

Physiological mechanisms of thalamic ventral intermediate nucleus stimulation for tremor suppression

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Ventral intermediate thalamic deep brain stimulation is a standard therapy for the treatment of medically refractory essential tremor and tremor-dominant Parkinson's disease. Despite the therapeutic benefits, the mechanisms of action are varied and complex, and the pathophysiology and genesis of tremor remain unsubstantiated. This intraoperative study investigated the effects of high frequency microstimulation on both neuronal firing and tremor suppression simultaneously. In each of nine essential tremor and two Parkinson's disease patients who underwent stereotactic neurosurgery, two closely spaced (600 μm) microelectrodes were advanced into the ventral intermediate nucleus. One microelectrode recorded action potential firing while the adjacent electrode delivered stimulation trains at 100 Hz and 200 Hz (2–5 s, 100 μA , 150 μs). A triaxial accelerometer was used to measure postural tremor of the contralateral hand. At 200 Hz, stimulation led to $68 \pm 8\%$ ($P < 0.001$) inhibition of neuronal firing and a $53 \pm 5\%$ ($P < 0.001$) reduction in tremor, while 100 Hz reduced firing by $26 \pm 12\%$ (not significant) with a $17 \pm 6\%$ ($P < 0.05$) tremor reduction. The degree of cell inhibition and tremor suppression were significantly correlated ($P < 0.001$). We also found that the most ventroposterior stimulation sites, closest to the border of the ventral caudal nucleus, had the best effect on tremor. Finally, prior to the inhibition of neuronal firing, microstimulation caused a transient driving of neuronal activity at stimulus onset (61% of sites), which gave rise to a tremor phase reset (73% of these sites). This was likely due to activation of the excitatory glutamatergic cortical and cerebellar afferents to the ventral intermediate nucleus. Temporal characteristics of the driving responses (duration, number of spikes, and onset latency) significantly differed between 100 Hz and 200 Hz stimulation trains. The subsequent inhibition of neuronal activity was likely due to synaptic fatigue. Thalamic neuronal inhibition seems necessary for tremor reduction and may function in effect as a thalamic filter to uncouple thalamo-cortical from cortico-spinal reflex loops. Additionally, our findings shed light on the gating properties of the ventral intermediate nucleus within the cerebello-thalamo-cortical tremor network, provide insight for the optimization of deep brain stimulation technologies, and may inform controlled clinical studies for assessing optimal target locations for the treatment of tremor.

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Abbreviations: DBS = deep brain stimulation; GPi = globus pallidus internus; HFS = high frequency stimulation; SNr = substantia nigra pars reticulata; STN = subthalamic nucleus; Vc = ventral caudal nucleus; Vim = ventral intermediate nucleus; Voa = ventral oral anterior nucleus; Vop = ventral oral posterior nucleus

Introduction

Tremor is characterized by involuntary rhythmic muscle contractions that can occur in one or more body parts. It can occur alone as in essential tremor, or with other motor symptoms as in Parkinson's disease and occasionally dystonia. Essential tremor is currently the most prevalent movement disorder in man (Louis *et al.*, 1998), and three of four patients with Parkinson's disease develop tremor at some point during the disease process (Hughes *et al.*, 1993). In Parkinson's disease, tremor is typically present at rest, while essential tremor patients possess postural or kinetic tremor (Deuschl *et al.*, 1998; Elble and Deuschl, 2009). Tremor is regarded as the most difficult to treat symptom of Parkinson's disease as it may not respond well to dopamine replacement therapy, and essential tremor has also proven quite intractable to treat pharmacologically in a subset of patients (Goldman *et al.*, 1992; Koller *et al.*, 1994; Ondo *et al.*, 1998; Fishman, 2008). Deep brain stimulation (DBS) of the thalamic ventral intermediate nucleus (Vim) is an efficacious and reversible standard of care that has largely replaced Vim thalamotomy for the amelioration of tremor (Benabid *et al.*, 1991, 1993, 1996; Nguyen and Degos, 1993; Deiber *et al.*, 1993). Numerous studies have supported the central origin of tremor by hypothesizing the presence of a single pathological oscillation frequency between 4 and 6 Hz (Rajput *et al.*, 1991; Deuschl *et al.*, 1998; Llinás *et al.*, 2005).

