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Clinical Validation of a Precision Electromagnetic Tremor Measurement System in Participants Receiving Deep Brain Stimulation for Essential Tremor

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Abstract

Tremor is characterized commonly through subjective clinical rating scales. Accelerometer-based techniques for objective tremor measurement have been developed in the past, yet these measures are usually presented as an unintuitive dimensionless index without measurement units. Here we have developed a tool (TREMBAL) to provide quantifiable and objective measures of tremor severity using electromagnetic motion tracking. We aimed to compare TREMBAL's objective measures with clinical tremor ratings and determine the test-retest reliability of our technique. Eight participants with ET receiving deep brain stimulation (DBS) therapy were consented. Tremor was simultaneously recorded using TREMBAL and video during DBS adjustment. After each adjustment, participants performed a hands-outstretched task (for postural tremor) and a finger-nose task (for kinetic tremor). Video recordings were de-identified, randomized, and shown to a panel of movement disorder specialists to obtain their ratings. Regression analysis and Pearson's correlations were used to determine agreement between datasets. Subsets of the trial were repeated to assess test-retest reliability. Tremor amplitude and velocity measures were in close agreement with mean clinical ratings ($r > 0.90$) for both postural and kinetic tremors. Test-retest reliability for both translational and rotational components of tremor showed intra-class correlations > 0.80. TREMBAL assessments showed that tremor gradually improved with increasing DBS therapy – this was also supported by clinical observation. TREMBAL measurements are a sensitive, objective and reliable assessment of tremor severity. This tool may have application in clinical trials and in aiding automated optimization of deep brain stimulation.

Introduction

Tremor is a common symptom that can arise from a diverse range of disorders including Parkinson's disease, dystonia and Essential tremor (ET). Tremor can progress to affect function and quality of life, requiring treatment by medication and deep brain stimulation (DBS). The development of novel treatment strategies calls for a method to objectively and sensitively assess tremor severity in real-time to allow feedback control. For example, with current generation thalamic DBS, there are a large number of parameter permutations that remain unexplored by clinicians, yet these may render improved outcomes. This process of titration has potential to be automated given precise and reliable information regarding tremor severity. However, current tremor severity measurement tools either require offline analysis or provide results which are unintuitive. Thus we have developed the Tremor Biomechanics Analysis Laboratory (TREMBAL) to report, in real-time, tremulous limb displacement in millimeter units while simultaneously suppressing artifact from volitional movement.

DBS of structures, such as the posterior subthalamic area (PSA) and the ventral intermediate nucleus (Vim), has provided significant, sustained relief of symptoms for those with ET (Blomstedt et al., 2010; Chopra et al., 2013). The programmable nature of DBS, where stimulation parameters, such as amplitude, rate, and pulse duration, can be adjusted, allows mechanisms of functional tremor pathophysiology to be investigated. Conversely, inordinate numbers of parameter permutations can lead to time-consuming optimizations within the clinic when attempting to minimize tremor severity whilst preventing stimulation-induced side-effects. Although guidelines are available for programming DBS (Montgomery, 2010; Volkmann et al., 2002), this task is often based on trial-and-error. A precise measurement of tremor is required to assist scientific investigation and improve clinical outcomes via automated DBS programming.

Several devices exist for objective tremor assessment (Engin et al., 2007; Joundi et al., 2011; Rigas et al., 2012; Wile et al., 2014), with some designed for continuous in-home monitoring through wearable technology (Giuffrida et al., 2009). These devices utilize accelerometers and apply processing methods such as Hidden Markov Models (Rigas et al., 2012) and Neural Networks (Engin et al., 2007) to classify tremor and output a rating score based on severity. While these methods provide results comparable to clinical ratings, they also obfuscate the relation of the measurement to the measurand, making it difficult to interpret. Spyers-Ashby *et al.* (Spyers-Ashby et al., 1999) and O'Suilleabhain and Dewey (O'Suilleabhain and Dewey, 2001) have investigated the possibility of utilizing electromagnetic motion tracking to determine tremor severity. Both groups found these devices had adequate spatiotemporal resolution and accuracy to measure tremor. Also, the raw unfiltered measurements indicated displacement in millimeters, which could be easily interpreted. O'Suilleabhain and Dewy found their measurements correlated strongly (r = 0.88) with clinical estimates, and had sufficient test-retest reliability as well as specificity and sensitivity for clinical assessment of tremor. However, this system relied on offline data analysis using computational software scripts making it less accessible to clinicians.

