Movement Disorders
CLINICAL PRACTICE
RESEARCH ARTICLE

Differentiating Postural and Kinetic Tremor Responses to Deep Brain Stimulation in Essential Tremor

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Abstract: Background: While deep brain stimulation (DBS) targeting the ventral intermediate nucleus (VIM) of thalamus or posterior subthalamic area (PSA) can suppress forms of action tremor in people with Essential Tremor, previous studies have suggested postural tremor may respond more robustly than kinetic tremor to DBS.

Objectives: In this study, we aimed to more precisely quantify the (1) onset/offset dynamics and (2) steady-state effects of VIM/PSA-DBS on postural and kinetic tremor.

Methods: Tremor data from wireless inertial measurement units were collected from 11 participants with ET (20 unilaterally assessed DBS leads). Three postural hold tasks and one kinetic task were performed with stimulation turned off, in 2-min intervals after enabling unilateral DBS at the clinician-optimized DBS setting (15 min), and in 2-min intervals following cessation of DBS (5 min).

Results: At baseline, kinetic tremor had significantly higher amplitudes, standard deviation, and frequency than postural tremor ($P < 0.001$). DBS had a more robust acute effect on postural tremors (54% decrease, $P < 0.001$), with near immediate tremor suppression in amplitude and standard deviation, but had non-significant improvement of kinetic tremor on the population-level across the wash-in period (34% decrease). Tremor response was not equivalent between wash-in and wash-out timepoints and involved substantial individual variability including task-specific rebound or long wash-out effects.

Conclusions: Programming strategies for VIM/PSA-DBS should consider the individual temporal and effect size variability in postural versus kinetic tremor improvement. Improved targeting and programming strategies around VIM and PSA may be necessary to equivalently suppress both postural and kinetic tremors.

In people with Essential Tremor (ET), action tremors are generally acknowledged to respond robustly (30–80% total reduction[1,2]) and quickly (within seconds[3]) to VIM/PSA-DBS therapy. Surprisingly, however, DBS therapy has not been rigorously quantified or compared between (1) postural and kinetic subtypes of action tremor and (2) wash-in versus wash-out dynamics.[4] These factors have particular relevance to knowing how frequently one can evaluate stimulation settings during DBS programming visits,[3] as well as providing design parameters for future closed-loop DBS systems.[5]

Individuals with ET typically exhibit two forms of action tremor in the upper extremities: postural tremor and kinetic tremor.[6,7] Postural tremors manifest by holding a limb statically against gravity (eg, arms outstretched forward, wing-beating posture, dot approximation), whereas kinetic tremors present during voluntary movement (eg, finger-nose-finger).[8] Kinetic tremor often occurs more frequently and with greater severity than postural tremor in people with ET[9,10]; however, there are limited data as to how DBS specifically affects each type of action tremor in the upper extremities.[11–13]

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Studies using clinical rating scales have suggested that DBS suppresses the amplitude of tremors emerging from postural tasks more than from kinetic tasks, and that the effects of DBS on postural tremors are sustained more robustly over time.[14] Yet, while the gold standard, these clinical rating scales rely on subjective ratings based on an ordinal scale.[8,15–19] Recent efforts with inertial measurement unit (IMU) devices have enabled a more objective method to quantify tremor intensity with higher amplitude resolution,[20–23] providing opportunities to more precisely assess how DBS impacts different forms of action tremor. For instance, Earhart et al investigated the IMU response of postural tremor (arms outstretched) and intention tremor (finger-nose-finger) to VIM-DBS as a function of frequency and suggested that stimulation near 130 Hz provided maximal suppression of both postural and kinetic tremors, but did not track how those responses changed over time.[24]

The temporal effect dynamics following DBS onset (wash-in) and after discontinuing DBS (wash-out) are an important consideration, particularly as they are known to vary considerably amongst brain disorders.[25] In cases of Parkinson's disease, wash-in and wash-out time constants for treating bradykinesia can be similar,[26,27] but the time course depends on both the anatomical target of stimulation[28] and the duration of the disease.[29] Especially for the postural components of dystonia, the time constants of response and reoccurrence after disabling DBS can vary over days, weeks, or months.[30–32] Perera et al remains the only study to have tested DBS wash-in and wash-out responses in people with ET, suggesting at least 10 min are needed between consecutive trials of DBS[3]; however, this high-level summary of tremor responses was evaluated over long 5-min intervals and did not independently assess different forms of action tremor.

In this study, we investigated the differential efficacy and temporal responses of postural and kinetic tremor to clinician-optimized DBS in people with medication-refractory ET by using objective measurements with IMUs. We hypothesized that (1) kinetic tremors have greater amplitude than postural tremors in both off and on DBS conditions, (2) DBS controls postural tremors more robustly than kinetic tremors, (3) postural and kinetic tremor levels reach a rapid (within seconds) steady-state after turning on DBS, and (4) wash-in and wash-out time dynamics are equivalent across both forms of action tremor.

Methods

Participants

Individuals with a diagnosis of ET and with directional VIM/PSA-DBS lead implant(s) were recruited into a clinical trial investigating programming of DBS systems for ET (NCT03984643) (Table 1). Each participant was deemed to be at the optimized DBS setting, following standard-of-care outpatient programming (monopolar review) that was performed by a movement disorders clinician over a series of sessions occurring prior to study participation. For participants with bilateral implants, each DBS lead was evaluated independently on separate study visits while the contralateral DBS lead remained off. Participants were not blinded or randomized to whether DBS was on or off, but were blinded to the study question that postural and kinetic tremors respond differently to DBS. The clinical study was approved by the University of Minnesota Institutional Review Board and all participants gave written, informed consent prior to participation in the study.