In Parkinson's disease, an early thalamo-centric theory of tremor genesis stated that 12–15 Hz oscillations in pallidal output found in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine monkeys were converted into 4–6 Hz tremor oscillations by intrinsic thalamic membrane hysteresis (Llinás and Paré, 1995). A more recent pallido-centric theory (Helmich *et al.*, 2011), termed the dimmer-switch hypothesis, suggests that Parkinson's disease tremor is initiated by the basal ganglia (the switch) and its amplitude is modulated by the cerebello-thalamo-cortical network (the dimmer). Indeed, single neurons with 4–6 Hz tremor oscillations are present in the human globus pallidus internus (GPi; Hutchison *et al.*, 1997). This theory suggests that the GPi sends tremorigenic output to the thalamus, which then ascends through the thalamo-cortical network. However, that would suggest a predominant role for the pallidal thalamic input nuclei, ventral oral anterior and posterior (Voa, Vop), in tremor-genesis, but this does not fit with DBS intraoperative findings, which show that intervention of the cerebellar thalamus (Vim) is superior for treating tremor (Atkinson,

et al., 2002), or that there are more 'tremor cells' in the Vim than in Vop/Voa (Magnin *et al.*, 2000). However, studies (reviewed in Duval, *et al.*, 2016) suggest that bursting activity can propagate to different nuclei within the thalamus by way of relay nuclei that can either induce bursting activity in neighbouring neurons, or simply relay bursting activity that is already present. Furthermore, burst firing of thalamic neurons has been demonstrated to provide a non-linear amplification of sensory signals (Guido and Weyand, 1995). Thus, periodic oscillations at tremor frequency could be amplified in cortical regions. The same cortical regions that receive this thalamic input exhibit oscillatory tremor-related activity, and send projections to the striatum (Volkmann *et al.*, 1996), as well as direct projections to the subthalamic nucleus (STN; Monakow *et al.*, 1978; Nambu *et al.*, 1996; Mathai and Smith, 2011), which could explain the presence of tremor-related oscillations within the basal ganglia.

Essential tremor is regarded as a disorder of the cerebellum. Post-mortem studies have described various levels of neurodegeneration in essential tremor patients including Purkinje cell loss and Purkinje cell axonal swelling in the neocerebellum and vermis (Louis *et al.*, 2007; Axelrad *et al.*, 2008; Shill *et al.*, 2008; Louis *et al.*, 2011; Yu *et al.*, 2012). However, other studies have not found neurodegenerative changes, rather that there is neurophysiological evidence of a reduction in GABAergic tone. In the dentate nucleus of essential tremor patients, post-mortem studies have revealed lower levels of GABA-A and GABA-B receptors compared to control subjects (Paris-Robidas *et al.*, 2012). Thus, the restricted inhibitory influence of Purkinje cells may result in increased disinhibition of deep cerebellar neurons, and the subsequent overactivity may spread through the cerebello-thalamo-cortical network. Indeed, the Vim has a distinct role within essential tremor pathophysiology. DBS studies have demonstrated tremor-related local field potential clusters (Pedrosa *et al.*, 2012) and intraoperative studies have shown single-unit tremor-related discharges (tremor cells; Lenz *et al.*, 1988; Takahashi *et al.*, 1998) in Vim that are coherent with tremor. What drives these oscillatory networks is still unsubstantiated. Early theories hypothesize that unique ion channel dynamics in the thalamus, inferior olive, and cerebellum can generate oscillations (Jahnsen and Llinas 1984a, b; Llinás, 1988). Movement-related activation of nucleolary cells may cause Purkinje cells to synchronously inhibit deep cerebellar nuclei, which generate oscillatory rebound potentials (inhibition-induced excitation) that make

their way through the cerebello-thalamo-cortical network. However, studies (reviewed in Helmich *et al.*, 2013) have moved away from single oscillator hypotheses, and suggest that there may be shifting modes of cooperation in all nodes of the tremor network, and that all components are capable of acting as resonators and entraining each other.