Using the latest commercially-available electromagnetic motion tracker, TREMBAL reports simultaneous real-time measurements of tremor from four sensors. It guides clinicians through assessments and automates the process of collecting data. Real-time measurement of tremor severity is graphically presented on the screen, and other pertinent data such as patient information, medications, and assessment conditions can be entered. All data are encrypted and stored in a

password-secured database which can be sorted and exported to comma-separated value (CSV) files for statistical analysis. The tremor data series is automatically filtered to remove influence of volitional motion. The primary objective of this study is to validate tremor metrics generated in TREMBAL against clinical observation of ET patients receiving DBS.

Methods

Subjects

Eight participants (mean age 64.25±12.51 years; 6 males) gave written consent and were enrolled in the study after receiving approval from the St. Vincent's Hospital Human Research Ethics Committee. The participants were diagnosed with ET and had disease durations greater than ten years. They were receiving PSA or Vim DBS therapy. Tremor medication was withheld overnight prior to assessment.

Experiments

Two motion tracking sensors were placed on the proximal phalanges of participants' middle fingers. Participants were tested under six conditions: DBS amplitude was systematically reduced from 100% (clinically-optimized level) to 75%, 50%, and 0% (DBS off); we then repeated the 100% and 50% conditions to establish test-retest reliability. A minimum of 12 minutes rest was allocated following changes to DBS to account for wash-in/out effects (Perera et al., 2015c). At each condition, patients sat comfortably and performed the following tasks: both hands outstretched for ten seconds (postural tremor); left hand finger-nose exercise for ten seconds with right hand resting on lap (kinetic tremor); and right hand finger-nose exercise for ten seconds with left hand resting on lap. Each task was video recorded using a tripod-mounted GoPro Hero3 camera (GoPro Inc., San Mateo, California) with the following parameters: narrow field-of-view, 120 frames/s, and 1280x720 pixel resolution. Video was recorded at a high frame rate to avoid aliasing, and a narrow field-of-view was used to minimize fish-eye distortion. These recordings were later anonymized (by cropping or obscuring any identifiable participant features) and randomized. A panel of four movement disorder experts rated the video recordings using the Bain Tremor Rating Scale (Bain et al., 1993). Only the self-reported worst-affected side was rated for the finger-nose exercise.

Data Acquisition

Raw displacement data were acquired from a 3D Guidance trakSTAR electromagnetic tracker (figure 1) with a wide-range transmitter and four type-800 sensors (Ascension Technology Corp., Shelburne, Vermont). The transmitter energizes three orthogonal electrical coils sequentially to emit electromagnetic pulses into the assessment area. Fluctuations in these pulses are detected by the sensor using integrated miniature inductive coils. The processing hardware can transform the relative strength of each electromagnetic pulse into three-dimensional distances (x, y and z in Cartesian space) with respect to the transmitter, which acts as the origin. Given the orthogonal topology of the coils, sensor orientations (azimuth, elevation and roll) can also be calculated. This allows translational and rotational components of tremor to be recorded simultaneously. The tremor data series is automatically band-pass filtered between 3 and 14 Hz to remove influence of purposeful motion. The filter was designed not to attenuate the pass-band, yet retain a sharp roll-off to the stop-band and is described in more detail in a separate paper (Perera et al., 2015b).