Data Collection

Participants arrived in the lab in the off-stimulation state (>8 h duration) (Fig. 1A). Participants were allowed to continue with any medications, which were documented at the beginning of the visit. A 6-axis (xyz-accelerometer, xyz-gyroscope) wireless IMU sensor (MbientLab) was attached to the dorsal surface of the middle finger just above the metacarpophalangeal joint of both hands. During each assessment interval, participants performed four tasks from The Essential Tremor Group Rating Assessment Scale (TETRAS): (1) forward arms outstretched posture (10 s), (2) lateral wing-beating posture (10 s), (3) dot approximation posture (10 s), and (4) finger-nose-finger reaching task (5 repetitions) (Fig. 1B). Tasks 1–3 were designed to elicit postural tremor, whereas Task 4 elicited kinetic tremor. Participants first performed these tasks in the off-stimulation state (baseline), and then at 2-min intervals (1–15 min) following unilateral stimulation turned on to the clinician-optimized setting (Table 1). For a subset of participants for whom time allowed (14 leads), tasks were also assessed at 1-, 3-, and 5-min following cessation of unilateral DBS (Fig. 1A). At each interval, a TETRAS hand tremor subscore (0–4 on 0.5 point scale, in which 0 indicates no tremor and 4 indicates tremor ≥20 cm amplitude) was evaluated for each task by a movement disorders specialist. Additionally, accelerometer and gyroscope data were sampled from the IMU at 100 Hz and wirelessly streamed to a mobile app for data collection. Participants were video recorded during the assessment and clapped at regular intervals to enable synchronizing of the videos to the IMU data.

IMU Processing

IMU sensor data from the metacarpophalangeal joint contralateral to the brain hemisphere being stimulated with DBS were processed in MATLAB (vR2023b) using the following algorithm (Fig. 1C). First, each axis of the accelerometer data was bandpass filtered with a 5th-order Butterworth filter between 3 and 12 Hz, corresponding to the frequency range typical of action tremors observed in ET.[33,34] Since tremor is task-dependent and can fluctuate over time, each axis of time-series accelerometer data was processed with the Hilbert Transform, from which the instantaneous amplitude and instantaneous frequency were calculated across all three axes. Video recordings were used to segment the IMU data between the start and stop times of each task, from which the mean and standard deviation of the instantaneous amplitude and the maximum frequency from the instantaneous frequency was calculated.

TABLE 1 *Participant demographics and clinician-optimized DBS settings*

Subject	Sex	Age at diagnosis (years)	Disease duration (years)	Lead	Implant duration (years)	Active Contact location	Contralateral TETRAS score			Clinical DBS setting		
							OFF	ON	% change	Amp (mA)	Freq (Hz)	Pulse width (μs)
1	M	39	26	L	5.4	VIM	12	5.5	−54	1.85	180	60
				R	5.3	VIM	12.5	4	−68	2.2	180	60
2	M	47	31	L	4.5	PSA	13	2	−85	5	160	30
				R	4.4	VIM	10	2.5	−75	3	130	60
3	F	37	33	L	5.8	VIM	7.5	0	−100	4	180	60
				R	3.7	VIM	9	3	−67	1.15	180	60
4	F	46	11	L	4.7	VIM	9	4.5	−50	1.25	186	40
5	M	21	42	L	5.7	VIM	18	0.5	−97	5	180	30
				R	5.5	VIM	21.5	0.5	−98	4.05	180	50
6	F	42	33	L	2.8	PSA	9	2	−78	1.5	130	60
				R	2.7	PSA	7.5	4.5	−40	1.5	130	60
7	M	40	29	L	2.9	VIM	11	4	−64	1	179	80
				R	2.8	PSA	8	0.5	−94	1.5	179	60
8	M	29	44	L	2.8	VIM	8.5	0	−100	1.8	130	60
9	M	62	16	L	4.3	PSA	13.5	3.5	−74	2.9	180	30
				R	4.3	PSA	9.5	3.5	−63	2.8	130	30
10	F	52	23	L	2.3	VIM	8	0.5	−94	4	159	30
				R	1.8	PSA	13.5	2.5	−82	4	159	30
11	M	68	5	L	0.9	VIM	14	2	−86	3.9	130	60
				R	0.8	PSA	10.5	1.5	−86	2	143	60
Mean ± SD	4 F/7 M	43.9 ± 13.5 y	26.6 ± 12.2 y	11 L/9 R	3.66 ± 1.56 y	12 VIM/8 PSA	11.3 ± 3.6	2.4 ± 1.7	−78 ± 18%	2.72 ± 1.32 mA	160 ± 22.8 Hz	50.5 ± 15.4 us

Abbreviations: TETRAS, the essential tremor rating and assessment scale; DBS, deep brain stimulation; M, male; F, female; L, left; R, right; SD, standard deviation; y, years.

