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Computational modeling to improve treatments for essential tremor

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Abstract

Essential tremor (ET) is a neurological disorder of unknown etiology that is typically characterized by an involuntary periodic movement of the upper limbs. No longer considered monosymptomatic, ET patients often have additional motor and even cognitive impairments. Although there are several pharmacological treatments, no drugs have been developed specifically for ET [1], and 30–70% of patients are medication-refractory [2]. A subset of medication-refractory patients may benefit from electrical deep brain stimulation (DBS) of the ventral intermediate nucleus of the thalamus (VIM), which receives cerebellar inputs. Abnormal cerebellar input to VIM is presumed to be a major contributor to tremor symptoms, which is alleviated by DBS. Computational modeling of the effects of DBS in VIM has been a powerful tool to design DBS protocols to reduce tremor activity. However, far less is known about how these therapies affect non-tremor symptoms, and more experimental and computational modeling work is required to address these growing considerations. Models capable of addressing multiple facets of ET will lead to novel, more efficient treatment.

Introduction

ET is the most common neurological movement disorder that affects 4–5% of the adult population [3,4] and is up to twenty times more prevalent than Parkinson's Disease (PD) [5]. Upper limb tremor, and occasionally head and neck tremor, are the predominant symptoms of ET. Limb tremor usually appears with movement, sometimes with sustained postures, and is not usually present at rest [6,7].

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Despite mounting evidence to the contrary, ET is still often described as ‘benign’, an antiquated term that referred to the idea that ET was thought of as monosymptomatic and non-debilitating [8,6,9,10]. In reality, ET is a progressive disorder, possibly neurodegenerative, and can present with additional motor deficits of tandem gait and balance for up to half of patients, consistent with evidence implicating cerebellar pathology [11–13] (and see [9,14]). The precise mechanism by which these deficits contribute to tremor and non-tremor symptoms are not fully known [6,15].

Postural and intentional tremor are clearly the most prominent symptoms, but other non-tremor motor deficits have also been noted [16–22], though they are less obvious than the primary symptom of tremor and sometimes subclinical [6]. The most common problems concern tandem gait abnormalities [20,22,23], but several additional deficits have also been observed, including difficulty maintaining postural control [16], abnormal timing of ballistic movements [17], impaired finger tapping [18], impaired eyeblink conditioning [19], and deficits in motor learning [21].

Additionally, a growing body of work has demonstrated non-motor, cognitive symptoms in ET patients [24,25], including depression [26], apathy and anxiety [27], and changes in personality [28]. Tremor can even be detrimental for patients to the point of substantial social anxiety and depression [6,29]. Some studies have also suggested an increased probability of ET patients being diagnosed with Parkinson's Disease (PD) (reviewed in [30]). Regardless of whether ET is a neurodegenerative disorder [31], it is more complex than traditionally believed [6,32], and this growing body of evidence represents an opportunity for additional experimental and computational work to understand and define the disease more fully, toward improving all aspects of treatments.

Deep brain stimulation can be an effective treatment for tremor

The first line medications to treat ET include primidone, a barbiturate whose metabolite acts as a GABA_A-receptor agonist, and propranolol, a beta-adrenergic agonist with possibly both central and peripheral action [1]. Several additional drugs such as the anticonvulsant topiramate have been tested, but to date, no drugs exist that are specific to treat ET [1,33]. For those patients that do not respond to medication [2], deep brain stimulation (DBS) is sometimes available as a treatment to alleviate tremor.

Electrical stimulation of the thalamus for cessation of tremor was demonstrated in the 1960s [34], and the modern era of DBS in ET and PD was heralded in the 1980s [35,36]. DBS is also being investigated to treat Alzheimer's Disease [37,38], depression, obsessive-compulsive disorder, and other neurological diseases (see [39]). In its present form, DBS involves stereotactically guided surgical implantation of a multi-contact electrode at the stimulation site, connected to a subcutaneous stimulator and battery implanted in the chest wall just under the clavicle.

In most cases, DBS of the ventral intermediate nucleus of the thalamus (VIM) is an effective treatment of tremor in ET, but some patients do not respond [40], and DBS is sometimes associated with certain deficits in gait and balance [41] or speech [42,43] and can become

less effective over time [44,45]. Stimulator programming is typically performed by a neurologist to minimize tremor while avoiding side effects such as paresthesias, but it is not clear to what extent additional symptoms are also treated.

The evidence on the efficacy of DBS to treat gait and balance issues is also not clear. With both unilateral and bilateral DBS, increased problems with gait have been reported [46], but these differences may be highly individual [41]. Optimizing stimulation to address this problem along with tremor may be helpful, as one report found that over-stimulation led to increased problems with gait that was not present at reduced stimulation levels [23,47].