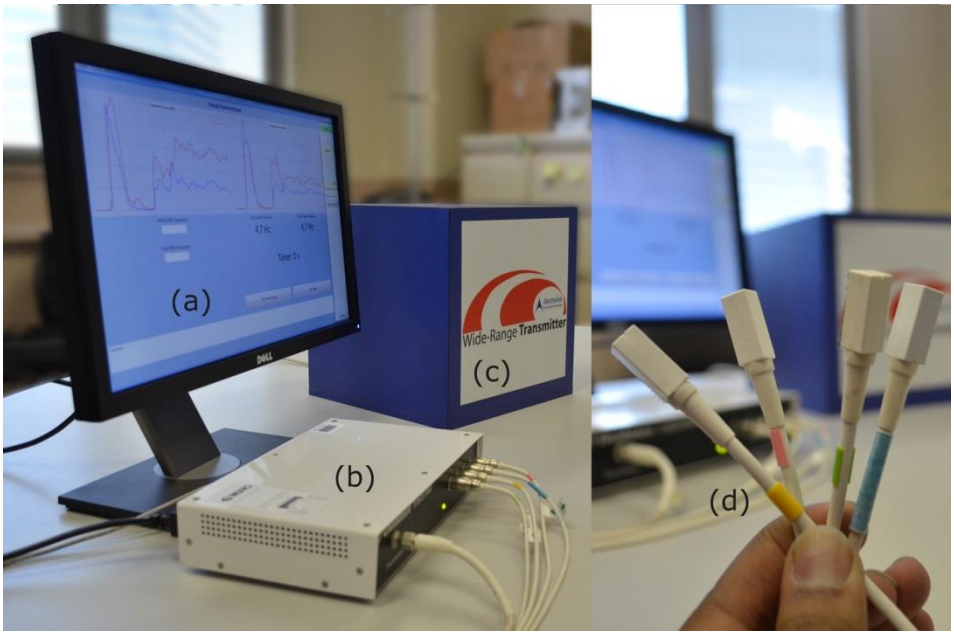

Figure 1. The TREMBAL software (a) is designed to record and report objective measures of tremor severity using an electromagnetic motion tracker. The tracking system encompasses a processing unit (b) which calculates three-dimensional positions of up to four sensors (d) with respect to an electromagnetic transmitter (c).

Data were sampled at 250 Hz and all filters built-in to the electromagnetic tracker were disabled. We bench tested this motion tracking system previously (Perera et al., 2015b) using a test-rig to emulate tremor (Perera et al., 2015a) and found accuracy to be $\pm$0.40 mm and $\pm$0.05° with sensitivity of 0.45 mm and 0.02° for translational and rotational tremor components respectively. Furthermore, we found the system was resilient to interference from large metallic objects and electronic devices. We did however attempt to keep the assessment area free from sources of interference and asked participants to remove any large jewelry and mobile phones during this study.

Statistical Analysis

Recorded TREMBAL tremor metrics included amplitude, velocity, frequency, and Power Spectral Density (PSD) at the tremor frequency for both translational and angular components of motion. Regression analyses between mean tremor ratings and TREMBAL metrics were performed to validate our measurements. Pearson's correlations were also determined to confirm any associations. Test-retest reliability of TREMBAL was assessed using intra-class correlation coefficients (ICCs).

Results

Participants and DBS Parameters

Eight participants with ET were assessed in this study. All but one participant had bilateral DBS with a Medtronic Activa neurostimulator (Medtronic, Dublin, Ireland). Participant 3 had a St Jude Brio neurostimulator (St Jude Medical, Minnesota, USA). Participants received standard DBS therapy (table 1) and were assessed at least six months after DBS surgery. DBS parameters were optimized by an experienced movement disorders expert at least one week prior to study enrollment.

Demographics and Clinically Optimal DBS Settings

	Age		DBS	Worst	Amplitude		Pulse Width (μs)		Frequency (Hz)	
ID	(years)	Sex	Target	Limb	Left	Right	Left	Right	Left	Right
1	39.42	M	Vim	Left	5	5	90	90	140	140
2	76.30	F	PSA	Right	1.6	2.1	90	90	150	150
3	74.93	M	PSA	Left	3	3	62	62	130	130
4	67.74	M	PSA	Right	2.8	1.6	90	90	130	130
5	75.70	M	PSA	Right	3	2.5	60	90	180	180
6	56.41	M	PSA	Right	3	2.4	90	90	150	150
7	60.62	M	PSA	Left	2	1.6	60	60	130	130
8	62.90	F	Vim	Left	5.2	3.8	90	90	130	130

Table 1. Participant demographics and clinically optimized deep brain stimulation (DBS) settings. DBS parameters localized to brain hemisphere and amplitude given in units of Volts, except participant 3 where milli-Ampere (mA) units were used. M = male; F = female; Vim = ventral intermediate nucleus; PSA = posterior subthalamic area.

