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Original Articles

Utility of routine surface electrophysiology to screen for functional tremor prior to surgical treatment of essential tremor

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ABSTRACT

Background: Patients with functional tremor may be clinically misdiagnosed as "medication-refractory" essential tremor (ET) and referred for surgical treatment. Electrophysiology can screen for functional tremor and avoid inappropriate surgery.
Objective: To report the utility of surface electrophysiology (SEMG) to screen for functional tremor in patients referred for ET surgery.
Methods: Retrospective review of consecutive ET patients referred to the Mayo Clinic DBS clinic over 1.5 years. Included subjects had a clinical diagnosis of medication-refractory ET and completed presurgical workup including routine SEMG tremor study.
Results: Of 87 subjects, 9 (10%) were clinically suspected of functional tremor by the DBS neurologist. Electrophysiology confirmed functional tremor features in 7/9 and ET in the other 2/9; and newly identified 5 additional cases of functional tremor. There were 12 total confirmed cases of functional tremor: isolated in 1, and mixed functional tremor and ET in 11. Of 11 mixed patients, 6 with mild functional overlay were approved for surgery. The remaining 5 patients with moderate-severe functional overlay and the single patient with isolated functional tremor were referred to the functional tremor motor retraining program. Of these, 1 patient with mixed tremor had residual disabling organic ET after program completion and was later approved for surgery. Thus, 5/87 patients (6%) avoided unnecessary surgery.
Conclusions: Functional tremor may frequently overlay "medication-refractory" ET amongst patients referred for surgery, affecting 1 of 7 patients in our quaternary referral DBS center. Electrophysiology studies are useful to routinely screen patients and prevent unnecessary surgery.

1. Introduction:

Essential tremor (ET) is one of the most common movement disorders with an estimated worldwide prevalence of 1% [1]. While most patients affected by tremor can be managed with pharmacotherapy, those with disabling medication-refractory ET are referred for surgical therapy, including deep brain stimulation (DBS) and MR-guided focused ultrasound thalamotomy (MRgFUS) [2–4]. Given the surgical risks and healthcare resources associated with these procedures, patients are carefully screened to exclude cognitive impairment, abnormal neuroimaging that may translate to a suboptimal outcome, and unrealistic goals [5,6]. However, functional tremor clinically masquerading as "medication-refractory" ET is not routinely screened for electrophysiologically.

While functional movement disorders are thought to represent 2–10% of patients seen in movement disorders clinics, prevalence in DBS clinics is unknown [7–9]. Limited reports describe DBS placement for a functional disorder which was preoperatively assumed to be organic [10,11]. These cases often demonstrated lack of expected benefit or improvement followed by worsening despite programming attempts. The placebo effect of surgery may potentially mask other cases.

Surface electrophysiology has been studied for its role in identifying tremors with functional features [12–15]. Our institution has used

Abbreviations: DBS, Deep Brain Stimulation; ET, Essential Tremor.

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surface electrophysiology for over 20 years to characterize tremor and screen patients being considered for ET surgery [16]. We have identified cases of functional tremor pre-operatively, despite a longstanding ET clinical diagnosis, thus avoiding unnecessary surgery. The goal of this study was to formally evaluate the utility of routine electrophysiology tremor analysis in screening for functional tremor disorders amongst a cohort of consecutive patients referred for ET surgery.

2. Methods

We retrospectively identified patients ≥ 18 years old referred for evaluation for DBS or MRgFUS to treat medication-refractory ET at Mayo Clinic (Rochester, MN) between January 2018 and June 2019. The electronic medical record was searched for DBS clinic referrals with a main indication of tremor. Chart review was conducted by one author (CZC).

We included patients with a clinical diagnosis of medication-refractory ET, defined as disabling tremor, typically having failed at least two adequate trials of ET medications. Pre-surgical evaluation included consultations with a DBS neurologist (BTK, AH), functional neurosurgeon, and speech pathologist; video recording of tremor; surface electrophysiology tremor study; and brain magnetic resonance imaging (MRI). A head computed tomography (CT) scan was obtained in cases in which MRgFUS thalamotomy was being considered to assess for skull density ratio. Additionally, patients ≥ 65 years old or with concern for cognitive impairment underwent neuropsychometric testing. Psychiatry evaluation was mandatory for patients with a history of psychiatric disease or an active mood or anxiety disorder.

We excluded patients with isolated parkinsonian tremor or orthostatic tremor, acquired causes of tremor, those with incomplete pre-surgical evaluation, and those with symptoms too mild for advanced surgical therapies.