Ultimately, DBS provides tremor relief in particular for a substantial portion of patients, but its impact on other symptoms is less well understood. DBS may be improved with a better mechanistic understanding of tremor and non-tremor symptoms of ET, and computational modeling has been a valuable tool in designing operational DBS parameters. To date, DBS modeling studies have focused largely on reducing tremor rather than non-tremor symptoms. Here we review computational modeling efforts that have helped to shape understanding of DBS mechanisms. We propose that future improvements in DBS for movement disorders can leverage prior modeling insights and benefit from experimental and computational studies considering non-tremor symptoms.

Overview of computational modeling

Computational modeling relies on mathematical description of activity in the brain to identify underlying mechanisms and to provide testable hypotheses for experiments (Fig. 1). In particular, conductance-based network models strive for a description of cellular and circuit-level interactions that underlie brain activity, such as oscillatory electrical signals or other dynamically changing states (Fig. 1a and b). These models often rely on a system of ordinary differential equations describing the membrane dynamics of individual cells and their synaptic interactions [48,49]. Of course, models necessarily represent reduced representations of activity; as such, they are often difficult to constrain meaningfully [50], and no perfect model exists. Nevertheless, just as animal disease surrogates are invaluable to biomedical research, it is possible to utilize computational modeling with specific constraints derived from human and non-human primate data where available to accurately capture relevant features of neural activity. This approach may accelerate the development of novel therapeutic targets and strategies and may be more effective than experimental work alone.

Leveraging computational models for understanding ET

A growing number of computational models have been published to address various aspects of dysfunction and treatment in ET, with most focused on understanding how pathological tremor oscillations in the brain are suppressed by DBS. Yet to our knowledge, none of these models have aimed to address non-tremor symptoms of ET that appear to be highly prevalent and not necessarily related to a specific oscillatory mode. Numerical simulations of the effects of DBS have been successful in helping to understand what was historically described as ‘benign essential tremor’; our present understanding of the far more

complicated profile of ET beyond tremor represents an opportunity for computational modeling to work toward understanding how non-tremor symptoms are affected by DBS.

Multiple levels of mathematical description exist to characterize the electrical fields induced by DBS and the resultant impact on neural circuits. The most descriptive of the field effects of DBS takes into account specific electrodes [51,52], including spatial geometry and materials of the electrodes using finite element modeling (FEM) in 3-space [53] and has shown the importance of explicitly accounting for tissue and electrode capacitance [54] and impedance [55] (Fig. 1c). These detailed models typically calculate the electric field due to the DBS electrode stimulation and apply it to a separate neural model, though these steps can also be done in the same framework, with each approach valid under specific assumptions [56]. Often, model simplifications are possible and informative; under certain assumptions, the electric field from the DBS electrode reduced to a point electrical source [45]. Further model simplifications have also been considered, which can have the advantage of being amenable to mathematical analysis. In the simplified models, DBS is often represented as an injected current, an additive term to the membrane voltage equation for cells [57,58].

Cells stimulated by DBS are often modeled with a class of compartmental models representing different cell structures (e.g. soma, dendrites, axons) using Hodgkin-Huxley-type systems of coupled ordinary differential equations [59] (Fig. 1a and b). The FEM electrical field solution of the DBS model is applied as an extracellular current term to cell compartments. These models have been successful at a variety of spatial scales, from the level of understanding the impact on cellular components to a broader level description of the effect of stimulation on the dentatorubrothalamic tract (see [60]).

In ET, tremor frequency activity in the VIM is often considered as a necessary waypoint toward expression in the affected limb. An attractive candidate mechanism for DBS-mediated tremor relief in ET (and PD) is that the high frequency stimulation disrupts transmission of a tremor frequency signal in the thalamus to downstream targets [61,62]. Indeed, reduction of pathological oscillatory activity may be a hallmark of successful DBS in other areas as well.

Models revealed that axons and cell bodies respond differently to stimulation

An important effort of DBS modeling related to ET has been to understand the biophysical mechanisms of DBS on cellular and subcellular components [53,63], which has not been confined to VIM but also other targets of DBS, such as the GPi for bradykinesia [64]. The FEM approach described above has helped to clarify early questions regarding whether the principal action of DBS was inhibitory or excitatory. DBS was postulated to be inhibitory because the outcome was similar to that of an irreversible tissue-ablating lesion [65,66]. However, downstream recordings observed an increase in activity during the stimulation, which led to the apparent contradiction. Applying FEM and cellular modeling, McIntyre and colleagues demonstrated that extracellular high frequency stimulation from DBS may inhibit the cell soma while simultaneously exciting axons [53]. Stimulation lower than the threshold

for activation of cells in VIM was found to disrupt somatic activity but drive axonal responses.

