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The temporal pattern of stimulation may be important to the mechanism of deep brain stimulation

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Abstract

Deep brain stimulation (DBS) has emerged as an important and potentially powerful treatment option for the management of carefully selected patients with advanced Parkinson's disease (PD) who are not adequately controlled by standard medication therapy. Though considerable advances have been made, the mechanisms underlying the therapeutic effects of DBS remain unclear despite its clinical efficacy. It is now widely held that both excitation and inhibition can occur secondary to stimulation, and it is suspected that abnormal synchronized oscillations may also be important in the mechanism of DBS. Other potentially important processes, including blood flow changes, local and upstream neurogenesis, and the modulation of neurotransmitters through stimulation of bordering astrocytes are also being investigated. Recent research has suggested that the temporal pattern of DBS stimulation is also an important variable in DBS neuromodulation, yet the extent of its influence on DBS efficacy has yet to be determined. As high stimulation frequency alone does not appear to be sufficient for optimal symptom suppression, attention to stimulation pattern might lead to more effective symptom control and reduced side effects, possibly at a lower frequency. Stimulation pattern may be potentially amenable to therapeutic modulation and its role in the clinical efficacy of DBS should be addressed through further focus and research.

Keywords

Deep brain stimulation; Frequency; Non-regular; Temporal pattern

Introduction

In 1987, a report of successful tremor reduction achieved through high frequency thalamic stimulation (Benabid et al., 1987) ushered in a new era of chronic deep brain stimulation (DBS), and a renewed interest in the surgical treatment of movement disorders. DBS has since become an invaluable tool in the management of advanced levodopa-responsive Parkinson's disease (PD) in patients who are not adequately controlled by medication, and who are appropriately screened by interdisciplinary teams (Okun, 2012). Despite the efficacy of DBS as a therapy, our understanding of the therapeutic mechanism of stimulation

remains to be completely elucidated. The reason for this discrepancy is multifaceted (Montgomery, 2012), yet it is clear that new approaches will be required to refine the clinical benefit provided by DBS and to minimize potential side effects. In this issue of *Experimental Neurology*, Brocker and colleagues (Brocker et al., 2012) explore the influence of temporal pattern regularity on high frequency stimulation (HFS), both clinically in patients with previously implanted DBS and in computational basal ganglia models. We review the state of current thinking regarding the role of frequency and temporal pattern in DBS mechanism, and discuss the study by Brocker and colleagues and other related works. We emphasize the implications of these studies on current theories of DBS mechanisms and future approaches in DBS treatment.

DBS mechanisms and theories of basal ganglia dysfunction

Initial theories regarding the therapeutic mechanism of DBS were based upon the classical theory of basal ganglia function known widely as the “rate model”, and the similarity between the clinical effect of DBS and surgical lesioning (Albin et al., 1989). However most experts now believe that there are significant problems associated with this approach. In the classic model of basal ganglia functioning (Fig. 1), the caudate nucleus and putamen (functionally known as the striatum) act as the primary input to the basal ganglia, and receive both glutaminergic excitatory cortical and thalamic input as well as neuromodulatory dopaminergic input from substantia nigra pars compacta (SNc). The internal segment of the globus pallidus (GPi) and the substantia nigra pars reticulata (SNr) act as the major output nuclei of the basal ganglia, ultimately projecting through the thalamus to the cerebral cortex. The classical model of basal ganglia emphasized two parallel pathways in motor processing: a “direct” pathway that promoted movement (the gas pedal) and an “indirect” pathway that inhibited movement (the brake) (Albin et al., 1989; Alexander et al., 1986). In both pathways dopaminergic modulation favors movement, and is mediated by the number of inhibitory connections within the circuit and also partially by the respective dopamine receptor type represented within each pathway. In hypokinetic movement disorders such as PD, the “balanced” activity of the direct and indirect pathways was thought to be disrupted, resulting in an increase in the tonic activity of the neurons in the STN and the GPi/SNr. This disruption was thought to further contribute to increased basal ganglia inhibition of neurons in the thalamus, which in turn have excitatory connections to the cortex. Similar to the proposed mechanism of action of surgical lesioning, it was theorized that HFS acted as a “virtual lesion”, suppressing neuronal activity in the electrode target (Benabid et al., 1998), perhaps by local depolarization blockade, depression of synaptic transmission, or activation of local inhibitory terminals (Dorval et al., 2010).