Clinical Validation

In total, 64 clinical ratings were averaged from four movement disorder specialists proficient in the use of the Bain Tremor Rating Scale (BTRS). This dataset included 32 samples of postural tremor and 32 samples of kinetic tremor. Inter-rater agreement amongst the four clinicians was strong with ICCs of 0.86 and 0.90 for postural and kinetic tremors respectively. TREMBAL metrics were square-root transformed (table 2) to match the distribution of clinical ratings where increased variance was observed with large tremors. Results were deemed significant if $p < 0.0063$ (Bonferroni correction for multiple comparisons).

Regression Transform Goodness-of-Fit Statistics

	Slope	$\boldsymbol{R^2}$	**SEM**	$\boldsymbol{r}$	$\boldsymbol{p}$
None	1.1	0.76	0.40	0.87	< 0.001
Logarithmic	0.43	0.72	0.17	0.85	< 0.001
Exponential	1456	0.44	724.7	0.66	< 0.001
Square-Root	0.31	0.80	0.11	0.90	< 0.001

Table 2. Comparison of different transforms applied to measured data to match the distribution of clinical ratings. The coefficient of determination (R^2) and standard error of the mean (SEM) indicate the goodness-of-fit of the regression model between clinical ratings and the tremor amplitudes measured during the hands-outstretched task. Pearson's correlations indicate the strength (r) and statistical significance (p) of the association.