Medical records were reviewed for demographic data (sex, age at DBS clinic evaluation) and clinical data (age at tremor onset; duration of tremor; surface electrophysiologic assessment of tremor; final electrophysiologic tremor diagnosis; findings of psychiatry evaluation; DBS committee recommendation; Fahn-Tolosa-Marin (FTM) score at baseline and follow-up; and surgical or other treatment outcomes). In patients for whom tremor onset was documented as an age range, an intermediate age within this range was selected for analysis. Patients with more than one tremor diagnosis were included if ET or ET plus (with rest tremor) was the main indication for surgery. We further reclassified the tremor diagnoses using the recent MDS Tremor Task Force criteria [17]. For patients who received DBS, data were routinely abstracted through second post-implantation programming visit.

The electrophysiology tremor study was conducted and interpreted by a movement disorders neurologist with training in movement electrophysiology (BTK, EAC, FA, JHB, AH). The routine study has been described previously and consisted of a montage of eight surface EMG electrodes placed over bilateral upper limb muscles (biceps, extensor digitorum communis, flexor carpi ulnaris and first dorsal interosseous muscles) [16]. This montage captured both distal and proximal muscles and muscles involved in flexion/extension of the wrist. Tremor was recorded during a set of standard conditions: while seated with hands relaxed in lap; with cognitive tasks (e.g., reciting the months of the year in reverse order); with upper limbs held in posture extended in front of the trunk and in the wing-beat position; and with action maneuvers including finger-to-nose and/or holding a cup to the face. Time frequency analysis using MATLAB was used to determine tremor frequency and variability over time.

Additional testing, including recording over additional sites (based on presence of tremor in other limbs or head); use of accelerometers in kinetic tremor; or limb loading to assess for enhanced physiologic tremor, was per the discretion of the movement disorders neurologist performing the study. Ballistic movements and frequency coherence between limbs were not routinely assessed.

All patients underwent routine screening for functional tremor with tapping studies. Patients were instructed to tap one hand (typically the less affected hand) to a metronome at three different frequencies (2, 2.5, 3 Hz), to determine whether tremor in the other hand distracted or entrained. In our movement lab, we use the following criteria for diagnosis of functional tremor: distractibility (disappearance of tremor); entrainment (tremor adopts the same frequency as the tapping hand); increased variability of tremor features spontaneously or with tasks, such as greater variability of frequency or amplitude reduction with tapping (often accompanied by poor tapping accuracy); variability in tremor vector (e.g., change in plane of movement around a joint from flexion/extension to abduction/adduction); or high coherence between muscles involved in tremor [16]. Tremor frequency with >2 Hz variability was also diagnosed as functional tremor, if there were no clinical and electrophysiological signs suggestive of dystonic tremor. These criteria are based on previous data from our group showing tremor frequency in ET can vary within 1 Hz and fluctuations in frequency of 1.5–2.5 Hz were seen in functional tremor, not ET [18]. Dystonic tremor was clinically and electrophysiologically excluded as could best be determined (absence of clinical dystonic posturing, null point of tremor, or phasic co-cocontraction tremor bursts in agonist/antagonist muscle pairs). If the tremor had persistent and replicable functional features that predominated the electrophysiological findings, it was categorized as moderate-severe functional features. Otherwise, if functional features were detected but were not the predominant findings on electrophysiology, they were categorized as mild. For example, a high amplitude, fixed frequency postural and/or action tremor consistent with essential tremor, but with significant reduction in tremor amplitude with tapping tasks and no other functional features, would be suggestive of functional overlay on ET. In cases where there appeared to be a mix of functional tremor features and organic ET, the movement electrophysiologist indicated this in the report.

In cases with a mixed resting and postural tremor, the rest tremor was assumed to reflect longstanding ET if it was milder than the postural component and occurred within 1.5 Hz of the postural/action tremor frequency. Alternatively, a parkinsonian tremor was documented if accompanied by other parkinsonian motor features or if rest tremor was more severe and/or >2 Hz slower than the postural/action component. Patients with isolated parkinsonian-predominant tremor were excluded from the final cohort.