While the classical rate model of basal ganglia functioning has been invaluable in framing theories of pathophysiology, our understanding of basal ganglia function has matured and expanded since it was first put forth, and the limitations of the model have been highlighted. The study of electrophysiologic recordings of local field potentials (LFPs) obtained during and after DBS surgery in humans and experimental lesioning in animals, as well as sophisticated computational models of basal ganglia networks, has suggested that dysfunctional firing patterns, rather than just absolute increases or decreases in firing rates, are occurring within the basal ganglia network (McIntyre and Hahn, 2010). In both animal models and in PD patients off of their dopaminergic medications, basal ganglia and thalamic neurons in the parkinsonian state seem to exhibit complex changes in discharge patterns, with increased bursting and beta band (13–35 Hz) oscillations, as well as a greater tendency toward hyper-synchronization (Birdno and Grill, 2008; Nambu, 2008; Wichmann et al., 2011). Abnormal beta synchronization has been reported in LFPs in the striatum, STN, and GPi, as well as in single unit recordings, with reports of suppression of beta power in LFPs by levodopa and associated improvements in bradykinesia and rigidity (Eusebio et al.,

2012). The spatial extent of beta band phase synchronization in the region of the STN has been shown to correlate with rigidity and bradykinesia (Pogosyan et al., 2010). However, beta activity in LFPs has not been consistently shown to correlate with motor UPDRS in the off state, nor is beta always present (Priori et al., in press; Weinberger et al., 2006). Recently studies have investigated whether abnormal synchronized oscillations could also be demonstrated in the sensorimotor cortex in patients with movement disorders (Air et al., 2012; Crowell et al., 2012), and whether this oscillatory activity could distinguish between different diseases. Similar to the techniques commonly used in epilepsy patients, concomitant subdural electrode recordings placed in patients undergoing DBS surgery (Crowell et al., 2012) for PD, dystonia, or essential tremor (ET) showed that patients with PD had increased broadband gamma frequency spectral power in M1, and a relatively higher alpha–beta range median peak frequency on spectral analysis compared to non-PD movement disorders (dystonia and ET). In addition, PD patients had an increase in high beta band (20–30 Hz) power relative to dystonia and ET, but only during the stop phase of a stop/start movement task. These results support the notion that dysfunctional beta oscillatory activity is reaching the cortex and altering sensorimotor cortical activity in movement disorders.

Similar to the progress in mechanistic theories of basal ganglia dysfunction, current notions of how DBS improves symptoms in movement disorders have evolved beyond the idea of a “virtual lesion” to recognize that the effects of DBS are likely more complicated than simple inhibition or excitation. Early theories held that DBS worked by inhibition or by “jamming the circuit” (Benabid et al., 1998). This sparked a transoceanic debate about the roles of inhibition versus excitation in the mechanism of the underlying DBS efficacy (Grill et al., 2004; Miocinovic et al., 2006). However, recent studies have shown that DBS can act both to inhibit and to excite; there is common inhibition of neuronal cell bodies immediately surrounding the electrode, but excitation of efferent projections and resultant activation of complex neural networks (Eusebio et al., 2012; Montgomery and Gale, 2008; Vitek et al., 2012). Beyond direct effects of excitation and inhibition, proposed therapeutic mechanisms of DBS include the masking of pathological activity with innocuous regularity, direct suppression of local pathological neuronal activity, and interactions with reentrant non-linear oscillations occurring in the basal ganglia–thalamocortical network (Johnson et al., 2008; Montgomery and Gale, 2008; Obeso et al., 2008). The degree to which the modulation of beta oscillations is involved in symptom suppression from DBS continues to be a topic of much research and debate (Eusebio and Brown, 2009).

