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Continuous in-home monitoring of essential tremor

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ABSTRACT

Background: Essential tremor (ET) is typically measured in the clinic with subjective tremor rating scales which require the presence of a clinician for scoring and are not appropriate for measuring severity throughout the day. Motion sensors can accurately rate tremor severity during a set of predefined tasks in a laboratory.

Methods: We evaluated the ability of motion sensors to quantify tremor during unconstrained activities at home. 20 ET subjects wore a wireless sensor continuously for up to 10 h daily on two days and completed hourly standardized tremor assessments involving pre-defined tasks. Mathematical models were used to predict tremor rating scores from the sensor data.

Results: At home tremor scores from hourly standardized assessments correlated with at home tremor scores estimated during unconstrained activities immediately following the standardized assessments. The hourly standardized assessments did not significantly fluctuate throughout the day, while fluctuations in the continuous assessments tended to follow changes in voluntary activity level. Both types of tremor ratings (standardized and continuous) showed high day-to-day test-retest reliability with intraclass correlation coefficients ranging from 0.67 to 0.90 for continuous ratings and 0.77 to 0.95 for standardized ratings.

Conclusions: Results demonstrate the feasibility of continuous monitoring of tremor severity at home, which should provide clinicians with a measure of the temporal pattern of tremor in the context of daily life and serve as a useful tool for the evaluation of novel anti-tremor medications in clinical trials.

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1. Introduction

Essential tremor (ET), characterized primarily by postural and kinetic tremor of the limbs, has a negative impact on quality of life, as it affects activities of daily living (ADL) and has psychological effects associated with tremor exacerbation in public [1,2]. Typical activities prominently affected by ET are handwriting, eating, dressing and self-care. In moderate to severe cases of ET, pharmaceutical interventions or deep brain stimulation are often needed to optimize quality of life. In order to monitor effects of treatment, it is important to accurately quantify motor function and disability associated with ET.

Currently, rating scales such as the Tremor Research Group Essential Tremor Rating Assessment Scale (TETRAS) [3], Washington Heights-Inwood Genetic Study of Essential Tremor (WHIGET) tremor rating scale (wTRS) [4], and Fahn-Tolosa-Marin tremor rating scale [5] are used to evaluate ET during a clinical examination. Each rates tremor on a subjective, qualitative 0–4 scale. While these rating scales are useful tools for clinicians treating patients with ET and are often used as an outcome measure for clinical drug trials, they require the presence of a clinician for scoring, are subject to clinical judgment and bias, and cannot be used practically for monitoring fluctuations in tremor throughout the day, especially in a patient's home environment. Even if these ratings provide an accurate momentary assessment, they are only a snapshot of tremor during the clinical visit. Indeed, quantitative assessments every 2 h for 6 h have found a maximal 23% absolute variation in tremor amplitude during this period [6]. This fluctuation in amplitude has to be considered when designing trials to assess therapeutic interventions. There is, therefore, a need to provide quantitative data on ET patients in their home environment during routine activities. Given current limitations in the

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understanding of how most ET therapies affect tremor throughout the day, such a system could allow clinicians to better discriminate which medications and doses are most effective for patients in their natural environment. The opportunity for home monitoring may also expand care to patients who are reluctant or unable to travel for research or numerous clinical visits for evaluation if the patients do not live near a movement disorders center or have significant mobility impairments.

Previously, accelerometers, gyroscopes, and EMG have been used to obtain quantitative measurements of tremor in both Parkinson's disease (PD) [7–10] and ET [11,12]. The motion sensing system used in the present study previously quantified PD tremor during standardized clinical exams, with high correlations to the Unified Parkinson's Disease Rating Scale [7,13]. More recently we demonstrated that this sensor system could be used to quantify tremor in patients with ET during simulated ADL performed in a laboratory setting [11]. Algorithms were developed and validated for using motion data to rate tremor severity during standardized motors tasks and ADL. The goals of this study were to evaluate the system during the performance of unconstrained activities in the home environment and to study the associations between unconstrained tremor recordings and those obtained during standardized tasks that are similar to those used in the office setting.

2. Methods

Twenty adults (11 male, 9 female; age 48–85 years; disease duration, 2–60 years) with ET were recruited. Subject medication use for treatment of ET-related symptoms was recorded, but not altered during participation in this study. Five subjects were not on ET-related medication. The remaining 15 subjects were on one or more drugs for management of their symptoms, with propranolol (11/15) and primidone (5/15) being the most common. All clinical testing was completed at Baylor College of Medicine and Rush University Medical Center under the purview of their respective institutional review boards and in accordance with the Declaration of Helsinki [14]. All subjects provided informed consent prior to their participation in the study.