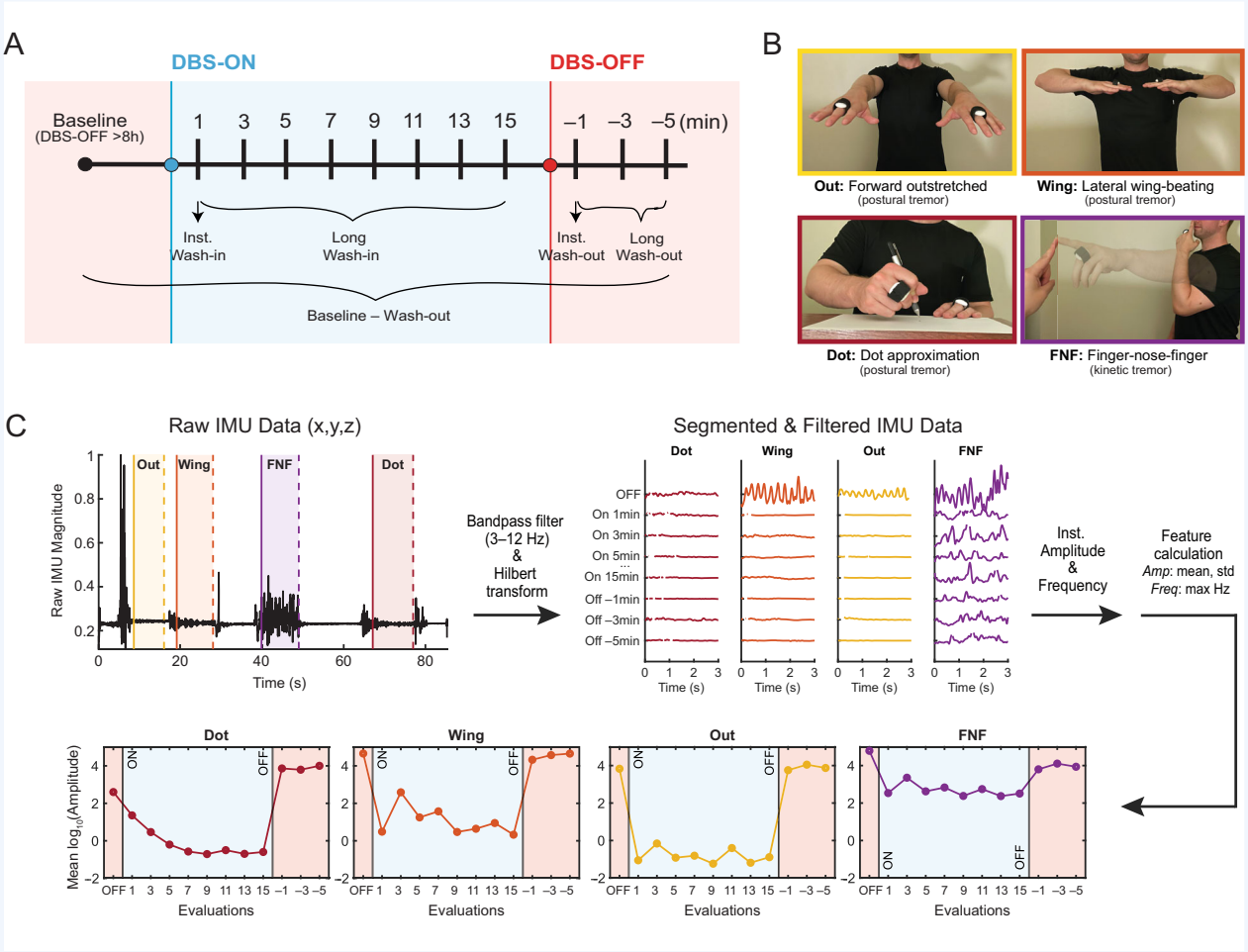

Figure 1. Methodology for collecting inertial measurement unit (IMU) data. (A) IMU data was collected at regular 2-min intervals following deep brain stimulation (DBS) being turned on (15-min) and then off (5-min). Brackets indicate the intervals across which temporal dynamics were calculated. (B) Four upper extremity tasks were performed at each interval to assess differences in postural and kinetic tremors. (C) Raw IMU data was segmented by task, after which signal processing filters were used to extract instantaneous tremor amplitude and frequency. Amplitude and frequency features are plotted across intervals to quantify task-specific wash-in/out changes.

The finger-nose-finger task was additionally processed to separate tremor into three phases: around the finger target, around the nose target, and during movement between targets. To accomplish this, the power spectrum of the raw IMU data was calculated using a Fast Fourier Transform and the frequency of the voluntary finger-nose-finger movement was defined as the maximum frequency peak <3 Hz. That frequency was used to fit a sine model to the data. For data with models achieving a goodness of fit at $\alpha < 0.05$, the data was segmented into three sections according to the model's period: "FNF-finger" included data $\pm 1/8$ of the period from the peaks, "FNF-nose" included data $\pm 1/8$ of the period from the troughs, and "FNF-movement" included any remaining data in-between.

IMU Validation

To evaluate if there was a relationship between the clinical rating scales and IMU data collected, the paired TETRAS subscores and mean IMU amplitudes were compared between baseline DBS-OFF and DBS-ON (80 data pairs). TETRAS and IMU data were fit to a logarithmic model, according to the relationship determined in Elble et al.[35] $(\text{IMU}) = \alpha \cdot \text{TETRAS} + \beta$.

Temporal Dynamic Calculations

Five different types of temporal dynamics were evaluated as the percent change in IMU values across baseline (DBS-OFF), DBS onset (ON 1–15 min), and DBS offset (OFF 1–5 min) data (Fig. 1A). Instantaneous wash-in was defined as the immediate (<1-min) decrease in tremor with DBS, which was determined between the baseline (DBS-OFF) and first onset (ON-1 min) timepoints. Long wash-in was defined between the first (ON-1 min) and final (ON-15 min) DBS onset timepoints. Similarly, instantaneous wash-out was determined between the final onset (ON-15 min) and first offset (OFF-1 min) timepoints, and long wash-out was determined between the first (OFF-1 min) and final (OFF-5 min) DBS offset timepoints. Finally, a

comparative Baseline–Wash-out metric was calculated between baseline (DBS-OFF) and final wash-out (OFF-5 min) timepoints.