Other considerations on the mechanism of DBS

While it is now widely held that both excitation and inhibition occur secondary to DBS and it is suspected that synchronized oscillations (especially in the beta frequency range) may play a critical role in its ameliorative effects, it is also important to keep in mind that several other simultaneous processes evolve in response to brain stimulation. In addition to target neurons, bordering astrocytes are also directly depolarized by DBS stimulation. This can modulate resultant calcium waves and release of gliotransmitters such as glutamate, D-serine, and ATP that are active at both pre- and postsynaptic receptors. Stimulation of astrocytes can also effect regulation of blood flow and the proliferation of neural progenitors and/or neurogenic astrocytes (Tawfik et al., 2010; Vedam-Mai et al., 2012). Additionally, adenosine has been shown to play a role in neuronal inhibition secondary to HFS and may play a role in the therapeutic effect of DBS in thalamic DBS for ET, and in particular the “microlesion” effect, in which symptom reduction occurs from electrode placement before stimulation is started (Bekar et al., 2008; Chang et al., 2012). In one of the most innovative approaches recently utilized, Gradinaru and colleagues attempted to address some of these proposed mechanisms through the use of novel optogenetic techniques, which avoid the

difficulties and artifacts of concurrent HFS and recording (Gradinaru et al., 2009). By genetically manipulating target neuronal populations to be activated or inhibited in response to in vivo light delivery in a 6-hydroxydopamine model of parkinsonism in rats, the authors found that neither inhibition or HFS of excitatory neurons, nor selective activation of astroglia in the STN, improved symptoms in the parkinsonian rat. However, optical HFS of afferent fibers to the STN and of layer VM1 neurons markedly improved measures of parkinsonism in the rat model, while optical stimulation at 20 Hz worsened measures of parkinsonism. The authors acknowledged that their finding of a lack of therapeutic effect of optical inhibition of the STN is inconsistent with the well-described motor improvement seen in primates and humans after STN inactivation by muscimol injections (Levy et al., 2001; Wichmann et al., 1994), but attributed this discrepancy to the increased selectivity of the optical method for inhibiting local excitatory neurons. While this approach has not settled the question of how the effects of DBS are mediated, it demonstrates the potential of optogenetics in unraveling the intricacies of basal ganglia–thalamocortical dysfunction and DBS mechanisms.

The role of frequency and temporal pattern in DBS

Regardless of the exact nature of the pathological processes that are altered by DBS, previous research has suggested that, among the stimulation parameters that can be modified (other than the obvious influence of amplitude/voltage), a relatively high frequency of stimulation may be critical to achieving symptom improvement. In PD maximal clinical reductions in tremor are typically observed only at stimulation frequencies above 90 Hz (Birdno et al., 2008), and worsening of motor symptoms can occur with low frequency stimulation (Chen et al., 2011; Eusebio et al., 2008; Timmermann et al., 2004); however this notion has been challenged in individual patients. A number of theories have been put forth to explain why low frequency DBS fails in improving PD symptoms or may alternatively worsen symptoms. Among the more intuitive theories is that the interpulse intervals in low frequency DBS are of sufficiently long duration to allow breakthrough of intrinsic pathological activity. Stimulation at such frequencies may also generate irregular spikes that could ultimately enhance a critical pattern and lead to disruption and worsening of symptoms. Another equally plausible possibility is that low frequency stimulation leads to abnormal synchronized activity by promoting rebound bursts in the stimulated nucleus and in downstream nuclei (Birdno and Grill, 2008; Montgomery and Gale, 2008). The question of whether stimulation at lower frequencies is ineffective or alternatively might actually reinforce abnormal activity is an important one (Baker et al., 2011), for which a definitive answer continues to be sought. Also of importance are the somewhat controversial reports of low frequency stimulation improving gait in PD (Moreau et al., 2008), which has not been widely replicated across groups (Brozova et al., 2009) but has been seen in individual patients.