During the study period, 144 patients were referred for surgical treatment for tremor (Fig. 1). Fifty-seven patients were excluded: 47 had a primary organic tremor diagnosis other than ET, which included Parkinson disease (n = 36); acquired tremor disorder (n = 6, including traumatic brain injury, encephalitis, and other CNS pathologies); isolated primary orthostatic tremor (n = 1); a genetic disorder with a complex movement disorder (n = 1); drug-induced tremor (n = 2); and indeterminate tremor (n = 1). One ET patient had symptoms too mild to consider surgery and 9 ET patients failed to complete pre-surgical evaluation. This left 87 patients to be included.

This study was approved by the Mayo Clinic Institutional Review Board.

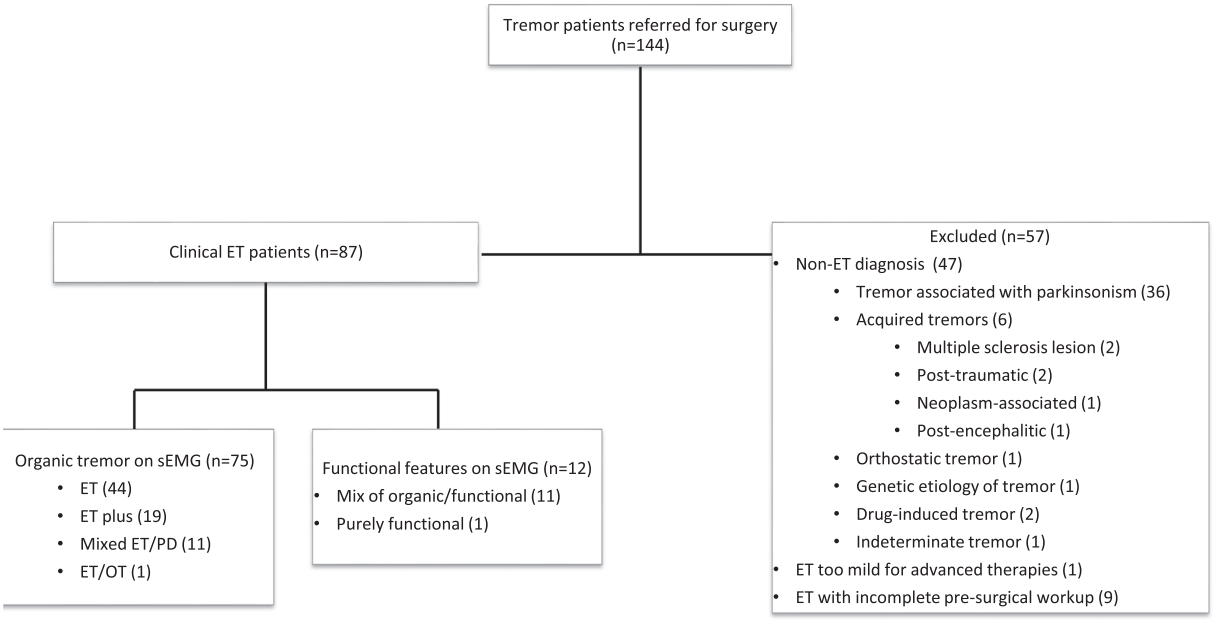
3. Results

3.1. Demographic and clinical data

Demographic and clinical features of the 87 patients are summarized in Table 1. Mean age at DBS clinic evaluation, 70 years; mean age at tremor onset, 38 years; mean tremor duration, 32 years; 54 (62%) were male. Data for tremor onset and duration were missing in two cases.

3.2. Clinical diagnosis of tremor

This is summarized in Table 2. For the 87 patients, tremor diagnoses were retrospectively classified using the MDS Tremor Task Force criteria



Records of patients with medication-refractory tremor referred to DBS clinic over a 1.5-year period were screened. Reasons for exclusion are noted, as well as the surface EMG findings of included patients.
Abbreviations: ET-essential tremor, **OT**-orthostatic tremor, **PD**-Parkinson disease, **sEMG**-surface EMG, **DBS-**deep brain stimulation

Fig. 1. Patients evaluated for advanced therapies for tremor. Records of patients with medication-refractory tremor referred to DBS clinic over a 1.5-year period were screened. Reasons for exclusion are noted, as well as the surface EMG findings of included patients. **Abbreviations: ET**-essential tremor, **OT**-orthostatic tremor, **PD**-Parkinson disease, **sEMG**-surface EMG, **DBS-**deep brain stimulation

Table 1
Demographic and clinical features of 87 patients referred for surgical treatment for ET.