In this study, we set out to elucidate how electrical stimulation interacts with the brain on a physiological level during therapeutic high-frequency stimulation (HFS) and how it leads to clinical benefit. While modelling studies (Meijer *et al.*, 2011; Kuncel *et al.*, 2012; Birdno *et al.*, 2014) have been used to predict the effects of thalamic DBS on neuronal firing, our unique intraoperative dual-microelectrode assembly allows us to record the activity of single neurons during stimulation from a nearby electrode while simultaneously quantifying effects on tremor. Our findings suggest that tremor reduction was associated with inhibition of neuronal firing, which occurred after a transient driving of neuronal activity. Additionally, our findings shed light on the complex pathophysiology of tremor-genesis, and could also provide insight for the optimization of DBS technology for the treatment of tremor.

Methods and materials

Patients

A total of 21 Vim sites were investigated during microelectrode-guided placement of DBS electrodes in 11 patients; nine with essential tremor and two with Parkinson's disease (who had an additional postural tremor component). The experiment conformed to the guidelines set by the Tri-Council Policy on Ethical Conduct for Research Involving Humans and were approved by the University Health Network Research Ethics Board. Furthermore, all of the patients in this study provided written, informed consent prior to taking part in the study.

Data acquisition

Two independently driven microelectrodes (25 μm tip lengths, 600 μm apart, 0.2–0.4 $\text{M}\Omega$ impedances, sampled at 12.5 kHz), which share a common ground on a stainless-steel intracranial guide tube, were used for recordings and microstimulation (Fig. 1A). Open filter recordings (5–3000 Hz) were amplified 5000 times using two Guideline System GS3000 amplifiers (Axon Instruments), digitized using a CED 1401 data acquisition system (Cambridge Electronic Design), and monitored using Spike2 software (Cambridge Electronic Design). Microstimulation was done using one of the two isolated constant-current stimulators (Neuro-Amp1A, Axon Instruments) with square wave, 0.3 ms biphasic pulses (cathodal followed by anodal).

Microelectrode recording procedure

Techniques used for intraoperative electrophysiological identification of Vim have been published previously (Lenz *et al.*, 1988; Ohye *et al.*, 1989). Briefly, stereotactic coordinates of the anterior commissure and posterior commissure were determined using a T_1 – T_2 fusion MRI (Signa, 1.5 T or 3 T, General Electric) on a surgical neuronavigation workstation (Mach 4.1, StealthStation, Medtronic, Minneapolis, USA), in addition to an estimation of the location of Vim based on the 14.5 mm sagittal section of the Schaltenbrand and Wahren (1977) standard atlas. The two microelectrodes were advanced through a tentative trajectory through the thalamus in an anterodorsal to ventroposterior direction towards coordinates of $x = 14.5$ mm (or 11 mm lateral to the third ventricle), $y = 6$ mm anterior to the posterior commissure and $z = 0$ mm from the mid-commissural point (Fig. 1B). Several techniques were used for the delineation of thalamic sub-nuclei. Single units were tested for responses to passive and active movements of the wrist, elbow, and shoulder. Units with movement-related responses were considered cells of the motor thalamus: Vop/Vim (Molnar *et al.*, 2005). Microstimulation (100–200 Hz, 100 μA , 2–5 s, 0.3 ms pulse width) was delivered every 1 mm along the trajectory to coarsely delineate Vim from Vop based on tremor reduction or tremor arrest. The first site along the trajectory with stimulation-induced paraesthesia was considered to be in the vicinity of the anterior border of the ventral caudal nucleus (Vc). We also confirm Vim recording sites by the presence of beta oscillatory activity in the absence of tremor, which is not otherwise found in surrounding structures (Basha *et al.*, 2014).

Experimental protocol

Based on the above criteria, the protocol was undertaken in recording sites that were determined to be in the Vim (maximum 5 mm away from Vc). Upon locating a well isolated single unit (cell), patients were asked to maintain a tremorgenic posture by holding up a bottle of isopropyl alcohol (filled to ~ 150 ml), while a triaxial accelerometer (Crossbow Technology) was used to measure the scalar sum of accelerations on the wrist of the contralateral hand. In two patients we also obtained EMG (Intronix Technologies) from the wrist extensor muscle. When stable tremor was present, stimulation trains at 100 Hz and 200 Hz were delivered (2–5 s, 100 μA , 150 μs) from the adjacent microelectrode (600 μm away in the mediolateral direction). A total of 88 stimulation trains were delivered (40 at 100 Hz and 48 at 200 Hz, at least one of each per stimulation site). At three recording sites only tremor reduction was measured as the units were lost (excluded from correlations).

