Reviews

Non-invasive Brain Stimulation for Essential Tremor

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Abstract

Background: There is increasing interest in the use of non-invasive brain stimulation to characterize and potentially treat essential tremor (ET). Studies have used a variety of stimulation coils, paradigms, and target locations to make these observations. We reviewed the literature to compare prior studies and to evaluate the rationale and the methods used in these studies.

Methods: We performed a systematic literature search of the PubMed database using the terms "transcranial," "noninvasive," "brain stimulation," "transcranial magnetic stimulation (TMS)," "transcranial direct current stimulation (tDCS)," "transcranial alternating current stimulation (tACS)," and "essential tremor."

Results: Single pulses of TMS to the primary motor cortex have long been known to reset tremor. Although there are relatively few studies showing alterations in motor cortical physiology, such as motor threshold, short and long intracortical inhibition, and cortical silent period, there may be some evidence of altered intracortical facilitation and cerebello-brain inhibition in ET. Repetitive TMS, theta burst stimulation, tDCS, and tACS have been applied to human subjects with tremor with some preliminary signs of tremor reduction, particularly in those studies that employed consecutive daily sessions.

Discussion: A variety of stimulation paradigms and targets have been explored, with the increasing rationale an interest in targeting the cerebellum. Rigorous assessment of coil geometry, stimulation paradigm, rationale for selection of the specific anatomic target, and careful phenotypic and physiologic characterization of the subjects with ET undergoing these interventions may be critical in extending these preliminary findings into effective stimulation therapies.

Keywords: Essential tremor, neuromodulation, non-invasive brain stimulation, motor physiology

Citation: Shih LC, Pascual-Leone A. Non-invasive brain stimulation for essential tremor. Tremor Other Hyperkinet Mov. 2017; 7. doi: 10.7916/D8G44W01

Introduction

Tremor is a distinct neurological symptom present among many entities, including Parkinson's disease, essential tremor, multiple sclerosis, and dystonia. Tremor can also occur after neurologic insults, including infarct or head trauma. Depending upon tremor characteristics, treatment of tremor can often be difficult and may respond variably to medications that may be effective for one type of tremor but not another. Essential tremor (ET) is the most common form of tremor affecting 4.8–6.7 million people in the United States.[1] It occurs in the absence of other neurologic signs suggestive of cerebellar degeneration or parkinsonism,

although there is debate concerning how variation in the clinical phenotype might suggest differing pathologic mechanisms. Rather, it seems likely that essential tremor is a heterogeneous collection of tremor disorders with varying degrees of severity and pathologic substrates.[2]

Neurophysiological studies can be helpful in characterizing and confirming the presence of tremor. Tremor can be distinguished from other disorders of movement by the presence of rhythmic sinusoidal alternating motion of agonist and antagonist muscles at a joint.[3] Although there are mechanical and mechanical reflex contributions to tremor, the presence of a central oscillator coherent with muscular activity defines tremor of central nervous system origin.[4] Oscillatory

motor unit activity is the central neurophysiological feature of tremor and has generated considerable interest in elucidating the precise interaction between various nodes of the tremor network. There is increasing interest in the use of non-invasive brain stimulation techniques such as transcranial magnetic stimulation (TMS) or transcranial current stimulation (tCS) as research tools to investigate the neurophysiology of tremor. In this article we review prior studies using TMS or tCS to gain insights into the neurobiology and pathophysiology of ET, as well as the evidence for potential therapeutic benefit.

Methods

We performed a systematic literature search of the PUBMED database using the terms "transcranial," "noninvasive," "brain stimulation," "transcranial magnetic stimulation," "transcranial direct current stimulation," "transcranial alternating current stimulation," and "essential tremor." The search was performed in December 2016 and included articles published in the English language from 1993 to 2016. This search strategy revealed 43 articles. Articles published in peer-reviewed journals reporting non-invasive brain stimulation studies on human subjects with ET were included in the review. Review articles were considered only if they included data from non-invasive brain stimulation studies on human subjects not otherwise reported. Studies involving transcranial focused ultrasound were excluded from this review. We also reviewed relevant articles that were present in the references sections of identified papers.

