associates (2001) studied long-term ECG recordings and found significant differences between patients with Parkinson's disease and aged matched controls [52]. In addition, they found a negative correlation between the Unified Parkinson's Disease Rating Scale and the power spectra in low frequency bands [52].

The most important demand of ambulatory assessment of the motor state of a patient with Parkinson's disease is that the

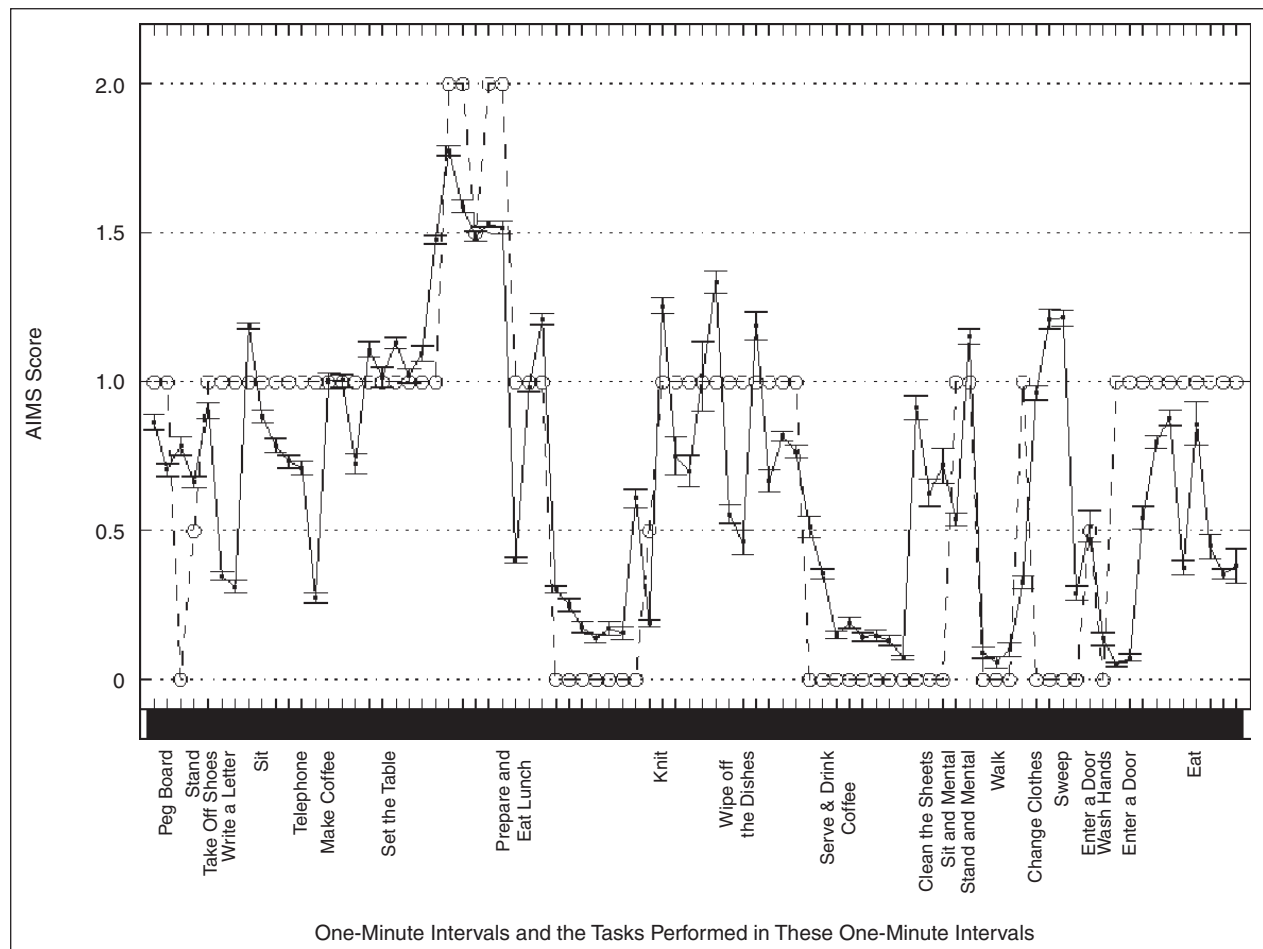


**Fig. 4.** Example of the AIMS rating given by the physicians (circles) and predicted by the neural network (dots with error bars) for the trunk for 81 one-minute intervals of various activities (from [31]) (figure ©2003 Movement Disorders).