Statistical Analysis

The Lilliefors test was performed to determine if TETRAS subscores and IMU features were normally distributed ($P < 0.05$). As both TETRAS subscores and mean IMU amplitudes were found to be non-normally distributed ($P = 0.001$), variables were reported as median (interquartile range [IQR]). Wilcoxon signed rank tests were applied to matched data, such as between IMU features collected with DBS-OFF versus DBS-ON. Kruskal-Wallis tests were used to compare means of three or more groups, such as between IMU features across wash-in/out assessment intervals or across the four tasks. To directly compare the wash-in versus wash-out responses in a subset of participants (14 leads), a Wilcoxon signed rank test was used to compare the percent change in mean IMU amplitude at 1-, 3-, and 5-min intervals from the amplitude at DBS-OFF or DBS-ON, respectively. Finally, χ^2 tests were conducted to evaluate associations between patient characteristics in Table 1 to different categories of temporal dynamic responses. For all statistical tests, a value of $P < 0.05$ was considered significant, and a Holm-Bonferroni correction was applied in the cases of multiple comparisons.

Results

Participant Characteristics

Eleven participants with a diagnosis of ET and with a total of 20 directional VIM/PSA-DBS lead implant(s) (2 unilateral/9 bilateral) were enrolled prospectively in the study. Lead implant location was classified from co-registration of pre-operative 7 T MRI and post-operative CT imaging,[36] with the ventral border of VIM separating active contacts in VIM versus PSA. Demographics, baseline TETRAS scores, and clinical DBS settings are reported in Table 1. Participants had a mean disease duration of 26.6 ± 12.2 years since diagnosis, implant duration of 3.66 ± 1.56 years since surgery, and a baseline contralateral limb TETRAS score of 10 (8.9–13) out of a possible 28. Stimulation at the clinician-optimized setting resulted in a mean 80% (66–94%) decrease in contralateral limb tremor as assessed by TETRAS: 2.3 (0.5–3.6). The logarithmic fit between baseline TETRAS subscores and mean IMU amplitude demonstrated a reasonable fit ($\log_{10}(\text{IMU}) = 0.34164 \times \text{TETRAS-1.841}$, $r^2 = 0.5269$, RMSE = 0.0479, $P < 0.0001$) (Fig. 2A).

Postural Tremor Demonstrated Lower Amplitude, Less Variation, and Lower Frequencies at Baseline

According to TETRAS subscores and IMU data (Fig. 2B), upper extremity tremor significantly decreased after 15-min of DBS-ON at the clinical setting ($P = 2e\text{-}11$). IMU data aligned well with TETRAS scores; however, the continuous, objective measurement provided more granular insight into the different responses to DBS between tremor types (Fig. 2C). Mean IMU amplitude demonstrated significant differences between the averaged postural tremor and kinetic tremor amplitudes, both without stimulation, postural: 0.0311 (0.0111, 0.0695) versus kinetic: 0.0892 (0.0532, 0.1031) ($P = 0.001$), and at the clinician-optimized setting, postural: 0.0068 (0.0054, 0.0089) versus kinetic: 0.0591 (0.0348, 0.0734) ($P = 8.9e\text{-}5$). Similarly, averaged postural tremor had a significantly lower standard deviation at both DBS-OFF ($P = 3.9e\text{-}4$) and DBS-ON ($P = 8.9e\text{-}5$). Without stimulation, maximum frequency of the averaged postural tremor was significantly lower than kinetic tremor, postural: 4.78 (4.37, 5.03) Hz versus kinetic: 5.19 (4.63, 5.71) Hz ($P = 6.8e\text{-}4$); however, no significant difference in maximum tremor frequency was observed between tremor types with DBS-ON, postural: 5.22 (4.56, 5.35) Hz versus kinetic: 5.16 (4.67, 5.53) Hz ($P = 0.48$). With DBS, all tasks experienced significant percent decreases in tremor amplitude and standard deviation (Fig. 2C). Postural tremor during arms outstretched was the only task to have a statistically significant change in tremor frequency with DBS, which caused an increase of 14% (2, 21) ($P = 0.002$) (Fig. 2C).

Tremor during Proximally Held Postures Decreased more Robustly with DBS

Figure 3A demonstrates how the mean IMU amplitude of each task changed after turning on DBS (assessments every 2-min over 15 min) and then after turning off DBS (assessments every 2-min over 5 min). On the group level, significant changes in tremor amplitude during the wash-in/out periods were only found for tremor during dot approximation and wing-beating postures. Postural tremor during dot approximation was significantly lower than baseline (DBS-OFF) at assessments after 3-min of DBS being on ($P < 0.0001$), and significantly increased as soon as DBS was turned off ($P < 0.0001$). During wing-beating, significant decreases in postural tremor amplitude were observed after 7-min of DBS being on ($P = 0.001$), but did not immediately return to the pre-DBS level once stimulation was turned off. For postural tremor during outstretched and kinetic tremor during finger-nose-finger, no significant differences between DBS-OFF and any onset time point or between DBS-ON and any offset time point were found at the group level.