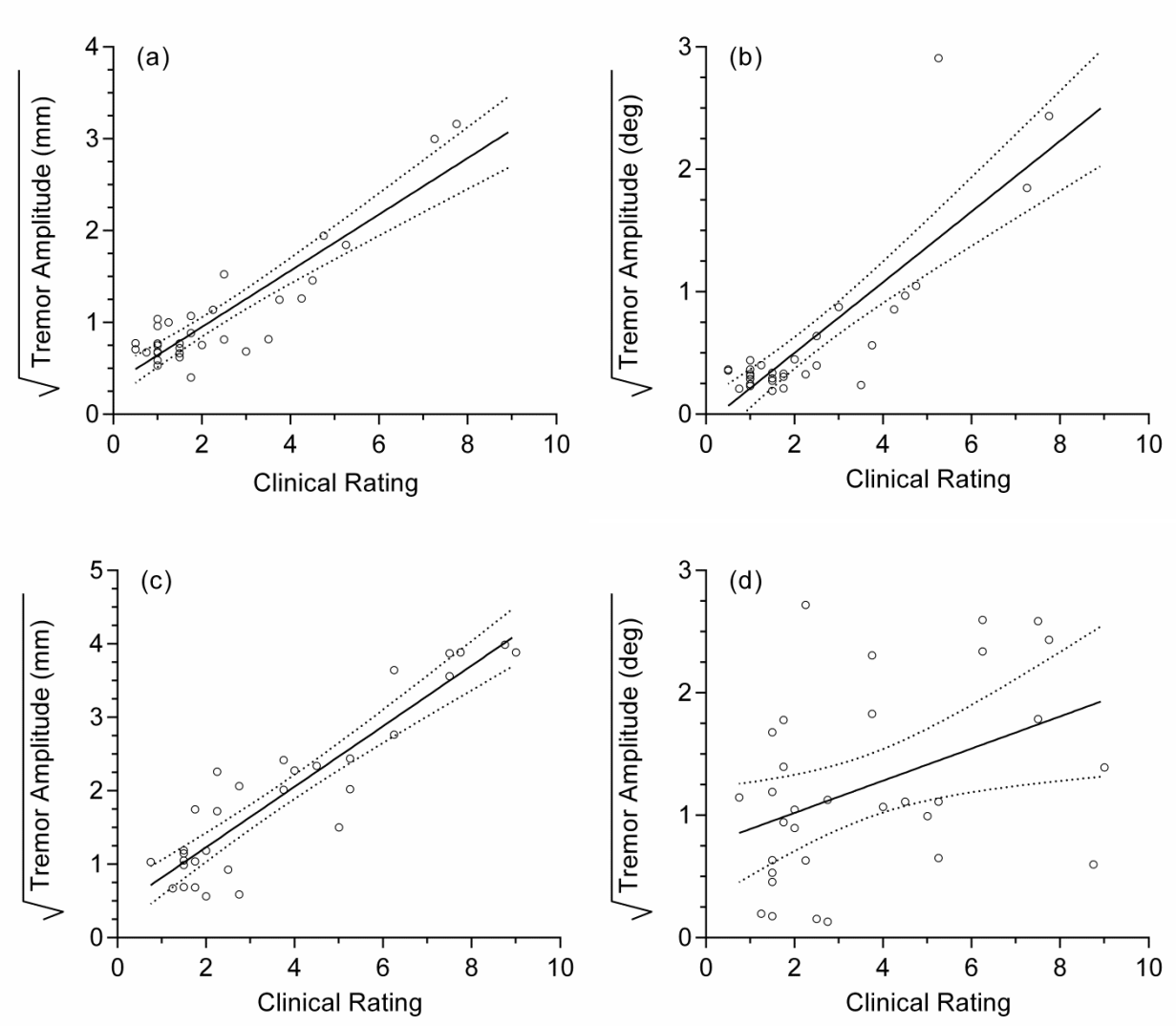

Figure 2. Congruence between clinical tremor ratings and square-root transformed tremor amplitude as measured by TREMBAL for postural tremor (a, b) and kinetic tremor (c, d). Subplots (a) and (c) show the translational component of tremor; (b) and (d) show rotation. The regression line is displayed between dotted lines indicating upper and lower 95% confidence bounds. Horizontal axis shows the mean Bain Tremor Rating score from four movement disorder experts.

Postural Tremor Regression Goodness-of-Fit Statistics

		Slope	R^2	SEM	r	p
Translation	**Amplitude**	0.31	0.80	0.11	0.90	< 0.001
	Velocity	1.38	0.85	0.50	0.92	< 0.001
	Frequency	0.07	0.50	0.03	0.71	< 0.001
	PSD	0.27	0.77	0.10	0.88	< 0.001
Rotation	**Amplitude**	0.29	0.71	0.11	0.84	< 0.001
	Velocity	1.33	0.69	0.53	0.83	< 0.001
	Frequency	0.06	0.33	0.03	0.57	< 0.001
	PSD	0.06	0.49	0.03	0.70	< 0.001

Table 3. The coefficient of determination (R^2) and standard error of the mean (SEM) indicate the goodness-of-fit of the regression model between clinical ratings and objective measures of postural tremor severity during the hands-outstretched task. Pearson's correlations indicate the strength (r) and statistical significance (p) of the association. PSD = Power Spectral Density.

Kinetic Tremor Regression Goodness-of-Fit Statistics

		Slope	R^2	SEM	r	p
Translation	**Amplitude**	0.41	0.84	0.20	0.92	< 0.001
	Velocity	1.63	0.85	0.77	0.92	< 0.001
	Frequency	0.03	0.17	0.03	0.41	0.019
	PSD	0.29	0.81	0.14	0.90	< 0.001
Rotation	**Amplitude**	0.13	0.18	0.14	0.42	0.017
	Velocity	0.55	0.19	0.55	0.43	0.013
	Frequency	0.03	0.13	0.04	0.36	0.040
	PSD	0.02	0.14	0.03	0.37	0.035

Table 4. The coefficient of determination (R^2) and standard error of the mean (SEM) indicate the goodness-of-fit of the regression model between clinical ratings and objective measures of kinetic tremor severity during the finger-nose task. Pearson's correlations indicate the strength (r) and statistical significance (p) of the association. PSD = Power Spectral Density.

Clinical ratings and translational amplitudes (figure 2a & c) showed strong agreement for both postural (table 3) and kinetic tremors (table 4). Yet this agreement was diminished when considering rotational components of tremor (figure 2b & d) with none of the metrics reaching statistical significance for kinetic tremors. Overall, translational amplitude and velocity measures had the greatest agreement with clinical ratings ($r \geq 0.90$, $p < 0.001$) for both types of tremor. Translational PSD was also in good agreement, although measurements of tremor frequency had little congruence with clinical observation.