	All patients (n=87)	Organic ET (n=75)	Functional tremor, with or without ET (n=12)	p-value
Male sex	54 (62%)	49 (65%)	5 (42%)	0.12
Age at DBS evaluation, y d (mean, SD, range)	70±12, 18-90	72±11, 21-90	56±13, 18-70	**0.0002**
Age at tremor onset, y (mean, SD, range)	38±21, 5-80	39±21[a], 6-80	30±18, 5-56	0.16
Duration of tremor, y (mean, SD, range)	32±20, 3-78	33±20, 3-78	26±16, 5-50	0.24
Psychiatry referral	50 (57%)	39 (52%)	11 (92%)	**0.0078**
- Normal profile	18 (36%)	14 (36%)	4 (36%)	0.98
- Anxiety/ depression	26 (52%)	20 (51%)	6 (55%)	0.84
- Childhood abuse/ neglect	4 (8%)	3 (7.7%)	1 (9%)	0.88
- Alcohol dependence	7 (14%)	6 (15%)	1 (9%)	0.56
- PTSD	3 (8.8%)	3 (8.8%)	0 (0%)	NA

a: Data missing for 2 patients; NA = not applicable; PTSD = post-traumatic stress disorder.

Table 2
Clinical and Electrophysiologic Tremor Diagnoses.

	All patients (n=87)	
	DBS neurologist clinical diagnosis	Electrophysiologic diagnosis
ET and ET plus	64 (74%)	63 (72%)
ET	38 (44%)	44 (51%)
ET plus	26 (30%)	19 (22%)
Combined tremor syndromes		
ET/parkinsonian tremor	11 (13%)	11 (13%)
ET/OT	1 (1%)	1 (1%)
ET/enhanced physiologic	1 (1%)	0
Mixed functional/ organic ET	7 (8%)	11 (13%)
Tremor associated w/ dystonia	1 (1%)	0
Functional	2 (2%)	1 (1%)

ET = essential tremor; OT = orthostatic tremor.

[17]: 38 (44%) had ET; 26 (30%) had ET-plus (coexistent rest tremor); 21 (24%) had combined tremor syndromes and 2 (2%) had clinically suspected functional tremor. For the 21 with combined tremor syndromes, 11 (13%) had ET with features of parkinsonism (excluding isolated rest tremor); 1 (1%) ET and orthostatic tremor; 1 (1%) bilateral upper limb tremor with dystonic head tremor, 1 (1%) medications that could enhance physiologic tremor, and 7 (8%) clinically suspected combined ET and functional tremor. In the 9 patients with either isolated functional or mixed ET/functional features, the functional feature most commonly observed was distractibility (n = 8).

3.3. Electrophysiology diagnosis of tremor

This is summarized in Table 2**.** In most cases, findings were consistent with ET: 44 (50%) had ET; 19 (22%) ET-plus (with rest component thought to reflect longstanding ET and not parkinsonian tremor), 11 (13%) mixed ET and parkinsonian tremor, 1 (1%) coexistent ET and orthostatic tremor. Twelve (14%) had functional tremor: 11 (13%) had features of both organic ET and functional overlay, and 1 (1%) had

isolated functional tremor.

The surface EMG findings of the 12 patients with functional tremor disorder are summarized in Table 3. The most common features in both mild and moderate-severe cases were distractibility (n = 9) and variability in tremor appearance or frequency (n = 7). Entrainment was uncommon (n = 2) and was only identified in moderate-severe cases.

Electrophysiologic tremor diagnosis matched clinical diagnosis in 59/87 (68%) of cases. Of the 28 cases with differing diagnoses, the majority (n = 20) were explained by amendment of ET or ET-plus diagnosis based on whether rest tremor was present. In the remaining 8 cases, electrophysiology newly identified functional tremor not suspected clinically (n = 5); organic ET where mixed ET with functional overlay had been suspected clinically (n = 2); and mixed ET with functional overlay where a purely functional tremor had been suspected clinically (n = 1). Electrophysiologic diagnosis was taken as final tremor diagnosis for the purposes of this study.

After completing clinical and electrophysiology evaluations, SEMG confirmed 12 patients with functional features. Of these, 6 had mild functional overlay with ET, 5 had moderate-severe functional overlay with ET, and 1 had isolated functional tremor. Of the 5 patients with functional features newly identified by SEMG, 4/5 were considered mild and offered surgery. One patient had clinical and electrophysiologic diagnoses of organic ET and dystonic head tremor. On electrophysiology, tremor in one arm varied in frequency > 2 Hz with holding a cup and distracted when tapping with opposite hand. Entrainment was not seen. Although electrophysiologic diagnosis debated between functional overlay vs dystonic tremor, the majority of electrophysiologic findings and disability were attributed to organic ET. In 1 patient with mixed functional and organic tremor where isolated functional tremor was suspected clinically, SEMG showed intermittent leg tremor concerning for functional tremor, but the more disabling bilateral upper limb tremor appeared organic. This patient underwent DBS with subsequent improvement.