Delving further into the instantaneous and long temporal responses to DBS, Figure 3B shows the percent change in mean tremor amplitude across the five different temporal dynamic evaluations. Within 1-min of DBS being turned on, postural tremors experienced greater instantaneous decreases than kinetic tremor, and a significant difference in the instantaneous response was observed between wing-beating and finger-nose-finger ($P = 0.003$). During the long wash-in period (15 min), tremor amplitudes were sustained as DBS remained on, with little

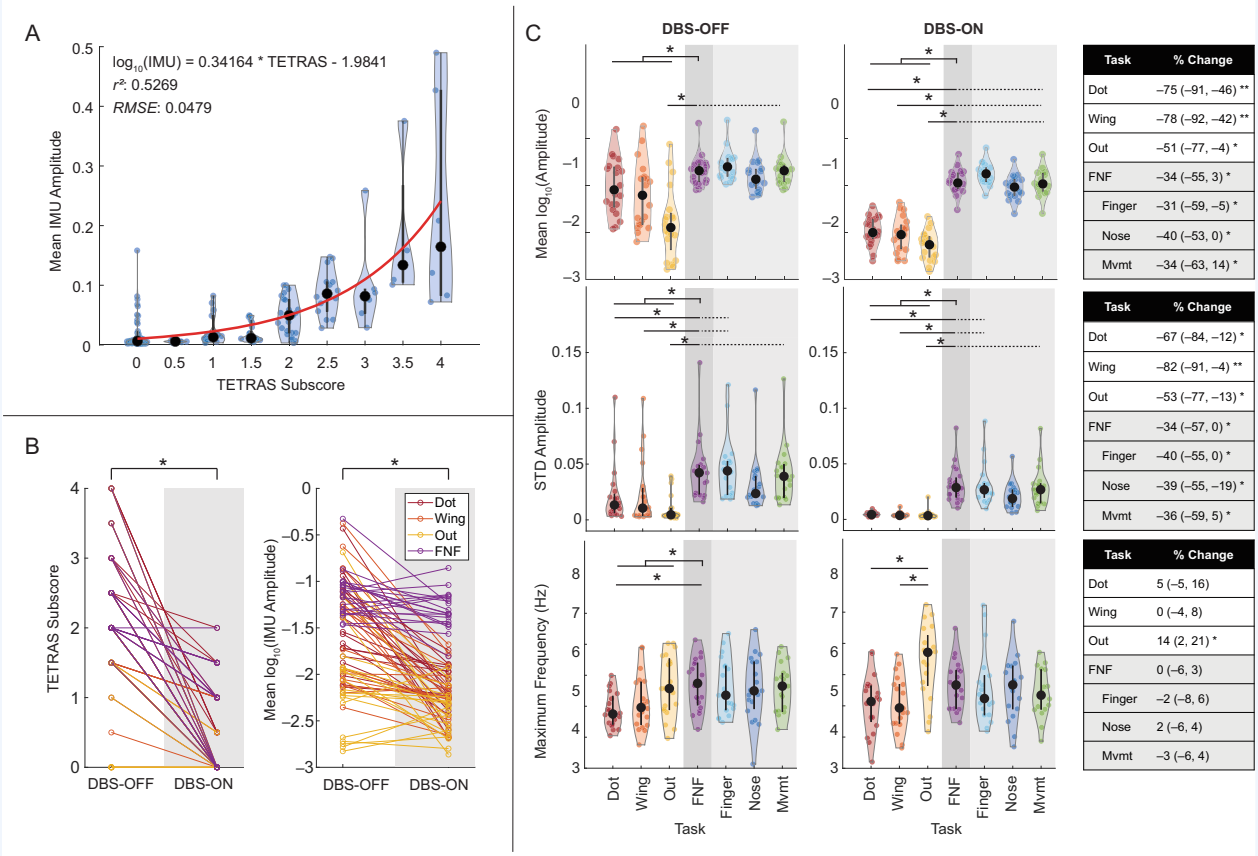

Figure 2. Baseline tremor amplitude with and without deep brain stimulation (DBS). (A) Mean inertial measurement unit (IMU) amplitude and the essential tremor group rating assessment scale (TETRAS) subscores followed a logarithmic relationship. (B) TETRAS subscores and mean log amplitudes significantly decreased with the clinician-optimized setting. (C) IMU features across tasks, presented without DBS and at clinician-optimized DBS. The total percent changes with DBS-ON are presented as median (IQR). Asterisks indicate a significant difference between tasks (*$P < 0.05$, **$P < 0.001$).

variation across both postural and kinetic tremors. Within 1-min of DBS being turned off, all tasks demonstrated an overall increase in tremor amplitude, with postural tremor during dot approximation experiencing the greatest increase. As DBS remained off during the long wash-out period (5 min), both postural and kinetic tremors generally decreased in amplitude compared to the first wash-out time point, but this rebound effect was not significant at the group level. In comparison to the baseline tremors present when participants came in, postural tasks sustained slightly lower amplitudes, whereas finger-nose-finger presented with a higher amplitude, following the period of DBS being on.

Tremor Wash-in and Wash-out Responses to DBS Were Not Equivalent

For all four tasks, there were significant differences between the wash-in and wash-out percent change values at 1-min (Fig. 3C). For postural tremors during outstretched and wing-beating, the wash-in response was slightly greater or equal to the wash-out response ($P = 0.004$). Conversely, postural tremor during dot approximation and kinetic tremor during finger-nose-finger had a greater change following DBS offset as compared to onset ($P = 0.002$ and $P = 0.001$, respectively). By 3- and 5-min, there were no significant differences in the wash-in/out responses of tremor during outstretched or finger-nose-finger, whereas the decreased wash-out response during wing-beating and the increased wash-out response during dot approximation were sustained ($P < 0.01$).