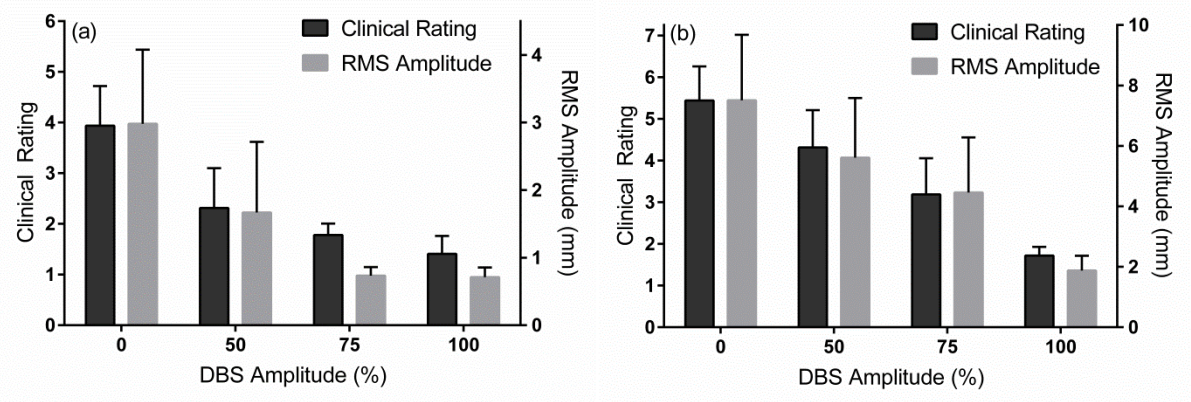

Figure 3. Mean postural (a) and kinetic (b) tremors as measured by clinical rating and TREMBAL shows gradual improvement with increasing deep brain stimulation (DBS) therapy relative to clinically set optimum level (100%). Error bars indicate the standard error of the mean.

Summary of Recorded Tremor Parameters

	DBS Amplitude (%)	Clinical Rating	RMS Amplitude (mm)	Angular Amplitude (deg)	Velocity (mm/s)	Frequency (Hz)	PSD
Postural Tremor	0	3.9±0.8	3.0±1.1	2.2±1.1	53.9±22.3	4.3±0.3	1.1±0.7
	50	2.3±0.8	1.7±1.0	0.6±0.4	24.4±16.5	3.4±0.3	0.7±0.7
	75	1.8±0.2	0.7±0.1	0.2±0.1	8.9±1.2	3.0±0.1*	0.1±0.02
	100	1.4±0.4	0.7±0.1	0.1±0.02	9.2±2.0	3.0±0.1*	0.1±0.02
Kinetic Tremor	0	5.4±0.8	7.5±2.2	3.5±1.0	107.0±34.9	4.2±0.3	2.4±1.0
	50	4.3±0.9	5.6±2.0	2.0±0.8	84.8±31.5	4.0±0.2	1.8±0.9
	75	3.2±0.9	4.5±1.8	1.8±0.9	59.4±25.9	3.6±0.2	0.8±0.5
	100	1.7±0.2	1.9±0.5	1.2±0.4	20.5±4.2	3.2±0.1*	0.3±0.1

Table 5. Tremor severity measurements show a decrease as Deep Brain Stimulation (DBS) amplitude is increased from off (0%) to optimal level (100%). Figures are represented as mean ± standard error from eight participants. RMS = Root Mean Square; PSD = Power Spectral Density. Asterisk (*) denotes frequency could not be measured in one participant.

DBS amplitude effects tremor in a predictable manner (figure 3) where a gradual improvement in tremor is observed with increasing therapy. As before, TREMBAL measurements track well with clinical observation for both postural and kinetic tremors. Tremor frequency was also modified by DBS intervention (table 5), however we were unable to measure frequency in one individual as tremor was almost completely suppressed by DBS.

Test-Retest Reliability

Data from two participants were excluded from this dataset; one with dystonic symptoms and another who did not complete the repeated measurements. A total of 28 measurement pairs were analyzed. Translational ICCs for amplitude and velocity were greater than 0.80, and frequency measurements reached 0.70. Rotational measurements were also comparable with translational measurements, having ICCs greater than 0.90. PSD did not show strong test-retest reliability (ICCs < 0.20).