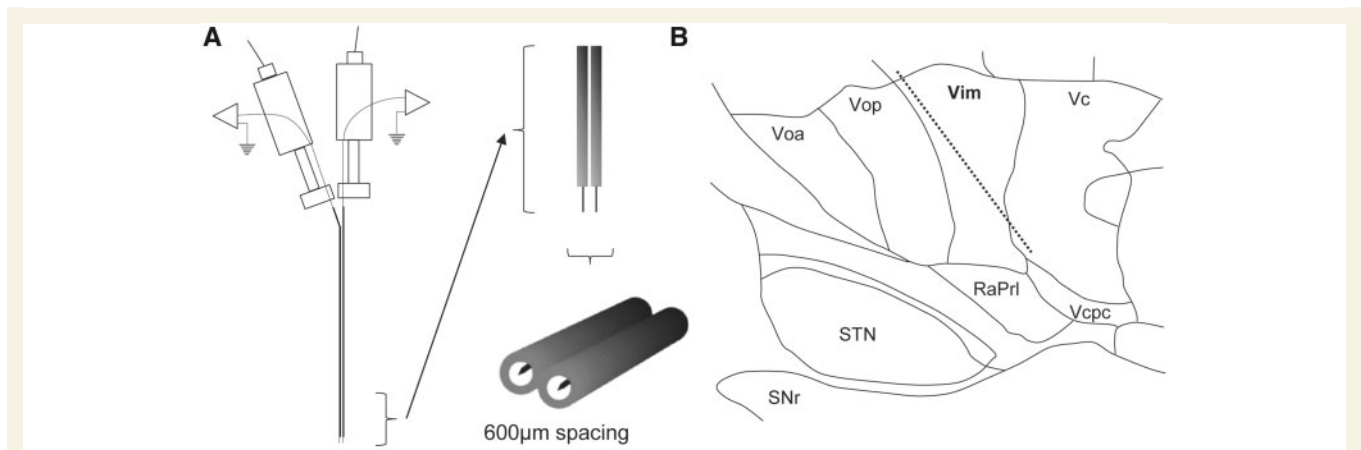


Figure 1 Experimental setup. (A) Our custom dual-microelectrode recording assembly with $\sim 600 \mu\text{m}$ mediolateral spacing between adjacent microelectrodes. Upon locating a well isolated spike on one microelectrode, the adjacent microelectrode was used to deliver stimulation trains at the same depth. (B) Representative microelectrode track of the Vim and surrounding structures, thalamic sub-nuclei, and fibres. RaPrI = prelemniscal radiations; Vcpc = ventral caudal parvocellular.

Offline analyses and statistics

To measure firing rates during stimulation trains, stimulus artefacts (0.3 ms pulse duration) were removed offline from the signal starting at the onset of the stimulation pulse to its end. Single units were discriminated using the waveform template matching tool in Spike2. Cell inhibition was measured as the ratio of the firing rate during the stimulation train to a 10-s pre-stimulation baseline firing rate of the cell. This value was subtracted from 1 and multiplied by 100 to get ‘% cell inhibition’ (i.e. a value of 100 represents complete inhibition). In recordings sites that had an initial transient driving of neuronal activity at stimulation onset (Fig. 5), the cell inhibition was measured after the initial burst. In these recording sites, we measured the burst duration (ms), firing rate (Hz), number of spikes, and onset latency (ms; from the first pulse of the stimulation train). For tremor reduction, the root mean square amplitude (0.2 s time constant) of the accelerometer signal was measured. A ratio was taken between the waveform averages during the tremor reduction period compared to a pre-stimulation baseline period immediately before the stimulation train. This value was subtracted from 1 and multiplied by 100 to get ‘% tremor reduction’ (i.e. a value of 100 represents complete tremor arrest). The duration of both the tremor reduction period and pre-stimulation baseline were equivalent to the duration of the stimulation train. However, we measured the maximal tremor reduction period, which always had a delay with respect to the stimulation train onset, as seen in Fig. 2. The average delay between stimulation onset and maximal tremor reduction period was $466 \pm 24 \text{ ms}$ [average \pm standard error (SE)]. Tremor phase resets were determined by comparing the instantaneous frequency of each phase of the tremor cycle before stimulation, to the instantaneous frequency immediately after onset of the