Non-invasive brain stimulation: neurophysiology studies in tremor

Transcranial magnetic stimulation over the primary motor cortex has been used to perturb and assess motor unit physiology. A single magnetic pulse delivered to the scalp overlying the motor cortex at appropriate stimulation intensity can result in a current strong enough to elicit a twitch or contraction of a contralateral target muscle that can be recorded electromyographically as a motor evoked potential (MEP). This allows us to assess corticospinal projections but also transiently disrupt cortical activity and assess the impact on ongoing tremor. It is important to realize that it remains unclear whether the net physiologic effect of TMS on the underlying cortex is consistently excitatory or inhibitory.

In addition, TMS paradigms can be used to assess features of motor physiology such as cortical excitability, plasticity, or inhibition within local interhemispheric circuits.[5]

Tremor is most frequently expressed in the limb at the finger or wrist joints, especially in the case of ET. Recordings of limb tremor, as such, have been measured using simple accelerometers or surface electromyography. The relative contributions of the central and the peripheral nervous system in the generation of tremor can be separated when evaluating the presence of the mass invariant frequency peak obtained in individuals with ET.[6] Although initial reports suggested that there was no coherence between peripheral limb tremor and motor cortex,[7] Electroencephalography and electromyography analysis has

reproducibly measured high degrees of corticomuscular coherence in ET in several studies,[8] suggesting a strong contribution by the motor cortex in the pathogenesis of tremor.

The motor cortex has been studied extensively, beginning with the observation that single pulse TMS applied to the M1 hand region can reset tremor.[9,10] These observations implicated the role of the motor cortex in the relay of descending impulses to corticospinal tract neurons or other subcortical structures, between intracortical structures, or in the peripheral feedback of the induced muscle twitch.[9] The resting motor threshold as a measure of cortical excitability has been studied several times in ET, with consistent results showing that resting motor thresholds are unchanged in ET versus healthy controls.[11–14] Cortical silent periods appear to be unchanged in ET.[14,15] Similarly, when local inhibitory circuits have been assessed via short and long intracortical inhibition (SICI and LICI), differences between ET and healthy controls have not been found.[14,16] However, at least one study suggests that ET subjects have reduced intracortical facilitation compared with healthy controls.[13] Additionally, although deep brain stimulation (DBS) of the ventrointermedialis thalamus is effective for ET, the influence it exerts on measures of cortical excitability is still unclear; Molnar et al.[13] show that although active DBS facilitates MEPs, it does not have any effect on local inhibitory or facilitatory circuits assessed by SICI, LICI, or ICF. Taken together, neurophysiological measures show surprisingly few differences in motor cortical physiology in patients with ET compared with healthy controls (Table 1).

Modification of physiologic properties in ET by behavioral tasks have also been attempted to ascertain whether certain responses to stimulation paradigms help differentiate ET from healthy controls or other forms of tremor. Several interesting applications of this have been exemplified by procedures involving simple motor imagery and variable positioning of the upper limb and touch kinematics. Lo et al.[11] tested the use of motor imagery on resulting MEPs. Imagery facilitated MEPs in healthy controls, but it did not in ET subjects, suggesting deficient motor imagery processes in affected subjects. Relevant to the effect that change in posture can have on tremor severity, Mazzocchio et al.[12] examined how arm and shoulder posture in either an anterior or adducted position might influence MEPs compared with a posterior or abducted position. MEPs were facilitated in both healthy controls and ET subjects in the abducted position, with the authors concluding that sensory information from the shoulder abducted position might act as an energizing influence on tremor cells in the thalamus. In Avanzino et al.[17], touch duration and intertapping intervals were found to be abnormal in ET versus healthy controls. When cerebellar repetitive TMS at 1 Hz was applied, these values normalized, which was not seen after sham stimulation.