Discussion

Here we present a new utility, TREMBAL, to provide accessible real-time tremor severity measures using a precise electromagnetic motion tracking system. Using a cohort of eight ET participants receiving DBS therapy, we validated TREMBAL via comparison with a clinical rating scale.

There was strong agreement between clinical observation and TREMBAL measurements of translational tremor amplitude and velocity for both postural and kinetic tremors. Tremor frequency, PSD, and rotational components of tremor did not show such an agreement. We believe clinical assessment of tremor relies primarily on the observation of amplitude and speed, therefore this outcome was somewhat expected.

Although rotational tremor components did not correspond well with clinical ratings, we postulate these measurements may be useful in further studies, particularly when attempting to diagnose tremor phenotypes; ET often presents as wrist extension and flexion, whereas Parkinsonian tremor commonly includes a wrist rotation (Benito-León and Louis, 2006).

DBS amplitude affects tremor in a predictable manner: as the amplitude is increased, there is a subsequent improvement in tremor. This effect was evident in both clinical assessments and TREMBAL measures. Given the congruence between these datasets, it is possible to hypothesize that TREMBAL could be utilized as part of an algorithm to automate DBS parameter optimization. However, this study was not designed to elucidate this notion and therefore further work is required to determine the effects of other parameters, such as stimulation pulse width and frequency. This preliminary result is encouraging, but several limitations require attention. Mainly, the study conditions were not randomized and a time-course bias may have confounded the findings. Also, we did not test DBS amplitudes above optimal settings, into the side-effect region. Some have found that tremor reaches steady-state when stimulating beyond the optimal level and invokes side-effects such as dysarthria (Kuncel et al., 2006; O'Suilleabhain et al., 2003). In order to implement a fully automated system, an objective measure of side effect severity must also be developed.

The agreement between TREMBAL measures and clinical observations is a testament to the highly-trained and experienced clinicians that rated the video recordings produced during this study. While it may be argued that clinical observation is just as accurate as an objective measurement, we must highlight that the procedure to obtain these ratings was cumbersome. To appropriately rate tremor in a clinical trial, one must first video record all trials, de-identify and randomize the videos, then have these rated by a panel of independent experts. An objective measure, such as TREMBAL, provides these measures in real-time and the software can be operated by a novice with minimal training.

In our repeated trials, almost all TREMBAL measures showed good (> 80%) test-retest reliability. Some repeated measures were collected up to one hour apart, and due to the variable nature of tremor it is difficult to compare these. This limitation can be mitigated by also obtaining repeated clinical ratings for comparison.

PSD failed to be a reliable measure of tremor in addition to disagreement with clinical ratings. TREMBAL calculates the PSD at the peak tremor frequency, which becomes undefined when there is no tremor. In one participant, we observed near complete suppression of tremor which resulted in a diminishing signal to noise ratio. The spectral peaks were dominated by noise peaks and

thus made frequency-domain measures prone to error. In future we hope to develop more robust frequency-domain measures of tremor classification to overcome this problem.

We found that a square-root transform fitted the data best, although a logarithmic relationship has been noted in the past (Elble, 2006). There are several noteworthy differences in study methodologies that may lead to this discrepancy. First, a five-point rating scale was utilized to determine the logarithmic model, whereas our study utilized the 11-point BTRS. Second, TREMBAL reports true displacement in contrast to other modalities that require displacement to be derived mathematically. Finally, our limited study of eight participants does not encompass a wide range of tremor severities and is particularly lacking in high severity tremors. This lack of a uniform tremor distribution across the BTRS may impact our square-root model. Notably, our results showed only a minor increase in congruence through the addition of a square-root transform to the raw data. Thus, it may prove in future that a transform may indeed not be required.

TREMBAL has been optimized to remove purposeful movement (occurring in a different frequency band to tremor) from output measurements, thus gaining the flexibility to monitor tremor during a variety of assessment tasks. Here we utilized the finger-nose task to assess kinetic tremor and the gross arm movements were automatically filtered, leaving only tremor. We posit that TREMBAL can be extended to discriminate tremor from other tremor-inducing tasks such as drawing and pouring water between cups. Additionally, TREMBAL can be used to record tremor during postural tasks which do not require purposeful motion, including resting conditions and holding weights. Although we studied the upper limbs, the motion sensors can be applied to any part of the body, hence head and leg tremor can be readily measured.