Variation in the DBS Response May be Patient-Specific

While, on the participant group level, both postural and kinetic tremors were found to generally decrease with DBS and increase upon turning it off, substantial differences in those temporal

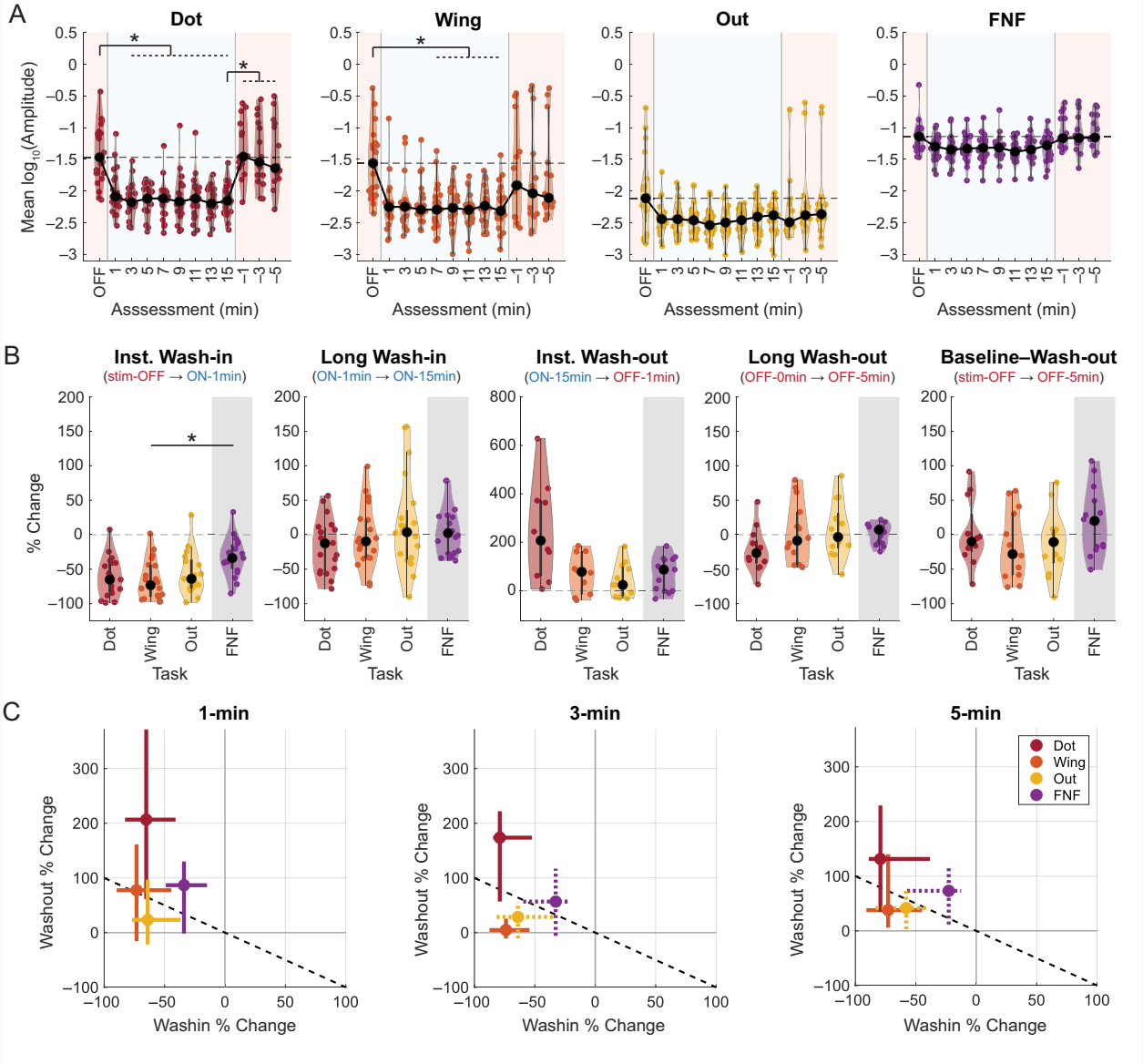

Figure 3. Temporal dynamic changes of ET-DBS on the participant group level. (A) The mean log amplitude was plotted across all 12 assessment intervals for each task across all 20 leads. Asterisks indicate significant differences between deep brain stimulation (DBS)-OFF and wash-in assessments and between DBS-ON and wash-out assessments. (B) Percent changes in the mean log amplitude across five different temporal dynamic evaluations. In all violin plots, the black dot indicates the median and the black vertical line the interquartile range for each group. (C) Median (IQR) of the percent change in the mean log amplitude at 1-, 3-, and 5-min after DBS was turned on (wash-in) or off (wash-out). Solid lines indicate a statistically significant difference between wash-in and wash-out at that assessment interval ($P < 0.0125$). The black dotted line indicates an equivalent wash-in/out response.

responses were present on the individual level (Fig. 4). The majority of leads experienced instantaneous decreases in tremor amplitude across tasks; however, three categories of response were found post-hoc during the long wash-in and baseline-washout contexts (Fig. 4C). In both contexts, cut-offs of ±23% in tremor amplitude were chosen to represent normal, spontaneous variations in tremor, as suggested by Mostile et al.[37] No significant associations were found between any participant characteristics in Table 1 (sex, disease duration, implant duration, TETRAS scores) and the three response categories during long wash-in or baseline–wash-out.