## Developments in microelectronics will lead to wireless, telemetric devices with much less discomfort for the patient.

procedure can assess all different motor states or symptoms and can distinguish between them. The ultimate device should record the behavior of a patient for at least 24 hours. Thereafter, algorithms should assess the severity of the motor state of patients with Parkinson's disease. Some Parkinsonian symptoms might be hard to assess by movement sensors alone and, therefore, the usefulness of EMG and ECG recordings in addition to the movement sensors has to be explored. Since the characteristics of Parkinsonian symptoms are hard to define, sophisticated analysis methods like neural networks are required to analyze the data and to provide a proper classification. In addition, developments in microelectronics will lead to wireless, telemetric devices with much less discomfort for the patient. Such a device can be attached easily by a physician or assistant, and after recording the data can be analyzed by a dedicated computer program.



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### References

- [1] P.F. Tang and M.H. Woollacott, "Inefficient postural responses to unexpected slips during walking in older adults," *J. Gerontol. Med. Sci.*, vol. 53A, no. 6, pp. M471-M480, 1998.
- [2] A.M. Schillings, B.M.H. van Wezel, Th. Mulder, and J. Duysens, "Stumbling over obstacles in older adults as compared with young adults," in *Control of Posture and Gait, Symposium of the International Society for Postural and Gait Research*, J. Duysens, B.C.M. Smits-Engelsman, and H. Kingma, Eds. Maastricht, The Netherlands, pp. 144-147, 2001.
- [3] B. Najafi, K. Aminian, F. Loew, Y. Blanc, and P.A. Robert, "Measurement of stand-sit and sit-stand transitions using a miniature gyroscope and its application in fall risk evaluation in the elderly," *IEEE Trans. Biomed. Eng.*, vol. 49, no. 8, pp. 843-851, 2002.

- [4] C.D. Marsden, "Parkinson's disease," *J. Neurol. Neurosurg. Psychiatry*, vol. 57, no. 6, pp. 672-681, 1994.
- [5] J.G. Nutt, R.N. Carter, and W.R. Woodward, "Long-duration response to levodopa," *Neurology*, vol. 45, no. 8, pp. 1613-1616, 1995.
- [6] J.G. Nutt, "Levodopa-induced dyskinesia: Review, observations, and speculations," *Neurology*, vol. 40, no. 2, pp. 340-345, 1990.
- [7] A.E. Lang and A.E. Lozano, "Parkinson's disease, second of two parts," *New Eng. J. Med.*, vol. 339, no. 16, pp. 1130-1143, 1998.
- [8] M.W. Horstink, J.C. Zijlmans, J.W. Pasman, H.J. Berger, and M.A. van 't Hof, "Severity of Parkinson's disease in a risk factor for peak-dose dyskinesia," *J. Neurol. Neurosurg. Psychiatry*, vol. 53, no. 3, pp. 224-226, 1990.
- [9] P. Brown and A. Manson, "Dyskinesia assessment and ambulatory devices," vol. 14, suppl. 1, pp. 67-68, 1999.
- [10] A. Lozano, A. Lang, N. Galvez-Jimenez, J. Miyasaki, J. Duff, W.D. Hutchinson and J.O. Dostrovsky, "Effects of GPI pallidotomy on motor function in Parkinson's disease," *Lancet*, vol. 346, no. 8987, pp. 1383-1387, 1995.