There is extensive evidence for alteration of function in the cerebellum and thalamus, in addition to the motor cortex, in patients with ET.[18,19] Post-mortem findings in ET raise the possibility of Purkinje cell dysfunction and cell loss with accompanying alterations in their synaptic connections,[20–25] and multiple imaging studies suggest widespread alterations in white matter, cerebellar gray matter, and deep cerebellar nuclei compared with healthy controls.[26–32] However, there

Table 1. Summary of Neurophysiological Studies in ET, by Year of Publication

Study	Methods Evaluated	TMS Measures Assessed	Findings
Britton et al.[10]	Single pulse TMS M1 (suprathreshold)	Tremor phase, resetting index	Pulse to M1 resets ET tremor and PD tremor phase; latency to first peak significantly longer in PD tremor than ET tremor
Pascual-Leone[9]	Single pulse TMS M1 (suprathreshold)	Tremor phase	Pulse to M1 resets tremor motor unit activity; resetting correlated with stimulus intensity and duration of post-stimulus silent period
Romeo et al.[14]	Single pulse TMS M1	Resting motor threshold, CSP, SICI	No difference in ET subjects compared to HC
Pinto et al.[34]	Single pulse TMS cerebellum and paired pulse TMS: Cerebellar-M1	MEP, CBI, tremor phase	Did reduce MEP at ISI 5–7 ms, but degree of inhibition not different in ET vs. HC (n=9 vs. 10) No tremor reset with cerebellar TMS but there was w/ M1 TMS
Shukla et al.[15]	Single pulse TMS M1, maximum stimulatory intensity	CSP	No statistically significant difference between ET subjects and HC; no correlation with disease duration
Molnar et al.[13]	Single pulse TMS M1 with and without active DBS	MEPs, SICI, ICF, LICI	DBS facilitates MEPs especially at higher intensities; DBS has no effect on SICI or ICF, nor LICI ET subjects had reduced ICF at rest compared to HC but otherwise SICI, LICI and active ICF were no different from HC
Lo et al.[11]	Motor imagery before and during single pulse TMS measures to M1	RMT and MEPs	Motor imagery increase MEPs in HC but not ET; RMT were reduced during motor imagery in HC and ET
Mazzocchio et al.[12]	Single pulse TMS to M1 in both adducted and abducted shoulder positions	MEPs	In subjects with ET, MEPs were facilitated in the abducted position, similar to HC, opposite of those with parkinsonian tremor
Avanzino et al.[17]	Cerebellar rTMS using figure of 8 coil, handle up, right lateral cerebellum, 1 Hz at 90% RMT for 10 minutes	Touch duration and intertapping interval	At baseline, ET subjects have longer touch duration (TD) and shorter intertapping interval (ITI); 1 Hz TMS appear to restore TD and ITI to normal values
Chuang et al.[16]	Premotor and motor cTBS	MEP, SICI, Tremor frequency and amplitude	cTBS reduces MEP in both HC and ET, but less durable in ET subjects; Reduces SICI No change in tremor frequency but significantly reduced tremor amplitude
Lu et al.[33]	Single and paired pulse TMS (LICI paradigm) to M1, SMA and cerebellum	Tremor reset	M1 and SMA single pulse resets postural tremor in ET subjects Cerebellar single and paired pulse TMS did not reset postural tremor in ET

Table 1. Continued

Study	Methods Evaluated	TMS Measures Assessed	Findings
Brittain et al.[50]	Cerebellar transcranial alternating current (tACS): active electrode (35 cm^2): 3 cm lateral to inion	Frequency tolerance (stability of tremor over range of tremor frequencies)	ET has narrow frequency tolerance while PD tremor has broad frequency tolerance Cerebellar tACS is able to entrain ET tremor more than PD tremor
Hanajima et al.[40]	Paired pulse cerebellar-M1 pulse using double cone 110-mm coil	CBI	CBI reduced in ET compared to HC

Abbreviations: CBI, Cerebello-brain Inhibition; cTBS, Continuous Theta Burst Stimulation; CSP, Cortical Silent Period; DBS, Deep Brain Stimulation; ICF, Intracortical Facilitation; ISI, Interstimulus Interval; LICI, Long Intracortical Inhibition; M1, Primary Motor Cortex; MEP, Motor Evoked Potential; RMT, Resting Motor Threshold; rTMS, Repetitive TMS; SICI, Short Intracortical Inhibition; SMA, Supplementary Motor Area; tACS, Transcranial Alternating Current Stimulation; TMS, Transcranial Magnetic Stimulation.

is considerable debate as to the nature of the cerebellar dysfunction in ET and whether it is mediated through superficial or deep cerebellar structures. The role of the cerebellum in tremor physiology in vivo has yet to be established.