stimulation (Fig. 6). Paired sample *t*-tests (two-tailed) were used to determine whether stimulation trains had a significant effect on tremor reduction and neuronal inhibition compared to baseline for each of the frequencies. To compare the effect of stimulation frequency on cell inhibition, tremor reduction, and the transient driving response variables (listed above), paired sample *t*-tests (one-tailed) were used, under the hypothesis that 200 Hz had a greater effect on each of the parameters than 100 Hz. A second-order polynomial regression line was fit to the correlation between cell inhibition and tremor reduction, and a Pearson’s coefficient of correlation was calculated. To determine the effect of tremor reduction as a function of depth though the trajectory at 100 Hz and 200 Hz, linear regression lines were fit and Pearson’s coefficients of correlation were calculated.

Results

Ventral intermediate nucleus recording sites

The average pre-stimulation baseline firing rate of all recorded neurons was $48 \pm 8 \text{ Hz}$ (average \pm SE). Of the recorded neurons, 56% (10/18) were tremor cells that exhibited 4–6 Hz tremor-related burst firing (with an average intraburst firing rate of $88 \pm 12 \text{ Hz}$) and movement-related responses (Fig. 7). In 61% (11/18) of the neurons, we recorded transient stimulation-induced driving of neuronal activity that was limited to the start of the stimulation trains (Fig. 5A). In 57% (12/21) of all recordings sites, a tremor phase reset occurred at the start of the stimulation trains (Fig. 6). Eight of the 11 (73%) neurons with transient driving responses had phase resets. Our EMG