Each subject underwent an initial training session during which the components and operation of the system were described. The subjects were then sent home with a modified motion sensor-based home monitoring system (Kinesia HomeView™, Great Lakes NeuroTechnologies, Cleveland, OH) and were monitored for two days. The system included a wireless motion sensor unit (Supplementary Fig. 1) and a tablet PC. At the start of data collection each day, subjects wore the wireless motion sensor unit on the base of the index finger of his/her more affected hand. The tablet PC then guided the subject through a standardized tremor assessment consisting of three pre-defined tasks to evaluate rest, postural, and kinetic tremor for 15 s each. These tasks included having the subjects place their hands in their laps (rest tremor), hold their arms extended horizontally (postural tremor), and repeatedly reach out and touch their noses (kinetic tremor). After completion of this assessment, subjects went about their normal activities while continuing to wear the sensor. At 1 h intervals, the subjects returned to the tablet PC and were prompted to repeat the standardized tremor assessment. Subjects were instructed to repeat this hourly cycle of a standardized tremor assessment followed by unconstrained activities for 10 h each of the two days. To minimize the burden placed on subjects by the protocol and interference with their normal routines, the start time of home tremor evaluation was not regulated.

Kinematic data recorded at each of the hourly standardized assessments were processed into 0-4 scores corresponding to the amplitude severity of rest, postural, and kinetic tremor using previously validated algorithms. These algorithms have been shown to output scores highly correlated with clinician UPDRS and wTRS ratings [7,11,13]. A repeated-measures ANOVA with a Greenhouse-Geisser correction for sphericity was used to determine if tremor severity, as quantified by the tremor scores from the standardized assessments, fluctuated across time. An additional multiple regression model was developed to rate tremor severity during unconstrained activities on a continuous basis (i.e., every 12 s), generating a "continuous" waveform throughout the day. The continuous waveform was low pass filtered with a 5-min sliding median filter, with 1 min of overlap between consecutive windows. Further details of the algorithm development and validation are available in the online Supplementary Material.

The test re-test reliability of each assessment type was calculated as the intraclass correlation (ICC) between tremor ratings from days 1 and 2. For the hourly assessments, the average severity scores were taken across time for rest, postural, and kinetic tremor, respectively, for each day. These averages were then used to calculate the day-to-day ICCs. For continuous ratings, the percentage of time during movement in each tremor category (i.e., 0, 1, 2, 3, and 4) was calculated for each day and subsequently used to calculate the ICCs between days 1 and 2.

Table 1
Summary tremor statistics for hourly standardized tremor assessments. Average and standard deviation are given for the intraday mean and range of the severity scores. Day-to-day ICCs are given as a measure of test-retest reliability.

	Intraday mean	Intraday range	ICC
Rest tremor	0.85 ± 0.52	0.94 ± 0.41	0.77
Postural tremor	0.96 ± 0.59	0.80 ± 0.50	0.91
Kinetic tremor	1.97 ± 0.47	0.50 ± 0.20	0.95

3. Results

3.1. Compliance

The twenty subjects were instructed to wear the sensors for 10 h on each of two separate days (40 subject-days total); however, the actual duration of monitoring varied across subjects. Consistent with our previous findings in patients with Parkinson's disease [15], the ET subjects in this study accurately and consistently performed the standardized motor tasks in the home. The motion sensor was worn for multiple hours in 39 of the 40 subject-days evaluated. Eighty-percent of subject-days (32/40) included the subject wearing the motion sensor for at least 8 h. Only five out of the 40 subject-days were comprised of six or fewer hours of wear.

3.2. Hourly standardized tremor assessments

Table 1 summarizes the intraday mean and intraday range across the 39 subject-days in this study and the ICCs between day 1 and 2 for each type of tremor. Kinetic tremor was, on average, more severe than rest or postural tremor, consistent with the typical phenomenology of ET. No statistically significant differences (repeated measures ANOVA, $p > 0.13$) were detected across time for rest, postural, or kinetic tremor, indicating that these subjects did not exhibit significant fluctuations throughout the day.

3.3. Continuous tremor ratings

An example of this continuous waveform for one subject, along with the scores for kinetic, postural, and rest tremor generated during the hourly standardized tremor assessments is shown in Fig. 1. As expected given the typical appearance of ET, the tremor ratings tended to increase during voluntary motions (indicated by the tick marks at the bottom of the panel). The standardized tremor assessments were immediately followed by voluntary unconstrained activity. As a result, most segments of the continuous waveform have an initial value that is approximately equal to the preceding kinetic tremor score (square marker). When voluntary motion was not detected immediately following the standardized assessment (e.g., at the assessment just before 17:00), the initial value is closer to the rest tremor score (circle marker). The accuracy of the continuous tremor waveforms was assessed by comparing the scores predicted during voluntary motion in the 5 min interval immediately following the standardized assessments to the standardized kinetic tremor scores. The continuous scores and standardized scores were generally consistent, with a strong correlation and low error (see Supplementary Results).

For clinical management of symptoms and evaluation of pharmaceutical agents in clinical trials, a graphical representation of the percentage of time at different levels of tremor severity (Fig. 2), generated by assigning the continuous scores into appropriate tremor categories, is a potentially useful tool. Since tremor

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