Single TMS pulses to M1 have been shown to reset ET, but single TMS pulses to the cerebellum have not.[33,34] It is unclear whether inefficient coil geometry or current shunting across cerebrospinal fluid spaces prevents direct stimulation of the relevant hand motor regions in the cerebellum. Paired pulse TMS between cerebellum and primary motor cortex can yield additional insights by measuring cerebellar physiology directly.[35] Single TMS pulses to the cerebellum reduce motor potentials elicited by motor cortex stimulation when given after a 5–7-ms delay after the cerebellar conditioning pulse.[36] This measure, termed cerebello-brain inhibition (CBI), is thought to be mediated by potentiation of Purkinje cell inhibition of dentatothalamic output, and therefore likely to be useful for interrogating the cerebellothalamocortical pathway[35,37] and to provide a strong basis for any potential therapeutic effect of cerebellar stimulation on tremor. CBI is reduced in subjects with degenerative cerebellar disease,[38,39] but there are conflicting reports on whether CBI is altered in subjects with ET compared with healthy controls.[34,40] Pinto et al.[34] and Hanajima et al.[40] both used 110-mm double cone coils with the cerebellar stimulus set at 95% of the active motor threshold to perform the measure. However, Pinto et al. found no reduction in CBI compared with healthy controls, whereas Hanajima et al. found a significant reduction in the ET cohort compared with controls. There was a slight difference in targeting, with Hanajima et al. targeting the midpoint between the inion and mastoid and Pinto et al. targeting 3 cm lateral to the inion along the inion–mastoid line. The two studies also differed in the number of study participants, with twice as many studied by Hanajima et al. It is unclear whether these differences could account for the different observations, but further studies will be helpful in resolving the issue, especially if neuronavigated TMS with imaging-based targeting is employed.

Non-invasive brain stimulation: studies of potential therapeutic effect on tremor

Although single and paired pulse paradigms provide information on the underlying physiology, TMS applied at varying frequencies and locations might be used to modulate a network in a specific manner to reduce symptoms. Low-frequency (1 Hz or less) repetitive stimulation of the motor cortex is thought to be inhibitory, whereas high frequency (5 Hz) is thought to be excitatory to motor circuits. Non-invasive brain stimulation has been relatively underexplored as a treatment option for ET. There have been at least seven studies conducted in human subjects with ET to assess preliminary efficacy in reducing tremor (Table 2).

Although repetitive TMS (rTMS) to the primary motor cortex has been extensively studied in Parkinson's disease symptoms, including tremor, direct targeting of M1 with rTMS to suppress tremor in ET has not been reported. Repetitive TMS to the cerebellum however has been studied, with variable results. Gironell et al.[41] studied acute effects of a single session of cerebellar rTMS at 1 Hz using a 70-mm butterfly coil at 100% maximal stimulator intensity in 30 trains lasting 10 seconds each for a total of 300 pulses. At 5 minutes up to 60 minutes, no changes were seen in either accelerometric recordings of hand tremor nor the Tremor Rating Scale.[41] Cerebellar rTMS was also studied by Popa et al. but using a much greater exposure to stimulation, consisting of five daily sessions of 1 Hz cerebellar rTMS, with each session consisting of 15 minutes for each cerebellar hemisphere, a total of 1,800 pulses each day for five days.[42] Improvement in the Tremor Rating Scale of approximately 23% was seen over the 3-week time frame. Tolerability of the stimulation procedures was good with no adverse effects reported. Aside from differences in total exposure to stimulation, there were important differences in coil geometry and target location between the two studies. Gironell et al. targeted their coil 2 cm below the inion, whereas Popa et al. used neuronavigation with magnetic resonance imaging to target their figure-of-eight coil over cerebellar lobule VIII, thought to represent the hand motor region. It remains unclear whether other locations in the cerebellum might be optimal for