Though not currently amenable to clinician modulation, the influence of stimulation pattern has been investigated in patients, animal models, and in simulated neuronal networks, and this was the focus of Brocker and colleagues in this issue of *Experimental Neurology*. There is a growing body of research suggesting that stimulation pattern may be important in mediating the effects of DBS in movement disorders, and even possibility to a greater degree than frequency alone (Baker et al., 2011; Birdno et al., 2007, 2008, 2012; Brocker et al., 2012; Dorval et al., 2010; Feng et al., 2007; Montgomery, 2005; Montgomery and Gale, 2008).

Studies that have investigated temporal pattern of stimulation in DBS have made use of animal models, computerized network simulations, and have made the most of required surgical revisions in patients to access patient leads and induce non-regular patterns of

stimulation (Table 1). A 2007 study (Birdno et al., 2007) examined the role of temporal spacing of pulses in thalamic ventralis intermedius (VIM) DBS for ET through the use of simulated computational models. The authors discovered that the degree of clinical tremor suppression (as measured by accelerometry) decreased as the difference between the interpair and interpulse intervals increased; thus patterns of stimulation with evenly spaced pulses were more effective at suppressing tremor in patients, and more effective at preventing burst activity and in entraining computer modeled neurons at a defined frequency. A 2008 review (Montgomery and Gale, 2008) described a single unpublished patient who, during surgical revision of their DBS lead, performed the finger-tapping task on the Unified Parkinson's Disease Rating Scale (UPDRS) for a blinded rater during five randomized patterns of stimulation. The same mean frequency (130 Hz) was utilized for this experiment. Regular DBS at 130 Hz improved tapping, while irregular stimulation worsened performance. Interestingly, slowly modulated stimulation produced the worst outcome for this patient. The same year, Birdno et al. (2008) investigated whether temporally irregular stimulation would be less effective at suppressing tremor in four patients with a variety of tremulous disorders (PD, ET, myoclonus–dystonia, multiple sclerosis) who were previously responsive to DBS (Vimor STN) and required implantable pulse generator (IPG) replacement. This group measured rest and action (postural and kinetic) tremor with accelerometry and tested patients off stimulation and with regular stimulation at varying frequencies. They used three patterns with the same mean interpulse interval that differed in the degree of irregularity, and found that reduction in tremor increased with increasing stimulation frequency, but decreased as stimulation patterns were adjusted to be more irregular.

A 2010 study lead by Grill (Dorval et al., 2010) pondered whether the ability of regular or irregular stimulation patterns to alleviate parkinsonian bradykinesia in patients with STN DBS was based on the differential ability to successfully reduce variability in GPi inhibition (of the thalamus). This study, which used a similar methodology to Brocker et al., utilized regular 130 Hz stimulation, and had three additional patterns of stimulation (also with a mean instantaneous frequency of 130 Hz), but the author cleverly used increasingly random interpulse times. They found that regular (and minimally irregular) stimulation patterns decreased variability in tap duration and interval, while highly irregular DBS did not improve tap variability compared to off stimulation (despite delivery at an average frequency that is typically clinically effective). In the computational model that they created, regular (but not irregular stimulation patterns) reduced transmission model errors.

Taken together, these studies demonstrate that temporal pattern regularity is an important but incompletely explored factor in the clinical efficacy of DBS. For a given therapeutic frequency, the temporal pattern of stimulation can mediate the effects of DBS in both patients and in computational models, suggesting that simply having a high stimulation rate is not adequate for symptom reduction. These findings have been shown across multiple diseases, multiple measures of motor performance, and in multiple DBS targets.