Disrupting transmission of a tremor signal is consistent with the clinical evidence that thermal ablations in thalamus can also be effective at alleviating tremor [61,62]. It is not yet clear whether it is the reduction of tremor frequency activity in VIM, the regularization of output, the effect of antidromic drive, or perhaps several effects, that is important in reducing physiological tremor, and the ultimate source of pathological tremor oscillatory activity in VIM remains to be determined fully [67].

Models help to improve DBS stimulation parameters

Another well-established avenue of computational modeling for ET is aimed at optimization of DBS stimulation itself based on understanding its impact on the biophysical activity of cells and circuits within the VIM (Fig. 1a and b). Presently, DBS parameters (stimulation amplitude, pulse width/duty cycle, frequency, electrode contacts, polarity) are selected by a trained clinician but largely based on trial and error for a specific patient, reducing tremor symptoms in the clinic while minimizing obvious side effects, such as paresthesias, dysarthria, and ataxia. A more principled understanding of the effects of these parameters on their neural targets may lead to more automated programming, battery efficiency, and ultimately better outcomes, an important step toward fully closed-loop adaptive systems [53,68,69].

Grill and colleagues, through a series of studies, have performed experiments and various scales of simulations to understand the role of temporal regularity in the efficacy of DBS [63,70–72]. They found that temporally irregular patterns, while able to reduce tremor, did not perform as well as regular patterns and have found that masking cerebellar burst-driving inputs to thalamus may be crucial in reducing tremor. Further investigation revealed that the pause length was important in determining whether tremor was effectively suppressed, and their computational modeling suggested that the rebound bursting attributed to tremor-like pathology had emerged during pauses [72]. Interestingly, non-regular patterns of stimulation were found to improve finger tapping in PD patients and simultaneously reduce pathological oscillations [73], demonstrating the possibility of disease and location-specific effects that should be considered in designing stimulation therapies. Novel pulse shapes have also been simulated, resulting in principled predictions that non-rectangular pulses may provide more efficient tissue activation [74,75].

Model-informed control of tissue activation volumes may lead to improved, patient-specific therapy

Recent modeling efforts have identified patient-specific strategies that combine magnetic resonance imaging-guided tractography with realistic FEM models of DBS stimulation [76–78] (Fig. 1d). DBS electrodes that enable granular, directional control over current (i.e. current steering) have been employed to change the activation volume and increase the amplitude of stimulation while avoiding regions associated with side effects [79,80]. These tools enable directionally specific stimulation to reduce tremor (in the case of ET) while

avoiding side effects that may arise from stimulation of nearby structures. This approach may also facilitate investigations into the origin of non-tremor symptoms and designing neuromodulation strategies to address them.

Future opportunities for computational modeling to improve ET treatment

Crucially, modeling DBS in ET would benefit from an improved understanding of the basic mechanisms giving rise to movements (including tremor) in the modulated circuit. Incorporating additional work on connectomics of brain areas implicated in ET pathology into network models may also help to drive development of new hypotheses [62]. Understanding the normal role of the cerebellar–thalamic–cortical pathway in motor behavior and motor learning will likely yield additional insight into the modes of its failure, giving rise to tremor as well as other, more subtle, motor deficits. Once these mechanisms are understood, rational neuromodulation strategies can be designed to address these specific circuit perturbations.

To this end, while substantial efforts have gone toward modeling the effect of DBS on various neural targets and have helped to shape present DBS protocols, comparatively few models have been created to address specific facets of ET pathology outside the context of the effect of DBS on tremor. Experimental work to study non-tremor symptoms has been increasing in recent years, and computational modeling has an opportunity to do so as well.

We suggest that further efforts in computational modeling of all aspects of ET pathology can lead to novel testable predictions on improved methods to reduce tremor as well as non-tremor symptoms. These efforts should integrate across scales of modeling and focus on both the identification of novel pharmacological treatments and electrical stimulation therapies that will ultimately improve patient care.

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Figure 1. Multiple scales of computational models. Integration across model scales can provide novel insights into mechanisms of DBS and improve therapeutic strategies. (a). Two-hundred compartment single thalamocortical relay cell with Hodgkin-Huxley-type dynamics [81]. (b) Circuit modeling one-hundred uniformly distributed random cell bodies simulated as single compartment Hodgkin-Huxley-type neurons. (c) 2D FEM mesh around a Medtronic Model 3387 electrode of electric fields, estimated with PyDistMesh 1.2 [82,83]. (d) Patient-specific anatomy with DBS electrode from intraoperative CT (gray), thalamic nucleus (green), and diffusion-based tractography (multicolor). Images registered using Waypoint Navigator and AFNI [84] and visualized in SUMA [85].