- [11] A.J. Manson, A. Schrag, and A.J. Lees, "Low-dose olanzapine for levodopa induced dyskinesias," *Neurology*, vol. 55, no. 6, pp. 795-799, 2000.
- [12] V. Fraix, P. Pollak, N. Van Blercom, J. Xie, P. Krack, A. Koudsie and A.L. Benabid, "Effect of subthalamic nucleus stimulation on levodopa-induced dyskinesia in Parkinson's disease," *Neurology*, vol. 55, no. 12, pp. 1921-1923, 2000.
- [13] A.T. Willemsen, J.A. van Alste, and H.B. Boom, "Real-time gait assessment utilizing a new way of accelerometry," *J. Biomech.*, vol. 23, no. 8, pp. 859-863, 1990.
- [14] R.C. Wagenaar and R.E. van Emmerik, "Resonant frequencies of arms and legs identify different walking patterns," *J. Biomech.*, vol. 33, no. 7, pp. 853-861, 2000.
- [15] R.E. Mayagoitia, A.V. Nene, and P.H. Veltink, "Accelerometer and rate gyroscope measurement of kinematics: An inexpensive alternative to optical motion analysis systems," *J. Biomech.*, vol. 35, no. 4, pp. 537-542, 2002.
- [16] S. Miyazaki, "Long-term unrestrained measurement of stride length and walking velocity utilizing a piezoelectric gyroscope," *IEEE Trans. Biomed. Eng.*, vol. 44, no. 8, 1997.
- [17] B. Kemp, A.J.M.W. Janssen, and B. van der Kamp, "Body position can be monitored in 3D using miniature accelerometers and earth-magnetic field sensors," *Electroencephalogr. Clin. Neurophysiol.*, vol. 109, no. 6, pp. 484-488, 1998.
- [18] J.B.J. Bussmann, P.J. Reuvenkamp, P.H. Veltink, and W.L.J. Martens, "Validity and reliability of measurements obtained with an 'Activity Monitor' in people with and without a transtibial amputation," *Phys. Ther.*, vol. 78, no. 9, pp. 989-998, 1998.
- [19] K. Kiani, C.J. Snijders, and E.S. Gelsema, "Recognition of daily life motor activity classes using an artificial neural network," *Arch. Phys. Med. Rehab.*, vol. 79, no. 2, pp. 147-154, 1998.
- [20] R.J.W. Dunnewold, J.I. Hoff, H.C.J. van Pelt, P.Q. Fredrikze, E.A.H. Wagemans, and B.J.J. van Hilten, "Ambulatory quantitative assessment of body position, bradykinesia, and hypokinesia in Parkinson's disease," *J. Clin. Neurophysiol.*, vol. 15, no. 3, pp. 235-242, 1998.
- [21] F. Foerster, M. Smeja, and J.U. Fahrenberg, "Detection of posture and motion by accelerometry: A validation study in ambulatory monitoring," *Comput. Human Behavior*, vol. 15, no. 5, pp. 571-583, 1999.
- [22] P.H. Veltink, H.B.J. Bussmann, W. de Vries, W.L.J. Martens, and R.C. van Lummel, "Detection of static and dynamic activities using uniaxial accelerometers," *IEEE Trans. Rehab. Eng.*, vol. 4, no. 4, pp. 375-385, 1996.
- [23] E.J.W. Someren, B.F.M. Vonk, W.A. Thijssen, J.D. Speelman, P.R. Schuurman, M. Mirmiran, and D.F. Swaab, "A new actigraph for long-term registration of the duration and intensity of tremor and movement," *IEEE Trans. Biomed. Eng.*, vol. 45, no. 3, pp. 386-395, 1998.