Table 2. Summary of Clinical Studies of Transcranial Stimulation in ET, by Year of Publication

Study	Method of Stimulation	Target Location	Method of Assessment	Outcome
Gironell et al.[41] (n=10 ET)	Single session repetitive cerebellar TMS, 1 Hz, 70 mm butterfly coil, 100% maximal output, 30 trains of 10 seconds each	2 cm caudal to inion	Tremor Rating Scale (TRS), accelerometry	Improved TRS and accelerometry ratings at 5 minutes but returned to baseline by 60 minutes
Hellriegel et al.[46] (n=20 total, 10 ET)	Single session of 40 seconds of continuous theta burst stimulation: 50 Hz, figure of 8 coil, 80% active motor threshold vs. 30% AMT (control intervention)	Primary motor cortex	TRS, accelerometry, MEPs	Improved accelerometry 45 minutes after cTBS, not TRS clinical scores; also real cTBS did not reduce MEP in ET subjects but did in HC
Popa et al.[42] (n=22 total, 11 ET)	Five sessions of repetitive cerebellar TMS 1 Hz, figure of 8 coil, daily × 5 days, 90% resting motor threshold, 900 pulses over 15 min, to each cerebellar hemisphere	Cerebellar lobule VIII (neuronavigated)	TRS	TRS total improved by 23% at day 29
Gironell et al.[48] (n=10 ET)	Transcranial direct current stimulation (tDCS): 2 cathodal electrodes (25 cm^2), 2 mA × 20 minutes, 10 consecutive sessions	Both cerebellar hemispheres, 3 cm lateral to the inion	TRS, accelerometry, disability rating scale	No change at day 1, day 10 or day 40 in either TRS or accelerometry
Bologna et al.[47] (n=27 total, 16 ET)	Single session cerebellar continuous theta burst stimulation: 50 Hz stimulation repeated 5 Hz over 40 seconds at 80% of active motor threshold, figure 8 coil	3 cm lateral and 1 cm below the inion	Cortical excitability, tremor frequency, tremor amplitude	Cerebellar cTBS reduced MEPs in HC but not ET cohort Intervention had no effect on TRS, tremor frequency or smoothness of reaching movements
Badran et al.[44] (n=10 ET)	15 daily sessions of 1 Hz rTMS to pre-SMA, butterfly coil for 20 minutes each; sham-controlled	Halfway between Fz and FCz	TRS	23% reduction in TRS vs 18% reduction in sham-TMS
Helvaci Yilmaz et al.[49] (n=6 ET)	10 daily weekday sessions of anodal tDCS to the dorsolateral prefrontal areas and inion at 2 mA for 20 minutes + 5 more tDCS sessions as above, delivered every other day after 30 days from initial intervention	Prefrontal areas (Fz and C4)	TETRAS motor and ADL rating scales	Statistically significant difference in TETRAS-motor 20% and TETRAS-ADL 17% at 50 days compared to pre-intervention baseline

Abbreviations: tDCS, Transcranial Direct Current Stimulation; TETRAS, The Essential Tremor Rating Assessment Scale; TRS, Tremor Rating Scale (Fahn Tolosa Marin).

suppressing tremor, or what exact cerebellar structures are influenced by rTMS depending on coil position.[43] In addition, coil design may play a significant role in determining whether stimulation is able to reach deeper structures which may be required to mediate the desired motor effects.[43] Specifically, the flat figure-of-eight coil may be inferior to a double cone or butterfly-shaped coil for affecting deep cerebellar structures[43] that may actually be required to generate motor effects.

Repetitive TMS has also been applied to the pre-supplementary motor area (pre-SMA) in a sham-controlled pilot study to assess preliminary efficacy in ET.[44] Badran et al.[44] tested 10 subjects with ET in a sham-controlled clinical trial using rTMS over pre-SMA at 1 Hz for 20 minutes per session over 15 daily sessions. Although Tremor Rating Scale scores declined by 23% in the active group, they also declined 18% in the sham group, barely reaching statistical significance.

