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Quantitative Assessment of Levodopa-Induced Dyskinesia Using Automated Motion Sensing Technology*

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Abstract— **The objective was to capture levodopa-induced dyskinesia (LID) in patients with Parkinson's disease (PD) using body-worn motion sensors. Dopaminergic treatment in PD can induce abnormal involuntary movements, including choreatic dyskinesia (brief, rapid, irregular movements). Adjustments in medication to reduce LID often sacrifice control of motor symptoms, and balancing this tradeoff poses a significant challenge for management of advanced PD. Fifteen PD subjects with known LID were recruited and instructed to perform two stationary motor tasks while wearing a compact wireless motion sensor unit positioned on each hand over the course of a levodopa dose cycle. Videos of subjects performing the motor tasks were later scored by expert clinicians to assess global dyskinesia using the modified Abnormal Involuntary Rating Scale (m-AIMS). Kinematic features were extracted from motion data in different frequency bands (1-3Hz and 3-8Hz) to quantify LID severity and to distinguish between LID and PD tremor. Receiver operator characteristic analysis was used to determine thresholds for individual features to detect the presence of LID. A sensitivity of 0.73 and specificity of 1.00 were achieved. A neural network was also trained to output dyskinesia severity on a 0 to 4 scale, similar to the m-AIMS. The model generalized well to new data (coefficient of determination = 0.85 and mean squared error = 0.3). This study demonstrated that hand-worn motion sensors can be used to assess global dyskinesia severity independent of PD tremor over the levodopa dose cycle.**

I. Introduction

Parkinson's disease (PD) affects nearly 2% of individuals over the age of 65 and is characterized by motor manifestations of bradykinesia, rigidity, and tremor. These motor symptoms can be relieved pharmacologically with the dopamine precursor, levodopa. However, levodopa-induced dyskinesia (LID), or abnormal involuntary movements, are a frequent complication of chronic levodopa therapy, occurring in approximately 40% of patients after 5 years of levodopa therapy, and close to 90% of patients treated for greater than 10 years [1]. Adjustments in medication to reduce LID often sacrifice control of motor symptoms, and balancing this tradeoff poses a significant challenge for management of advanced PD.

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Several clinical scales have been developed for monitoring LID, which utilize instruments that rely on patient and caregivers' historical recall, self-assessment home diaries, or clinician ratings. Accurate assessment is uniquely challenging for several reasons. First, the pattern and severity of LID varies substantially over time and during different activities. Thus a single evaluation in a clinical setting may not reflect LID experienced over the course of the day in the context of routine activities. Second, patients often underestimate the severity of the involuntary movements compared to caregiver or clinician ratings, and may even be completely unaware of them. Hence history-based instruments may fail to identify LID seen on exams that are not evident to the patient. Finally, patients may have difficulty distinguishing between LID and tremor. Therefore, a reliable method for detecting and monitoring LID at home would be highly valuable to aid clinicians with optimizing medication regimens. The objective of this study was to investigate kinematic features extracted from motion sensors positioned on the hand to accurately detect and rate levodopa-induced dyskinesia.

II. Methods

A. Technology Overview

Wireless motion sensing technology developed at Great Lakes NeuroTechnologies Inc. (Cleveland, OH) is capable of capturing synchronized three-dimensional kinematic data from small, body-worn sensors (Fig. 1). Each motion sensor unit contains three orthogonal accelerometers for measuring linear acceleration and three orthogonal gyroscopes for measuring angular velocity. All kinematic data are sampled at 128Hz and can either be streamed wirelessly to a computer

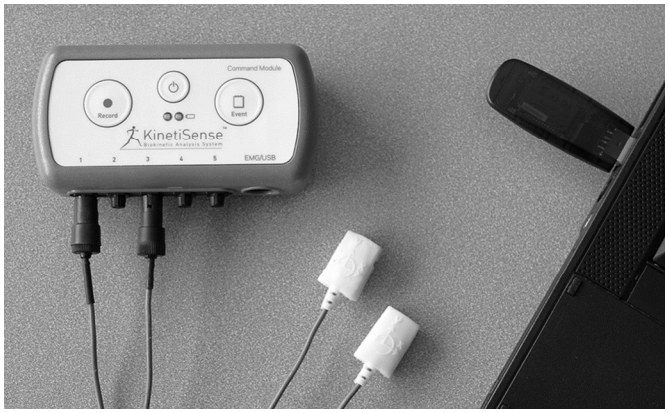

Figure 1. Motion sensing technology developed at Great Lakes NeuroTechnologies Inc. is capable of capturing synchronized three-dimensional kinematic data from small, body-worn sensor units, each which contain three orthogonal accelerometers for measuring linear acceleration and three orthogonal gyroscopes for measuring angular velocity. Data can be streamed wirelessly to a computer or stored to memory for later download and analysis.

in real-time or stored to memory for later download and analysis.