Brocker and colleagues

Brocker et al. (Brocker et al., 2012) sought to determine what specific features of irregular stimulation patterns might underlie the reduced clinical efficacy for worsening bradykinesia in PD patients. The authors drew from previous studies, and made use of the surgical replacement of IPGs due to battery drain. They connected ten PD patients who had DBS implanted (either STN or GPi) to custom software capable of generating temporally distinct patterns of stimulation, but with a constant geometric mean frequency of 185 Hz. In addition to regular stimulation (used by commercial DBS), two periodic (absence and presence) patterns with low entropy and two non-periodic (uniform and unipeak) stimulation patterns

with high entropy were presented in a randomized order. Based on a protocol used in previous studies (Dorval et al., 2010; Taylor Tavares et al., 2005) the authors quantified bradykinesia using the log-transformed coefficient of variation of index finger tap duration and intervals during an alternating finger tapping task performed using a computer mouse. The effect of each pattern of stimulation on simulated beta band oscillations in a computational model of thirty single compartment neurons in the STN, GPi, and GPe was also examined. The authors were surprised to find that three of the four non-regular stimulation patterns actually improved motor performance as compared to regular stimulation, and this improved ability was correlated with suppression of beta frequency oscillations in their computational model. Repeated measures ANOVA and post hoc testing showed greater tap variability off stimulation (baseline) compared to both regular and irregular stimulation patterns, with significantly lower index finger tap duration variability during both periodic (absence and presence) and one of two (uniform) non-periodic patterns as compared to regular stimulation. Pooling data in non-regular stimulation based on the presence or absence of specific pattern characteristics (bursts, pauses, and irregularity) did not reveal a significant effect of these attributes. They found no confounding effect of surgical target, state of medication, sedation, or switching to a bipolar configuration.

In summary, the work of Brocker et al. revealed that stimulation patterns improved performance relative to DBS off stimulation, regardless of temporal regularity. In fact, some non-regular patterns were actually more effective, and efficacy was correlated with beta suppression in their computational model. There were however some limitations to the study design: their manner of quantifying bradykinesia required considerable data processing (e.g. log transformation, limitation of data collection epoch, and limitation of analysis to the index finger) though it has been used in previous studies (Dorval et al., 2010; Taylor Tavares et al., 2005). In addition, their low sample size and heterogeneity of the stimulation sites were confounding variables. The authors themselves noted that it was unclear how non-regular patterns of stimulation would affect manifestations of PD other than bradykinesia as tested by a finger-tapping task, and their findings are limited to the acute effects of stimulation pattern, which may be different from long-term effects. Future studies could make use of more comprehensive quantitative motor control testing that could be implemented to investigate the effects of stimulation pattern (Shapiro et al., 2007; Sturman et al., 2004; Vaillancourt et al., 2004).

The main finding of Brocker et al., that temporally non-regular patterns of DBS stimulation can be effective in patients and in computational models, was surprising but is not without precedent. Baker et al. (2011) described the effect of variation in temporal stimulation on reach and retrieval time in primates rendered hemi-parkinsonian by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). The authors did not find a significant difference between temporally regular and irregular stimulation at a fixed frequency, and both regular and irregular burst pattern stimulation at 80 Hz did not differ from regular stimulation at 135 Hz. Similarly Birdno et al. (2012) found in non-parkinsonian tremor that temporally non-regular DBS can suppress tremor if there are no long pauses in the stimulation pattern. The authors studied eight patients with DBS responsive tremor (one MS and 7 ET) and they used stimulation patterns similar to Brocker and colleagues. findings included select high and low entropy patterns that could suppress tremor, and that patterns with pauses were the least effective clinically and led to burst firing in modeled thalamic neurons especially when pauses coincided with pauses in simulated cerebellar input.

The study by Brocker, as well as most of the other studies described above in which stimulation pattern was tested on humans with DBS, involved the connection of DBS leads to an external computer to generate experimental patterns of stimulation, as manipulation of stimulation pattern is not currently clinically available. However, studies (Kuncel et al.,