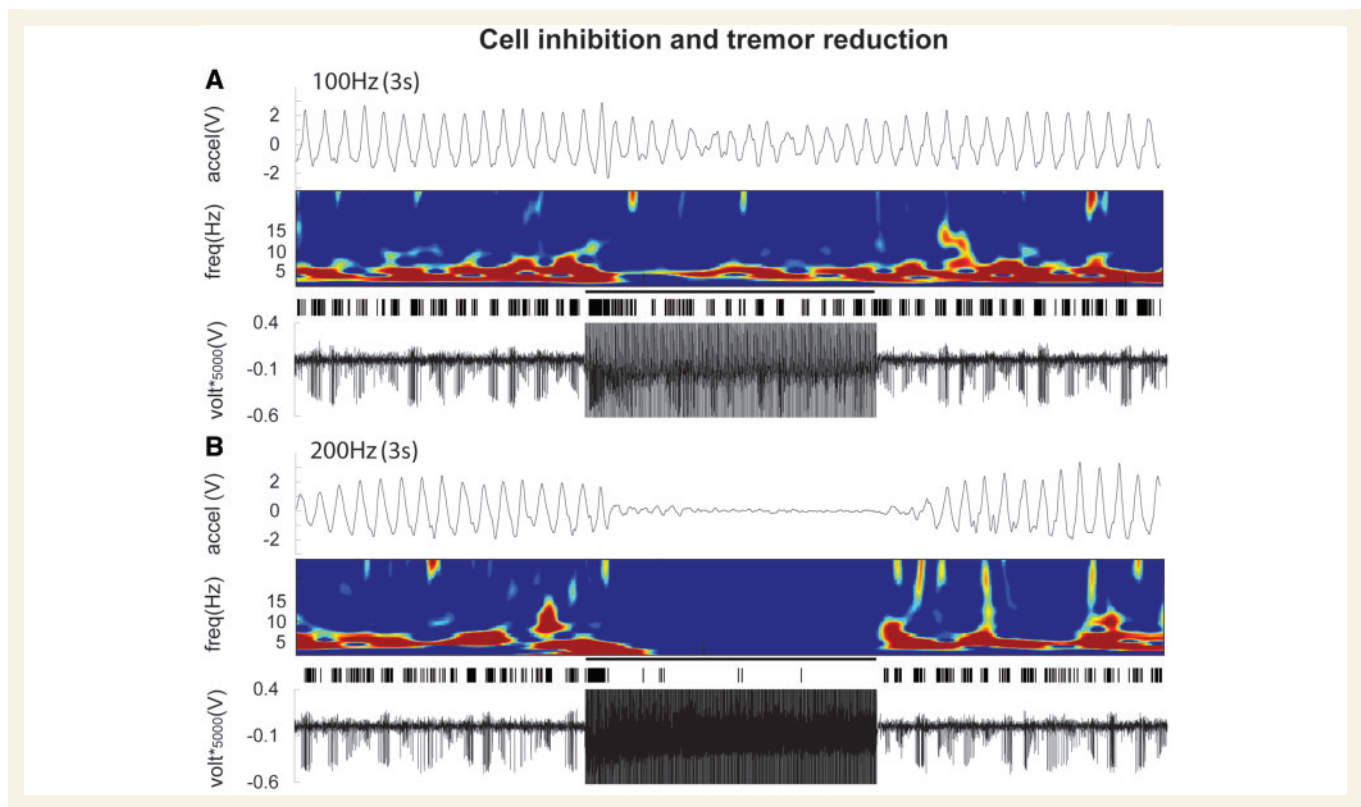


Figure 2 Sample data during 100 Hz (A) and 200 Hz (B) stimulations from a single patient. Collectively, the figures show that 200 Hz stimulation led to near complete cell inhibition and tremor reduction, while 100 Hz was insufficient for achieving these phenomena. The bottom trace in each panel is a raw microelectrode recording during stimulation from the adjacent microelectrode. Above that is the artefact-removed, template-matched spike, which shows the neuronal activity during the stimulation train. The spectrogram demonstrates the frequency of the spike bursting (depicting a 5 Hz synchronous discharge of the neuronal firing; tremor cell), and shows that at 200 Hz (when spike firing is mostly inhibited) the 5 Hz tremor-related activity is desynchronized, but at 100 Hz (when spike firing is persistent) the 5 Hz activity is still present. The top trace in each panel is the accelerometer signal during postural tremor of the contralateral hand.

recordings from the wrist extensor muscles showed an average fast latency muscle activation of 62 ± 4 ms from the start of the stimulation train during phase resets.

Tremor reduction and cell inhibition during stimulation

Higher neuronal inhibition was associated with improved tremor reduction, which was more prominent at 200 Hz. Figure 3A shows that 200 Hz stimulation led to $68 \pm 8\%$ ($P < 0.001$) inhibition of neuronal firing compared to baseline, and a $53 \pm 5\%$ ($P < 0.001$) reduction in tremor, while 100 Hz only reduced firing by $26 \pm 12\%$ (not significant) with a $17 \pm 6\%$ ($P < 0.05$) tremor reduction. At 200 Hz, both the cell inhibition ($P < 0.001$) and tremor reduction ($P < 0.001$) were significantly higher than at 100 Hz. Figure 3B shows that the degree of neuronal inhibition and tremor reduction were significantly correlated with a second-order polynomial fit ($R^2 = 0.28$, $P < 0.001$), most representative of the relationship. There was also a significant linear correlation ($R^2 = 0.28$, $P < 0.001$; not shown in the figure).

Spatial distribution of tremor reduction

The most ventroposterior stimulation sites, closest to the Vim-Vc border, had the best effect on tremor. Figure 4 shows that tremor reduction and proximity to the Vim-Vc border were significantly correlated at both 100 Hz ($R^2 = 0.17$, $P < 0.05$) and 200 Hz ($R^2 = 0.33$, $P < 0.001$). At 200 Hz, stimulation sites within 1 mm of the Vim-Vc border led to a tremor reduction of $70 \pm 4\%$.

Transient stimulation-induced driving of neuronal activity

In all recording sites with transient driving responses, the bursts were present during both 100 Hz and 200 Hz stimulations. Figure 5B shows that the duration of the bursts at 100 Hz (421 ± 24 ms) was significantly longer ($P < 0.001$) than at 200 Hz (194 ± 21 ms), there were significantly more ($P < 0.01$) spikes per burst at 100 Hz (71 ± 11) compared to 200 Hz (30 ± 4), the latency from stimulation onset to burst onset was significantly longer ($P < 0.05$) at 100 Hz (36 ± 4 ms) compared to 200 Hz (24 ± 3 ms), but