B. Data Collection Protocol

Fifteen patients affected by Parkinson's disease (9M/6F, 58.7±10.7 years old, 9.9±4.5 years since PD diagnosis), with varying severities of LID were recruited from the University of Rochester Medical Center (Rochester, NY). The levodopa equivalence daily dose averaged 1346±799 mg. This work was approved by the institutional review boards of Great Lakes NeuroTechnologies Inc. and the University of Rochester. All subjects gave prior informed consent.

Subject scheduling was closely supervised to ensure subjects were in the OFF-medication state at the start of the data collection. For subjects with milder disease, the study visit was scheduled to coincide with the first dose in the morning; these subjects were instructed to hold all anti-parkinsonian medications after 10PM the night before the study. Subjects with more advanced PD typically cannot tolerate medication withdrawal overnight and therefore were instructed to arrive near the end of a dosing interval, close to the time when their previous dose of medication was expected to wear off. For these subjects, the data recording session began when the clinician determined that the subject's clinical exam was consistent with an OFF-medication state.

Subjects were instrumented with one motion sensor unit on each hand and instructed to perform two stationary motor tasks in the OFF-medication state: 1) Arms Resting: Sit with elbows resting on lap and hands hanging down between legs and 2) Arms Extended: Both arms are extended horizontally forward at shoulder height. Each task was performed for 20 seconds.

Following the completion of these tasks, subjects were instructed to take their usual prescribed oral dose of dopaminergic medications, including levodopa/carbidopa. The two tasks were repeated at 1, 2, and 3 hours after levodopa was taken to capture a time course of medication effect that includes the period when the dose effect is near its typical maximum (usually 30-45 minutes after the medication dose). In total, 240 data sets were collected (15 subjects x 2 tasks x 2 hands x 4 recording sessions over the levodopa cycle). If the subject felt that a full ON-medication state was not achieved within 45 minutes to 1 hour of taking the dose, he or she took an additional partial dose of levodopa/carbidopa at the discretion of the clinician. Subjects could freely decline the extra dose. While the tasks were being performed, kinematic data were recorded by the motion sensor units, and the subject was videotaped for later clinical scoring. Prototype software was developed in LabVIEW (National Instruments) for facilitating data collection. The software allowed the administrator to specify a subject ID and task name as well as to start or stop data collection.

Videos of subjects performing motor tasks were randomized and loaded onto a secure server and scored by two movement disorder neurologists. Clinicians logged into the scoring interface and rated videos by entering 0-4 integer ratings per the modified Abnormal Involuntary Movement Scale (m-AIMS) to evaluate global dyskinesia severity. The raters' scores were averaged to minimize variability. Inter-rater reliability was evaluated by calculating the correlation coefficient (r) between raters.

C. Kinematic Features

Angular velocity recorded from the motion sensor gyroscope was processed into kinematic features used to characterize dyskinesia severity. Previous studies have shown that signal strength in 1-3Hz and 3-8Hz were effective at classifying dyskinesia severity [2, 3]. Therefore, seven different features from motion sensor data and their correlations to clinician scores for dyskinesia were calculated. Features 1-2 ($RMS_{1\text{-}3Hz}$ and $RMS_{3\text{-}8Hz}$) were calculated from the magnitude of the RMS of the three gyroscope channels (ω_x, ω_y, and ω_z) in each frequency band, and feature 3 ($RMS_{1\text{-}3Hz/3\text{-}8Hz}$) was the ratio of those two measures. Features 4-5 ($Power_{1\text{-}3Hz}$ and $Power_{3\text{-}8Hz}$) were calculated from magnitude of the peak power of ω_x, ω_y, and ω_z channels and feature 6 ($Power_{1\text{-}3Hz/3\text{-}8Hz}$) was the ratio of those two measures. Feature 7 ($Freq_{med}$) was calculated from the median frequency such that 50% of the power in the spectrum lies below that frequency. The logarithm of each of the seven features was also calculated.