Newer forms of stimulation have also been investigated in ET. To address the short duration of after effects from rTMS, theta burst stimulation (TBS), which applies repetitive TMS in protocols consisting of three stimuli given at 50 Hz, repeated at 5 Hz, has been applied in many experimental situations where a longer lasting effect on cortical excitability is desired. When applied as continuous TBS to the motor cortex, MEPs are robustly suppressed compared with when delivered as intermittent TBS, where MEPs become facilitated.[45] Two studies have examined continuous TBS (cTBS) in ET, one to the primary motor cortex and one to the cerebellum. Hellriegel et al.[46] applied cTBS to the motor cortex and observed reduced MEPs in healthy controls but not in ET subjects. ET subjects' tremor power was reduced on accelerometry, but no change was observed in clinical tremor rating scores. Bologna et al.[47] applied cTBS to the cerebellum, targeting 3 cm lateral and 1 cm below the inion. They observed again that MEPs were reduced in healthy controls but not in ET subjects, and there was no alteration of tremor frequency, displacement or change in the clinical rating of tremor.

Finally, as rTMS can cause some local discomfort to the posterior head and neck musculature, electrical stimulation in the form of transcranial direct current (tDCS) and transcranial alternating current stimulation (tACS) have also begun to be used in various experimental paradigms. Two studies have evaluated their use in ET. Gironell et al.[48] applied cathodal electrodes over bilateral cerebellar hemispheres 3 cm lateral to the inion, with the anode over the forehead, and delivered a 2-mA current for 20 minutes per session over 10 consecutive sessions. Tremor Rating Scale or accelerometric recordings of tremor were unchanged immediately after and at day 10 and day 40 of follow-up assessment. Helvaci Yilmaz et al.[49] assessed the impact of 10 daily weekday sessions of anodal tDCS to the dorsolateral prefrontal areas and inion at 2 mA for 20 minutes with five additional tDCS sessions, delivered every other day, starting 30 days after the initial intervention. Although the authors did not provide a rationale for the chosen target, they reported a statistically significant reduction in The Essential Tremor Rating Assessment Scale (TETRAS)-motor (20%) and TETRAS-Activities of Daily Living (17%) at 50 days compared with pre-intervention baseline scores. Brittain et al.[50] used tACS to assess whether temporal stability of ET tremor versus parkinsonian tremor frequency

was correlated with how well tremor could be entrained by the alternating current stimulation applied to the cerebellum. They found that ET tremor was much more easily entrained, and those with a narrow range of frequencies were even more likely to be entrained. This suggests that a single neural oscillator or multiple strongly entrained oscillators are more likely to be present in ET tremor versus parkinsonian tremor, which may have several underlying oscillators contributing to the broader frequency range it exhibits. These findings could suggest that tACS might hold some therapeutic promise in ET. It remains to be seen if tACS could be applied successfully to ET using phases associated with tremor suppression, as demonstrated in earlier studies in Parkinson's tremor.[51]

Implications for future targets and stimulation paradigms

A variety of stimulation methods have been applied to ET, but it is apparent that the precise stimulation paradigm and location of the target have varied substantially. Most studies have aimed to suppress MEPs, either directly through motor cortex stimulation or indirectly through cerebellar stimulation, although it is not known how effective our currently available strategies are at doing so. Studies to replicate the findings have been scarce, and it is conceivable that variation in the stimulation paradigm or a slight difference in the target location might influence the effectiveness of the stimulation and outcome on tremor severity. We also make considerable assumptions that relevant target structures are reachable by current coil technologies and stimulation paradigms. There is increasing rationale to target the cerebellum, and recent neuroimaging studies make it possible to target specific motor networks[52] involving structures functionally connected to the cerebellum. Further work in modeling and assessing whether new prototypes of deep field non-invasive brain stimulators may yield important new advances in the field of non-invasive brain stimulation for tremor. As the field begins to generate information that promises to converge neuroimaging and neurophysiologic techniques, we may have increased ability to test whether modulation of specific elements of the tremor network identified in neuroimaging experiments could be harnessed for therapeutic benefit in ET. However, in pursuing such goals, careful phenotypic characterization of the patients, quantitative approaches to characterize the tremor, appropriately powered studies, careful neurophysiologic guidance of the intervention, and methodological precision are imperative.

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