2012;Montgomery, 2005) have also made use of the cycling settings present in commercially available neurostimulators to investigate the effects of pause duration in stimulation trains on postural tremor. The more recent of these (Kuncel et al., 2012) cycled on and off times ranging from 100 to 500 ms in patients with VIM DBS, and postural tremor decreased as percentage of on time increased, requiring stimulation on time of at least 60% for tremor suppression to be equivalent to constant stimulation. They used a computational model to suggest that longer pauses in stimulation allowed rebound bursting originating from abnormal cerebellar activity to influence thalamic firing. Earlier, Montgomery (Montgomery, 2005) demonstrated that at individualized STN DBS settings, patients had faster movement times in a wrist extension/flexion to target task with constant stimulation as compared to cycling stimulation, and these were similar to the findings of worse motor performance seen as a result of oscillatory versus constant stimulation in non-human primates (Ma & Wichmann, 2004). While manipulation of pause durations in otherwise regular stimulation is a somewhat coarse means of approximating temporal pattern irregularity, these studies were remarkable in that they were conducted without external means of impulse generation.

Implications and future directions

The temporal pattern of stimulation in DBS is an important variable, and a variable that is potentially amenable to therapeutic modulation. Future research on stimulation paradigms is warranted. It appears that high frequency stimulation alone is not sufficient for symptom suppression, but we still don't know exactly what influence temporal irregularity, bursts, and pauses have on DBS efficacy, and it is unknown whether these effects are specific to DBS target, symptoms (e.g. tremor vs. others), or underlying disease. Attention to stimulation pattern might allow effective symptom control at a lower frequency. This possibility could be clinically important, as the development of alternative stimulation patterns could lead to increased battery life and possibly to reduced side effects, as well as to improvements in therapeutic efficacy, particularly in patients who have a less than ideal response to typical frequency DBS (Eusebio and Brown, 2009; Feng et al., 2007; Okun et al., 2012a). Many questions remain about the role of stimulation pattern and which pattern is most effective, and the recent work of Brocker et al. actually stimulates more questions than answers on the mechanism of DBS. However, as we move toward closed loop (adaptive) DBS (Priori et al., in press; Rosin et al., 2011) and implement new and innovative approaches in DBS therapy, such as patient-specific tailoring of DBS targets (Okun and Foote, 2010), field steering and interleaving stimulation (Sarem-Aslani and Mullett, 2011), constant-current stimulation (Okun et al., 2012b), and scheduled stimulation (Okun et al., 2012a), further investigation of the temporal pattern of stimulation will be critical in improving clinical outcomes.

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Fig. 1. Schematic of the classical model of the direct and indirect pathways in basal ganglia circuitry. Unfilled arrows are excitatory connections. Filled arrows are inhibitory connections. Grey and italics indicate updates to the classical model. D1=D1 dopaminergic receptors; D2=D2 dopaminergic receptors; GABA= γ -aminobutyric acid (GABA)-ergic; Glu=glutamatergic; GPe=external segment of the globus pallidus; GPi=internal segment of the globus pallidus; SNc=substantia nigra pars compacta; SNr=substantia nigra pars reticulata; STN=subthalamic nucleus; Thal=thalamus.

Table 1

Summary of studies and reports investigating the role of temporal pattern in deep brain stimulation (DBS).