TREMBAL coupled with electromagnetic motion tracking is able to quantify tremor severity in millimeter units. Our software algorithms, unlike many others (Engin et al., 2007; Giuffrida et al., 2009; Joundi et al., 2011; Rigas et al., 2012; Wile et al., 2014), do not report the tremor using a dimensionless index or reproduce a clinical rating scale using machine learning algorithms. Displacement-based results are intuitive measures that humans can effortlessly understand, unlike acceleration which is comparatively more difficult to comprehend. Despite accelerometers being inexpensive, advanced signal processing techniques are required to accurately report tremor by compensating for gravitational artifact (Elble, 2005) and nonlinear frequency bias (Perera et al., 2015a). As described by (O'Suilleabhain and Dewey, 2001), displacement-based measurements can also be easily calibrated and tested for accuracy by moving the sensor across a known distance.

As far as we are aware, only two groups have utilized electromagnetic motion tracking in the past to measure pathological tremor (O'Suilleabhain and Dewey, 2001; Spyers-Ashby et al., 1999). Both groups collected data using a 3Space Fastrak (Polhemus Inc., Colchester, Vermont) motion tracker which uses alternating current to energize electromagnetic coils. Conversely, the device we used (Ascension trakSTAR) uses direct current. This fundamental difference gives the trackSTAR system greater immunity against metallic interference (Ascension Technology Corporation, 2012). In our previously reported bench tests (Perera et al., 2015b) we found the trakSTAR to be resilient to most metallic interference, even at close range.

In a similar study to our own, (O'Suilleabhain and Dewey, 2001) showed a strong (r = 0.88) agreement between objective measurement of tremor amplitude and clinical observation. Furthermore, a high Pearson's correlation (r = 0.93, p < 0.001) between repeated measures in their

test-retest reliability was reported. The algorithms used to define tremor amplitude were different to those implemented in TREMBAL, and tremor was rated by an investigator visually estimating amplitude in millimeters. Though there are some fundamental differences, the main features of the experimental results are similar to our own.

In agreement with (O'Suilleabhain and Dewey, 2001), we also found the manufacturer's bundled software (Cubes, Ascension Technology, version 32) to be error prone with significant numbers of missing samples in data recordings (Perera et al., 2015b). TREMBAL bypasses the bundled software and acquires data directly from the motion tracker. We have been able to reliably record from four sensors simultaneously at the maximum sampling rate of 250 Hz using appropriate software buffering techniques.

Spyers-Ashby et al. and O'Suilleabhain and Dewey have noted a decrease in measurement accuracy with increased separation between electromagnetic transmitter and motion sensors. Both groups restricted the participant to be within a 0.76 m radius of the transmitter. In our assessments (Perera et al., 2015b), we found this range can be improved to 1.2 m while maintaining accuracy by adopting a wide-range transmitter instead of the mid-range devices that other groups utilized. Despite the additional cost and the increased size and weight of the wide-range transmitter, the improved range allows greater flexibility during assessments and the positioning of the device relative to the participant. Portability can be maintained by mounting the system on a sturdy, non-metallic trolley.

Conclusion

Here we have presented TREMBAL, an objective tremor measurement system, and validated its measurements against clinical ratings. Results show that translational measures of tremor are in agreement with clinical observation and can reliably show changes in tremor caused by DBS modification. Using TREMBAL, we plan to extend this study to include other tremor phenotypes and also to explore the parameter space of DBS systematically. Our goal is to develop TREMBAL to allow phenotype diagnosis as well as treatment optimization in the near future. Healthcare providers are facing increasing burdens as the number of patients suffering from movement disorders grow. TREMBAL might facilitate rapid diagnosis and drug titration as well as DBS optimization through guided assessment – perhaps requiring minimum intervention from clinicians. Thus, making healthcare more accessible to these patients and alleviating the burden on healthcare providers. We believe TREMBAL is also a useful tool for clinical trials. Additionally, objective and reliable measures may lead to a reduction in repeated trials for intra- or inter-patient comparisons. Protocols relying on tedious and time-consuming blinded assessments of video recorded tremor can gain the most benefit from using TREMBAL instead.

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