Discussion

In this study, we compared the temporal response of DBS on postural and kinetic tremors in ET. The IMU measurements

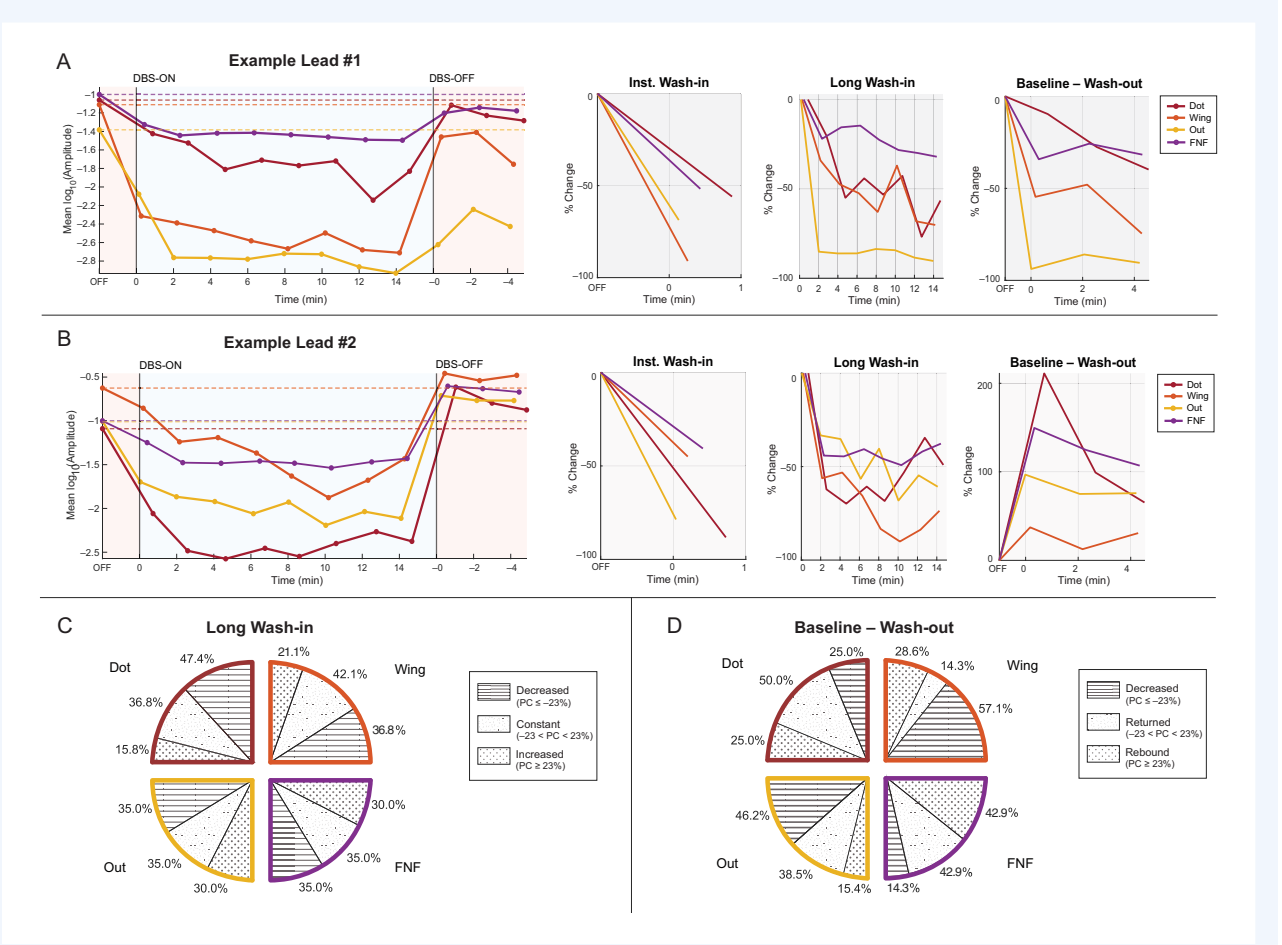

Figure 4. Temporal dynamic changes across tasks on the participant level. (A,B) Two examples of the differing tremor response to deep brain stimulation (DBS) across tasks. (C) Percent of leads (N = 20) that resulted in decreasing, constant, or increasing values over the long wash-in period. (D) Percent of leads (N = 14) that resulted in a decreased, returned, or rebound (increased) tremor amplitude during wash-out.

collected before, during, and after DBS suggest two important findings. First, in accordance with previous studies,[9–12] with DBS turned off, kinetic tremor amplitude was more severe than the average postural tremor amplitude. Second, the degree of tremor suppression with clinician-optimized DBS was greater for postural tremor than for kinetic tremor (Fig. 2). Within 1-min of DBS turning on, postural tasks resulted in greater instantaneous decreases in tremor than kinetic tasks; after 15-min of DBS, these decreases were sustained, with postural tremors exhibiting a greater overall suppression. Within postural tasks, more proximally held postures were found to be more affected by DBS, with wing-beating exhibiting the most suppression (−73.2%), followed by dot approximation (−65.2%) and outstretched (−64%) postures. This trend also was present when separating the kinetic finger-nose-finger task into different targets, with tremor around the nose target exhibiting lower amplitudes than tremor during movement or around the outstretched finger target (Fig. 2C).

Postural and kinetic tremor responses to DBS also differed in their wash-in and wash-out dynamics (Fig. 3). Our study aimed to expand on the work of Perera et al who established that the overall tremor wash-in response reached a steady-state within seconds, whereas wash-out required more than 10 min.[3] We evaluated how multiple postural and kinetic forms of tremor respond to DBS across shorter evaluation windows (ie, 2-min). In comparison to the distally-held outstretched posture and kinetic finger-nose-finger task, the more proximally-held postures of dot approximation and wing-beating were the only two tasks to achieve significant decreases from baseline that were sustained within the 15-min wash-in period on the group level. Furthermore, only postural tremor during dot approximation significantly increased instantaneously when turning DBS back off, which stemmed in part from a rebound effect.