Study	Disease	DBS target	Stimulation pattern	Clinical measures	Clinical findings	Computational model findings
Montgomery, 2005 (n=7)	PD	STN	Cycled stimulation at 50 and 100 ms	Dominant hand wrist flexion/ extension task to target	Faster movement times for constant vs. cycling stimulation at 100 ms	N/A
Birdno et al., 2007 (n=5)	ET	VIM	Pulse-pairs at 65 Hz (mean 130 Hz) with intra-pulse intervals varying between 0.3 and 7.7 ms	Postural tremor by accelerometry	Tremor improved with increasing regular stimulation frequency; 130 Hz but not 65 Hz regular stimulation reduced tremor; improvement in tremor decreased with as the difference between intra-pair and inter-pair intervals increased	Increased intra-pair and inter-pair intervals increased neuronal bursting and irregularity and decreased entrainment to stimulation
Montgomery and Gale, 2008 (n=1)	PD	STN	Regular, randomly irregular, and regular modulated at 2, 5, and 10 Hz	UPDRS finger-tapping task	Regular stimulation improved performance and irregular worsened performance, with greatest worsening occurring with 2 Hz modulated stimulation.	N/A
Birdno et al., 2008 (n=4)	Tremor (PD, ET, M-D, MS)	VIM or STN	Regular stimulation at multiple frequencies and eight patterns of irregular stimulation (constant mean inter-pulse intervals but varying CV)	Rest and action tremor by accelerometry	Tremor reduction increased with increasing regular frequency but decreased with increasing irregularity (CV)	N/A
Dorval et al., 2010 (n=9)	PD	STN	Regular stimulation and three patterns of randomly irregular stimulation (with increasing variability) at mean instantaneous frequency of 130 Hz	Variability in finger tapping duration and interval	Regular stimulation increased tap rate from baseline; regular and minimally irregular stimulation decreased tap duration and interval variability from baseline;	Regular stimulation regularized ISI, reduced entropy, and reduced "thalamic errors"; irregular stimulation increased ISI irregularity, entropy, and "thalamic errors"
Baker et al., 2011 (n=1)	MPTP parkinsonism (primate)	GPI	Regular, irregular (random inter-pulse interval), regular or irregular bursting, and oscillating inter-pulse interval	Reach and retrieval time	Performance improved with increasing frequency of regular stimulation; temporally irregular stimulation did not worsen performance compared to regular stimulation at the same frequency; burst pattern stimulation (regular and irregular) at 80 Hz	N/A

Study	Disease	DBS target	Stimulation pattern	Clinical measures	Clinical findings	Computational model findings
Birdno et al., 2012 (n=8)	Tremor (ET and MS)	VIM	Regular, three irregular (uniform, unipeak, and bimodal), two periodic (absence or presence of pauses or double frequency bursts), all with geometric mean frequency of 185 Hz	Postural tremor by accelerometry	<p>improved performance compared to off stimulation and regular stimulation at 80 Hz and was not different from regular stimulation at 135 Hz; decreasing oscillatory frequency worsened performance</p> <p>Tremor was suppressed compared to off stimulation by all patterns except bimodal and absence; patterns with pauses suppressed tremor less than patterns without pauses;</p>	Patterns that were clinically effective overrode cerebellar bursting and prevented rebound bursting in thalamic neurons; patterns with pauses lead to burst firing in thalamic neurons, especially when pauses coincided with pauses in simulated cerebellar input.
Brocker et al., 2012 (n=10)	PD	STN or GPI	Regular, two irregular (uniform and unipeak), two periodic (absence or presence of pauses or double frequency bursts), all with geometric mean frequency of 185 Hz.	Variability in finger tapping duration and interval	<p>All patterns of stimulation improved variability in tap duration relative to off stimulation; both periodic (absence and presence) and one irregular (uniform) patterns decreased tap duration variability compared to regular stimulation; pooling patterns based on the presence of bursts, pauses, or irregularity did not produce a significant effect</p>	<p>All stimulation patterns suppressed beta band power compared to baseline; both periodic (absence and presence) and one irregular (uniform) patterns suppressed beta band power more than regular or uniform stimulation.</p>
Kuncel et al., 2012 (n=10)	ET and PD	VIM	Regular stimulation at multiple frequencies (100–250 Hz) and cycling stimulation with on time ranging from 100 to 500 ms and off time ranging from 100 to 300 ms with constant average frequency of 125 Hz	Postural tremor by accelerometry	<p>All regular stimulation patterns reduced tremor compared to off stimulation; tremor reduction improved with as percentage of on time increased with cycling stimulation patterns; patterns with on time greater than 60% were equivalent to regular stimulation.</p>	<p>All stimulation patterns reduced entropy; regular stimulation reduced entropy more than cycling stimulation; entropy decreased with increasing on time</p>

CV=coefficient of variation; ET=essential tremor; GPI=internal segment of the globus pallidus; ISL=inter-stimulus interval; M-D=myoclonus-dystonia; MTP=1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MS=multiple sclerosis; PD=Parkinson's disease; STN=subthalamic nucleus; UPDRS=Unified Parkinson's Disease Rating Scale; VIM=ventralis intermedius of the thalamus.