Patients with functional features were significantly younger at DBS clinic evaluation compared to those with organic tremor (56 vs 72 years, p = 0.002). However, male sex (42% vs 65%, p = 0.12), mean age at tremor onset (30 vs 39 years, p = 0.16) and mean duration of tremor (26 vs 33 years, p = 0.24) were not significantly different between the two groups. There was no significant difference in major psychiatric diagnoses of anxiety or depression, childhood abuse or neglect, history of alcohol dependence, or post-traumatic stress disorder between the two groups.

Table 3
Features and Outcomes of Functional Tremor Disorders.

Clinical features suggestive of functional tremor (n = 9)	
Distractibility	8 (89%)
Entrainment	1 (11%)
Increased variability in tremor appearance and/or frequency	4 (44%)
Intermittent tremor	0
Poor tapping/indeterminate	0
Electrophysiologic features suggestive of functional tremor (n = 12)	
Distractibility	9 (75%)
Entrainment	2 (17%)
Increased variability in tremor appearance and/or frequency	7 (58%)
Intermittent tremor	1 (8%)
Poor tapping/indeterminate	1 (8%)
Recommendation from DBS Committee (n = 12)	
Motor retraining for functional movement disorder	6 (50%)
Referred for advanced therapy	6 (50%)
Outcomes from motor training referrals (n = 6)	
Did not attend motor retraining	
Tremor improved, no surgical intervention	3 (50%)
Tremor improved, re-evaluated and approved for DBS surgery	2 (30%)
Outcomes from motor training referrals (n = 6)	1 (17%)
Did not attend motor retraining	

3.4. Outcomes of management of functional tremor

All organic tremor cases (n = 75) and the 6 cases with ET plus mild functional features were approved for surgery, as the predominant tremor disability was attributed to ET.

Of the 6 patients with mild mixed features, one chose not to pursue surgery. The remaining 5 patients underwent DBS of the bilateral ventral intermediate (Vim) nucleus of the thalamus with clinical and FTM score improvement at the second post-operative programming visit. However, one patient had residual tremor despite programming adjustments, and repeat electrophysiology study 1 year post-operatively demonstrated prominent distractibility and tremor variability consistent with a residual isolated functional tremor disorder. This patient was referred for motor retraining.

Of the 6 patients with moderate-severe functional tremor referred for motor retraining, 3 were lost to neurologic follow-up and 3 completed the motor retraining program: 1 reported significant improvement and no longer required medical treatment and 2 reported partial improvement with residual disabling tremor. One of these had a follow-up neurologic examination and SEMG study demonstrating residual organic ET; this patient chose to continue strategies acquired from motor retraining rather than pursue surgical options. The other patient had improvement of functional tremor, with residual organic ET confirmed on repeat clinical and electrophysiologic exams. After review by the DBS committee, this patient was approved for bilateral Vim thalamic DBS, with clear improvement in tremor after the first programming visit. The patient elected to continue subsequent programming locally.

4. Discussion

This study highlights the important finding that functional tremor features are relatively common amongst surgical referrals for medication-refractory ET. In our DBS clinic, 12 of 87 (14%), or approximately 1 in 7, patients had electrophysiologically-confirmed functional tremor, frequently superimposed on ET. Five of these patients (6%) avoided unnecessary surgery. Conversely, one patient with a clinical diagnosis of isolated functional tremor was found to have mixed functional and organic tremor on electrophysiology; as their predominant disability arose from organic tremor, this patient underwent DBS with improvement. In patients with clinically mild functional tremor, where the main disability arose from ET, the presence of functional tremor did not change the decision to approve for surgery. However, it was important to recognize and document preoperative functional features, as persistent and refractory post-operative tremor could be mistakenly perceived as suboptimal DBS surgery, as occurred in one patient. Thus, recognition and correct diagnosis of tremor disorders has very important implications for neurosurgical treatment practices.