The differences in overall postural and kinetic tremor responses to DBS suggest that these two forms of action tremor may require either different DBS parameters[38] or distinct neural targeting for suppression.[39] In the case of a central oscillator causing ET pathophysiology,[40,41] abnormal firing across a neural network is responsible for ET motor symptoms. Within the thalamus, Hirai et al found that larger coagulative lesions in

VIM were required to suppress larger amplitude tremors and tremors occurring during movement.[42] Furthermore, electrophysiological mapping studies in VIM performed by Hua and Lenz demonstrated that neurons associated with active movement display greater spike activity at tremor frequencies than do nonvoluntary neurons.[43] As a result, kinetic tremors may be the result of abnormal firing at either a greater intensity or across a greater volume within the tremor network, and thus would require greater amplitudes of current to be equivalently controlled. On the other hand, suppression of each action tremor type may require targeting of distinct, rather than a greater quantity of, neural pathways in and around VIM/PSA. Studies have shown that kinetic processes, when compared to postural holds, likely require differing involvement of projections within the cerebello-thalamo-cortical loop, in addition to a higher degree of sensory integration to achieve goal-directed movement.[4,44–46] Serial assessments of directional DBS lead contacts found a relationship between the ventrodorsal location of stimulation and postural tremor reduction, suggesting that contacts steered more towards subthalamic white matter are more effective than those targeting thalamic nuclei.[39] While the study was not designed to compare responses to DBS target locations, in exploratory analysis there was no clear relationships between wash-in or wash-out responses based on target location (VIM or PSA) for any of the four postural and kinetic tasks. Future studies that combine pathway activation models of directional VIM/PSA-DBS with assessments of postural and kinetic tremor data could be used to determine whether larger volumes of activation or different pathway targets in and around VIM are required to effectively suppress both postural and kinetic tremors with equal efficacy.

Some of the differences in DBS response across the population could also be explained by patient and disease characteristics.[47] As can be seen in Figure 4, stimulation resulted in three general temporal profiles across the long wash-in and wash-out periods. While most participants' tremors demonstrated a quick onset response, there were considerable differences in how that response was sustained as DBS remained on and how that response returned to baseline after DBS was once again turned off. Our results suggest that, as DBS remains on during the 15-min wash-in period, approximately 1/3 of patients will experience a sustained decrease in tremor amplitude (change ≤ −23%), whereas another 1/3 of patients will see an increase in tremor amplitude (change ≥23%). Greater variation between tasks was present when considering tremor amplitude following a period of stimulation. As DBS was turned off and monitored for 5-min of wash-out, most leads saw lower amplitude tremors as compared to baseline during outstretched (46.2%) and wing-beating (57.1%) tasks; however, some leads experienced a rebound effect,[48] in which amplitudes were higher than those collected originally, particularly in wing-beating (28.6%) and dot approximation (25%). While we did not find any significant effects of sex, tremor severity at baseline, disease duration, implant duration, or baseline tremor scores on tremor dynamics, a larger sample size is likely necessary to relate these patient- and disease-related factors to the temporal responses to DBS. Furthermore, lead location and DBS parameters when targeting VIM versus PSA may have a substantial effect on not only the overall, but also the task-specific, response to DBS.[49,50] Future studies should consider active contact position relative to VIM/PSA (eg, anterior/posterior, medial/lateral) across a larger cohort to understand how lead location may contribute to this subject variability.

This study has several limitations. While participants were blinded to the study question that postural and kinetic tremors are different, participants were not blinded to whether stimulation was turned on or off, potentially introducing a bias attributed to a nocebo effect. Additionally, the effect of DBS was only tested with the clinician-optimized setting, which is a subjective assessment that depends on patients' individual goals for the therapy (eg, tuned to a specific task) and the programming physician's strategy. Other DBS settings (eg, electrode configurations) may yield different responses across the various postural and kinetic tasks. Due to testing constraints, wash-in dynamics were evaluated across a 15-min period, whereas wash-out effects were only evaluated for 5-min in a subset of participants (14 leads). An equivalent testing period for both wash-in and wash-out is needed to provide a more complete comparison of these dynamics, especially for wash-out to determine more precisely when tremor returns to steady-state. Furthermore, the design of this study resulted in tremor evaluation at discrete intervals, rather than providing continuous measurements of tremor amplitude during the wash-in and wash-out periods. In the case of closed-loop DBS, continuous monitoring may be necessary to more precisely determine when tremor has reached steady-state after turning DBS on and off.

This study demonstrates that postural and kinetic tremors respond differently to VIM/PSA-DBS, both in amplitude and temporal dynamics. Individual variability is also important to consider when assessing postural versus kinetic tremor improvement in clinical and research settings. Future studies should consider patient characteristics and subject-specific activation of pathways around VIM/PSA to determine how these factors affect action tremors on a task-specific basis in ET.

Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the first draft, B. Review and Critique.

R.D.B.: 1A, 1B, 1C, 2A, 2B, 3A
A.K.B.: 1A, 1B, 1C, 2C, 3B
M.B.: 1C, 3B
M.N.B.: 1C, 3B
P.M.G.: 1C, 3B
S.R.P.: 1C, 3B
C.S.C.: 1C, 3B
D.S.: 1C, 3B
J.K.: 1C, 3B
M.U.: 1C, 3B
J.L.V.: 1A, 2C, 3B

L.A.: 1C, 2C, 3B
T.O.: 1C, 3C
S.E.C.: 1B, 1C, 2C, 3B
M.D.J.: 1A, 1B, 2A, 2C, 3B

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Disclosures

Ethical Compliance Statement: This study was approved by the Institutional Review Board of the University of Minnesota. Written, informed consent was obtained from all participants by the clinical research coordinator prior to participation in the study and in accordance with the Declaration of Helsinki. All authors confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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Data Availability Statement

The datasets collected and analyzed for this study are openly available through our GitHub account at https://github.com/NRTL-Repository/. Please contact the corresponding author for any questions. ■

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