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Computational Models of Neurological Disorder

Computational modeling to improve treatments for essential tremor

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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.

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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].

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].

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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 barbituate 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 overstimulation 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