This study highlights the challenges to accurately diagnose functional tremor disorders. While most of our cases had coexistent ET, the functional features were often not clinically suspected prior to DBS referral. Functional tremor can be misdiagnosed as organic tremor over decades, resulting in potentially unnecessary medical and surgical treatments. Experienced movement disorders neurologists have a valuable role, as functional tremor was first suspected clinically in 9 of 87 cases by the DBS neurologist, despite a longstanding ET diagnosis determined by previous general or movement disorders neurologists. However, as not all cases of functional tremor were identified clinically, electrophysiology can improve the sensitivity and specificity of the clinical tremor diagnosis [13]. Furthermore, it can help stratify the presence of mixed functional tremor and organic ET, and their severities relative to each other. Thus, 7 of 9 clinically suspected functional tremors were confirmed by electrophysiology, and an additional 5 cases with functional features were newly identified. Ultimately, in our study cohort, 5 potential brain surgeries were averted.

The use of electrophysiology for tremor evaluation is part of our institution's standard pre-surgical tremor workup and is also used in tremor characterization for patients who are not being considered for surgery [16]. Center for Medicare Services compensates approximately $200 for the study (utilizing billing CPT codes 96,002 for surface EMG technical, 96,004 for surface EMG physician interpretation, and 95,999 for accelerometry) compared with DBS reimbursement of about $29,000 and MRgFUS reimbursement of about $15,000 [19,20]. For our cohort of 87 patients, surface electrophysiology studies would be estimated to total $17,400 for all patients. The savings from avoiding 5 bilateral DBS surgeries (5 × $29,000 = $145,000) or MRgFUS thalamotomies (5 × $15,000 = $75,000) far outweighed the cost of surface electrophysiology. This makes the case for acknowledging the value of electrophysiology studies to help guide appropriate patient selection for surgery.

This study had some limitations. The occurrence of functional tremor amongst DBS referrals may have been higher at our institution, a quaternary referral center; thus, there may have been referral bias for patients with complex or refractory tremor disorders, which may be more likely to include patients with functional disorders. It would be helpful to replicate this study in other DBS centers, to compare the frequency of functional tremor disorders in DBS clinics. Due to the retrospective nature of this study, and lack of "gold standard" for movement electrophysiology testing, the electrophysiology study was not uniform for all patients and did not routinely include all aspects of previously validated electrophysiologic criteria for functional tremor, including coactivation and ballistic movements [12,13].

Future studies could include these criteria as a standard part of pre-surgical electrophysiologic testing. Additionally, distinguishing between dystonic and functional tremors is difficult and similarly lacks a gold standard for evaluation [15]. While a dystonic versus functional component was suspected in one patient with organic ET and dystonic head tremor who was offered DBS, proposed criteria for distinguishing dystonic tremor and functional tremor were not uniformly applied to all patients with suspected functional component to tremor [15]. Finally, while we described the prevalence of psychiatric diagnoses, this study was not powered to identify differences in diagnoses between groups.

Strengths of this study included the large cohort of consecutive patients examined by experienced movement disorders clinicians in the DBS clinic. Moreover, all patients underwent standardized preoperative evaluations, including SEMG in a single laboratory by trained movement disorders clinicians with a tremor study protocol [18], which also provided a "second clinical opinion" of the tremor. Finally, our institution is one of a few nationwide with a motor retraining program for functional movement disorders, providing an alternative treatment pathway [21]. For potential surgical candidates with a functional component to tremor, treatment of functional movement disorder and repeat neurologic evaluation could occur in the same medical center. In several cases, motor retraining eliminated the need for surgery. In other cases, sequential motor retraining and DBS surgery provided tailored treatment for each tremor component.

In summary, surface electrophysiology can identify features of functional tremor disorder, which can have significant implications in pre-surgical evaluation for medication-refractory ET. Accurately diagnosing functional tremor can potentially avoid the risks and costs of unnecessary surgery.

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CRediT authorship contribution statement

Claudia Z. Chou: Conceptualization, Methodology, Investigation, Data curation, Writing – original draft, Writing – review & editing, Visualization. **J. Eric Ahlskog:** Investigation, Writing – review & editing. **Bryan T. Klassen:** Investigation, Writing – review & editing. **Elizabeth A. Coon:** Investigation, Writing – review & editing. **Farwa Ali:** Investigation, Writing – review & editing. **James H. Bower:** Investigation, Writing – review & editing. **Rodolfo Savica:** Investigation, Writing – review & editing. **Anhar Hassan:** Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft, Writing – review & editing, Visualization, Supervision, Project administration.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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