D. Dyskinesia Assessment Models

Two models were used to assess LID while subjects performed the Arms Resting and Arms Extended tasks. The first model type, binary detection, was designed to output either a 0 (no dyskinesia) or 1 (dyskinesia present). Mean clinician scores were assigned a value of 1 for all scores greater than 0. Receiver operator characteristic (ROC) analyses determined the sensitivity and specificity for the kinematic features extracted from motion data. The optimal threshold value per feature was selected by maximizing the sensitivity and specificity on the ROC curve.

The second model type, incremental severity, was designed to output 0 (no dyskinesia) through 4 (severe dyskinesia) scores, representative of the m-AIMS. A neural network with a multilayer perceptron comprised of an input, hidden, and output layer was trained using a backpropagation algorithm. Input data was repeatedly applied to the network as model outputs were compared to the observed target scores, and an error was computed and fed back into the neural network to adjust weights between each layer and minimize the computed error. Inputs layer variables were selected as the two kinematic features with the best correlation to mean clinician m-AIMS scores. The hidden layer was assigned two units. The output layer was designed to generate 0 to 4 scores, representative of the m-AIMS. Generalization performance of the neural network was done by training the model with 80% of the data and testing it with the remaining 20%. The coefficient of determination (R^2) and mean square error (MSE) were calculated for the training and test data sets.

III. Results

Levodopa-induced dyskinesia were successfully captured and quantified over the medication dose cycle. Raters showed good agreement for rating m-AIMS global dyskinesia severity (r = 0.83, MSE = 0.4). Clinician scores demonstrated that dyskinesia peak severity occurred at different time points and some subjects may not have reached that within the three hour data collection session (Fig. 2A). Based on linear

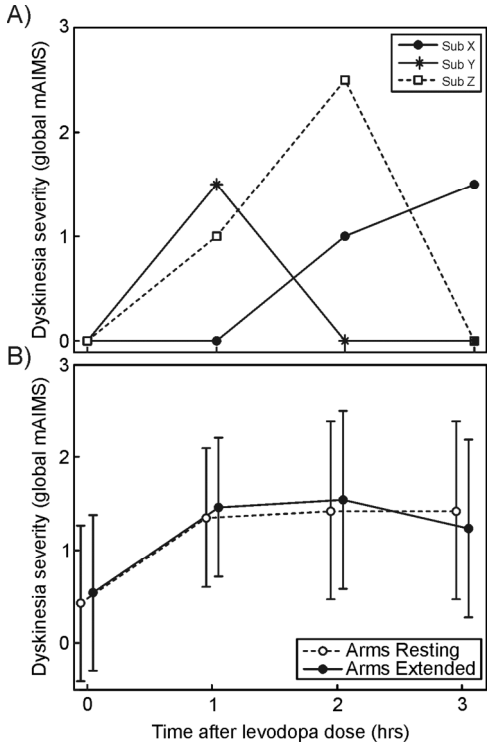

Figure 2. Mean clinician global m-AIMS dyskinesia scores at hours 1, 2, and 3 after levodopa dose. A) Examples from three subjects illustrate the varied dyskinesia response over time. While Subject X and Y manifested the highest dyskinesia severity at hour 1 and 2, respectively, this did not occur until hour 3 for Subject Z. B) Scores averaged across all subjects at each hour time point are plotted for the Arms Resting (dotted line) and Arms Extended (solid line) tasks.

regression analysis, there was no statistically significant relationship between time to peak dose dyskinesia and disease duration, levodopa dose, or dose interval. Although dyskinesia time profiles varied by subject, when clinician scores were averaged across all subjects at each hour interval (Fig. 2B), dyskinesia severity worsened from hour 0 to hour 1 for the Arms Resting and Arms Extended tasks ($p < 0.007$ and $p < 0.008$, respectively).