- [24] J.H.M. Tulen, W.H. Groeneveld, J.H.G.J.K. Romers, S.J.A. de Vries, and B.J.M. van de Wetering, "Ambulatory accelerometry to quantify involuntary movements and tics in the syndrome of Gilles de la Tourette," *Behav. Res. Methods, Instruments, Comp.*, vol. 33, no. 3, pp. 357-363, 2001.
- [25] H.J. Luinge, P.H. Veltink, and C.T.M. Baten, "Estimating orientation with gyroscopes and accelerometers," *Technol. Health Care*, vol. 7, no. 6, pp. 455-459, 1999.
- [26] S. Fahn and R.L. Elton, "The unified Parkinson's disease rating scale," in *Recent Developments in Parkinson's Disease*, vol. 2, S. Fahn, C.D. Marsden, D.B. Calne, and M. Goldstein, Eds. Florham Park, NJ: Macmillan Healthcare Information, 1987, pp. 153-169.
- [27] C.G. Goetz, "Rating scales for dyskinesia in Parkinson's disease," *Mov. Disord.*, vol. 14, suppl. 1, pp. 48-53, 1994.
- [28] J. Hertz, A. Krogh, and R.G. Palmer, *Introduction to the Theory of Neural Computation*. Reading, MA: Addison-Wesley, 1991.
- [29] H.J. Kappen and C.C.A.M. Gielen, *Neural Networks: Best Practice in Europe*. Singapore: World Scientific, 1997.
- [30] N.L.W. Keijsers, M.W.I.M. Horstink, J.J. van Hilten, J.I. Hoff, and C.C.A.M. Gielen, "Detection and assessment of the severity of levodopa-induced dyskinesia in patients with Parkinson's disease by neural networks," *Mov. Disord.*, vol. 15, no. 6, pp. 1104-1111, 2000.
- [31] N.L.W. Keijsers, M.W.I.M. Horstink, and C.C.A.M. Gielen, "Detection and assessment of the severity of levodopa-induced dyskinesia in patients with Parkinson's disease by neural networks," *Mov. Disord.*, vol. 18, no. 1, pp. 70-80, 2003.
- [32] E.J.W. Someren, W.A. van Gool, B.F.M. Vonk, M. Mirmiran, J.D. Speelman, D.A. Bosch, and D.F. Swaab, "Ambulatory monitoring of tremor and other movements before and after thalamotomy: A new quantitative technique," *J. Neurological Sci.*, vol. 117, no. 1-2, pp. 16-23, 1993.
- [33] J. Timmer, M. Lauk, and G. Deuschl, "Quantitative analysis of tremor time series," *Electroencephalogr. Clin. Neurophysiol.*, vol. 101, no. 5, pp. 461-468, Oct. 1996.
- [34] V. Rajaraman, D. Jack, S.V. Adamovich, W. Hening, J. Sage, and H. Poizner, "A novel quantitative method for 3D measurement of Parkinsonian tremor," *Clin. Neurophys.*, vol. 111, no. 2, pp. 338-343, 2000.
- [35] R. Letz and F. Gerr, "Reliability of some tremor measurement outcome variables in field testing situations," *Neurotoxicology*, vol. 21, no. 5, pp. 737-742, 2000.
- [36] J.I. Hoff, E.A. Wagemans, and J.J. van Hilten, "Ambulatory objective assessment of tremor in Parkinson's disease," *Clin. Neuropharmacol.*, vol. 24, no. 5, pp. 280-283, 2001.
- [37] C.D. Marsden, "Slowness of movement in Parkinson's disease," *Mov. Disord.*, vol. 4, suppl. 1, pp. S26-S37, 1989.
- [38] M.J. Majsak, T. Kaminski, A.M. Gentile, and J.R. Flanagan, "The reaching movements of patients with Parkinson's disease under self-determined maximal speed and visually cued conditions," *Brain*, vol. 121, no. 4, pp. 755-766, 1998.