Kinematic data captured by the hand-worn motion sensor units were not only able to detect LID, but also differentiate them from PD motor symptoms such as tremor. Angular velocity of the three orthogonal gyroscope axes and corresponding power spectra shown in Fig. 3 highlight the power concentrated in the 1-3Hz frequency band typical of LID at hour 2 while the hour 1 and 3 power spectra have a large narrow peak in the 3-8Hz frequency band typical of tremor. Corresponding clinician dyskinesia scores for hours 1, 2, 3 were 0, 2, and 0, respectively; corresponding UPDRS upper extremity tremor scores were 1, 0, and 2. Table I summarizes the correlation coefficients between each kinematic feature and the mean m-AIMS global dyskinesia score. $RMS_{1\text{-}3Hz/3\text{-}8Hz}$ and log $Freq_{med}$ were the most correlated ($r = 0.64$ and $r = -0.70$, respectively).

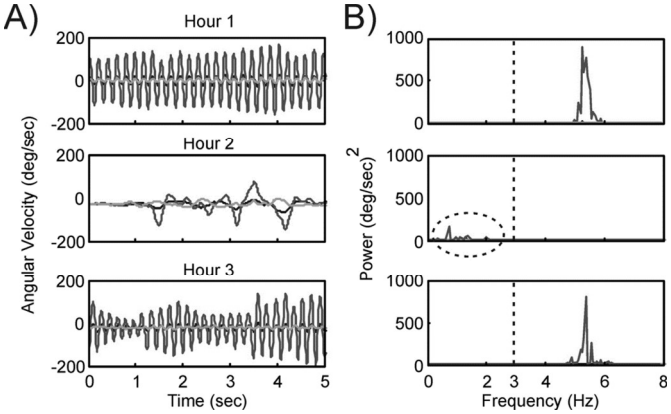

Figure 3. Hand kinematics collected during the Arms Extended task at hours 1, 2, and 3 after levodopa dose intake. A) Angular velocity is plotted over time for ωx, ωy, and ωz. B) Angular velocity power spectrums corresponding to each hour illustrate higher frequency movement typical of tremor greater than 3Hz (dotted line) and lower frequency movement typical of LID less than 3Hz (dotted ellipse).

TABLE I. Correlation coefficients (r) between kinematic features and mean clinician global dyskinesia m-AIMS scores.

Feature	Description	r	r (log)
1	$RMS_{1\text{-}3Hz}$	0.33	0.50
2	$RMS_{3\text{-}8Hz}$	-0.14	0.16
3	$RMS_{1\text{-}3Hz/3\text{-}8Hz}$	0.64	0.61
4	Peak $Power_{1\text{-}3Hz}$	0.32	0.58
5	Peak $Power_{3\text{-}8Hz}$	-0.14	0.10
6	Peak $Power_{1\text{-}3Hz/3\text{-}8Hz}$	0.28	0.47
7	$Freq_{med}$	-0.61	-0.70

Both types of dyskinesia assessment models showed strong agreement with clinician scores. The binary detection model achieved the highest summed sensitivity (0.73) and specificity (1.00) using the kinematic feature, $RMS_{1\text{-}3Hz/RMS3\text{-}8Hz}$ (Table II). Calculating the logarithm of a feature did not change model performance.

The incremental severity neural network model was developed using the two features with the highest correlation to clinician scores, $RMS_{1\text{-}3Hz/3\text{-}8Hz}$ and log median frequency. Model performance between the observed target and model score achieved an R^2 of 0.77 and MSE of 0.4 for the training data set and an R^2 of 0.85 and MSE of 0.3 for the generalization data set (Fig. 4).

IV. Discussion

Study results demonstrated that a motion sensor unit worn on the hand could be used to detect and rate global dyskinesia severity. Agreement between mean clinician m-AIMS scores and the incremental severity model performance was comparable to clinician inter-rater reliability. This suggests that the kinematic features and models developed in this study are a valid method to quantify global dyskinesia severity even in the presence of PD motor symptoms such as

TABLE II. Dyskinesia detection algorithm performance.

Feature	Description	sensitivity	specificity
1	$RMS_{1\text{-}3Hz}$	0.85	0.68
2	$RMS_{3\text{-}8Hz}$	0.29	0.42
3	$RMS_{1\text{-}3Hz/3\text{-}8Hz}$	0.73	1.00
4	Peak $Power_{1\text{-}3Hz}$	0.51	0.76
5	Peak $Power_{3\text{-}8Hz}$	0.91	0.26
6	Peak $Power_{1\text{-}3Hz/3\text{-}8Hz}$	0.73	0.94
7	$Freq_{med}$	0.67	0.92

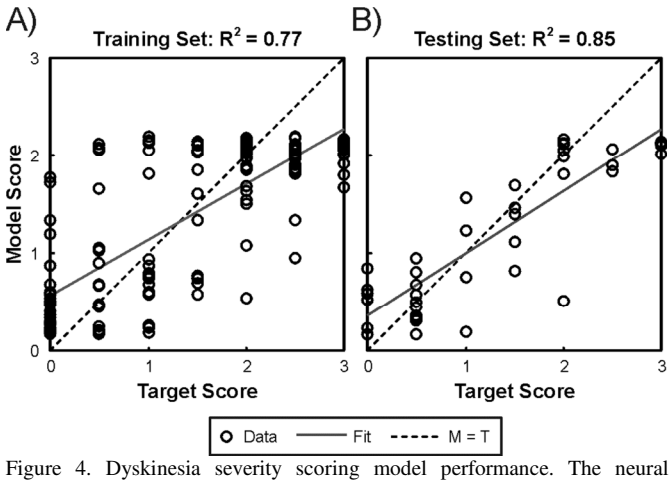

Figure 4. Dyskinesia severity scoring model performance. The neural network was A) trained using 80% of the data set and B) tested to how well the model generalized to new data (remaining 20%). The linear fit between the model and target scores (solid line) and ideal fit (dotted line) are shown.

tremor.

Previous research studies have utilized motion sensors to quantify PD symptoms including tremor [4-7] and therapy-induced side effects including dyskinesia [3, 8, 9]; however, accelerometers measuring linear acceleration were the primary sensor type. In contrast, gyroscopes can record rotation about the sensor and may better reflect the natural limb movement during dyskinesia. Furthermore, these studies correlated sensor data to the clinician score based only on the specific sensor location, not global dyskinesia. Also models were trained using data from the most dyskinetic side [9]. Therefore, multiple sensor units were first required to determine which sensor data was needed to generate the dyskinesia severity score.

This study was conducted in a controlled laboratory setting; however, the real clinical benefit of this technology is adapting it for home use in order to capture LID at multiple time points during the day as a measure of treatment effectiveness. The motion sensor technology used in this study was previous leveraged for PD patients to perform motor tasks to generate clinically-validated tremor [10] and bradykinesia [11, 12] scores in response to treatment throughout the day. The system, referred to as Kinesia HomeView, instructs patients to perform the same discrete

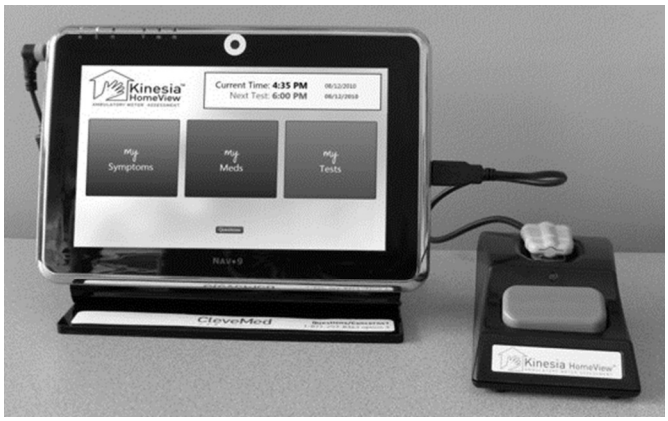

Figure 5. Kinesia HomeView patient station: a touch screen tablet for video-guided motor tasks with a USB docking station for charging the hand-worn motion sensor.

tasks used in this presented study (Arms Resting and Arms Extended) to assess rest and postural tremor, respectively. Therefore, having demonstrated that tremor and LID can be differentiated using the kinematic features and models developed in this study, combining these two motor assessments into a single task will minimize patient burden during home testing.

Although the models presented in the study performed well in detecting and rating dyskinesia severity, this work was done using only stationary motor tasks. In order to translate the scoring models for continuous assessment throughout the day, the scoring models will need to rate dyskinesia severity independent of voluntary movements associated with activities of daily living. Therefore, additional sensor locations (e.g. lower extremity and torso) and kinematic features will need to be investigated. This may provide clinicians with a more complete measure of PD treatment effectiveness to balance PD motor symptom improvement and LID severity and occurrence.

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