- [39] M.W. Horstink and P.K. Morrish, "Preclinical diagnosis of Parkinson's disease," *Adv. Neurol.*, vol. 80, pp. 327-333, 1999.
- [40] S. Katayama, "Actigraph analysis of diurnal motor fluctuations during dopamine agonist therapy," *Eur. Neurol.*, vol. 46, suppl. 1, pp. 11-17, 2001.
- [41] J.J. van Hilten, G. Hoogland, E.A. van der Velde, J.G. van Dijk, G.A. Kerkhof, and R.A. Roos, "Quantitative assessment of Parkinsonian patients by continuous wrist activity monitoring," *Clin. Neuropharmacol.*, vol. 16, no. 1, pp. 36-45, 1993.
- [42] J.J. van Hilten, J.F. Kabel, H.A. Middelkoop, C.G. Kramer, G.A. Kerkhof, and R.A. Roos, "Assessment of response fluctuations in Parkinson's disease by ambulatory wrist activity monitor," *Acta Neurol. Scand.*, vol. 87, no. 3, pp. 171-177, 1993.
- [43] J.J. van Hilten, E.A. Braat, E.A. vd Velde, H.A. Middelkoop, J.G. van Dijk, G.J. Lighart, and R.A. Roos, "Hypokinesia in Parkinson's disease: Influence of age, disease severity, and disease duration," *Mov. Disord.*, vol. 10, no. 4, pp. 424-432, 1995.
- [44] R.J.W. Dunnewold, C.E. Jacobi, and J.J. van Hilten, "Quantitative assessment of bradykinesia in patients with Parkinson's disease," *J. Neurosci. Meth.*, vol. 74, no. 1, pp. 107-12, 1997.
- [45] P.R. Burkhard, H. Shale, W. Langston, and J.W. Tetrad, "Quantification of dyskinesia in Parkinson's disease: Validation of a novel instrumental method," *Mov. Disord.*, vol. 14, no. 5, pp. 754-763, 1999.
- [46] A.J. Manson, P. Brown, J.D. O'Sullivan, P. Asselman, D. Buckwell, and A.J. Lees, "An ambulatory dyskinesia monitor," *J. Neurol. Neurosurg. Psychiatry*, vol. 68, no. 2, pp. 196-201, 2000.
- [47] J.I. Hoff, A.A. van de Plas, E.A.H. Wagemans, and J.J. van Hilten, "Accelerometric assessment of levodopa-induced dyskinesias in Parkinson's disease," *Mov. Disord.*, vol. 16, no. 1, pp. 58-61, 2001.
- [48] P. Laar, T.M. Heskens, and C.C.A.M. Gielen, "Partial retraining: A new approach to input relevance determination," *Int. J. Neural Syst.*, vol. 9, no. 1, pp. 75-85, 1999.
- [49] M.T. Tuomisto, D.W. Johnston, and T.F.H. Schmidt, "The ambulatory measurement of posture, thigh acceleration, and muscle tension and their relation to heart rate," *Psychophysiol.*, vol. 33, no. 4, pp. 409-415, 1996.
- [50] S. Spieker, V. Strole, A. Sailer, A. Boose, and J. Dichgans, "Validity of long-term electromyography in the quantification of tremor," *Mov. Disord.*, vol. 12, no. 6, pp. 985-991, 1997.
- [51] E. Scholtz, M. Bacher, H.C. Diener, and J. Dichgans, "Twenty-four-hour recordings in the evaluation of the treatment of Parkinson's disease," *J. Neurol.*, vol. 234, no. 8, pp. 475-484, 1988.
- [52] T.H. Haapaniemi, V. Pursiainen, J.T. Korpelainen, H.V. Huikuri, K.A. Sotaniemi, and V.V. Myllyla, "Ambulatory ECG and analysis of heart rate variability in Parkinson's disease," *J. Neurol. Neurosurg. Psychiatry*, vol. 70, no. 3, pp. 305-310, 2001.