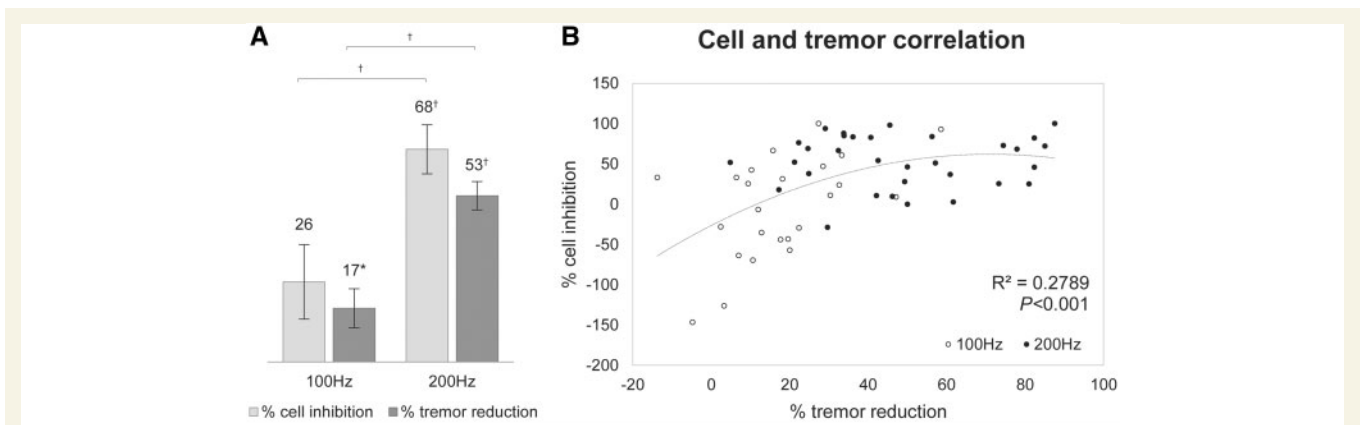


Figure 3 Neuronal inhibition and tremor reduction. (A) The degree of cell inhibition and tremor reduction during stimulation trains at 100 Hz and 200 Hz compared to baseline for stimulations across all recording sites. At 200 Hz, there was significantly more cell inhibition and tremor reduction compared to 100 Hz. (B) The correlation between cell inhibition and tremor reduction across all recording sites, fitted with a second order polynomial. * $P < 0.05$, † $P < 0.001$.

there was no significant difference between the burst firing rates between 100 Hz (166 ± 21 Hz) and 200 Hz (154 ± 16 Hz), likely due to the refractory period of spike firing.

Discussion

A major finding of the present study is that—following an initial transient driving response—both the firing of Vim neurons and contralateral hand tremor were strongly suppressed during 200 Hz microstimulation, and not affected or only partially reduced during 100 Hz. Therefore, thalamic neuronal inhibition seems necessary for tremor reduction and may function as a thalamic filter to uncouple thalamo-cortical from cortico-spinal reflex loops.

The likely reason for this pattern of brief excitation followed by inhibition is the activation of afferent inputs to the neurons. The Vim is primarily innervated by excitatory glutamatergic projections from both the dentate nucleus of the cerebellum (Asanuma *et al.*, 1983; Anderson and Turner, 1991; Kultas-Ilinsky and Ilinsky, 1991; Kuramoto *et al.*, 2011) and the cerebral cortex (Bromberg *et al.*, 1981; Sherman and Guillery, 1996). The less prominent afferent inputs are the inhibitory GABAergic thalamic reticular projections (Ambardekar *et al.*, 1999; Ilinsky *et al.*, 1999; Kuramoto *et al.*, 2011). The activation of glutamatergic presynaptic terminals by electrical stimulation would explain why the somadendritic part of the neurons produced the initial burst of action potentials. It may also explain why Vim neurons were not as prone to inhibition compared to neurons in the STN, substantia nigra pars reticulata (SNr), and GPi that we have previously studied (Liu *et al.*, 2012; Milosevic *et al.*, 2017). The predominant afferent inputs of these basal ganglia structures are GABAergic (Rinvik and Ottersen, 1993; Parent and Hazrati, 1995a,b), and we found that 100 Hz stimulation

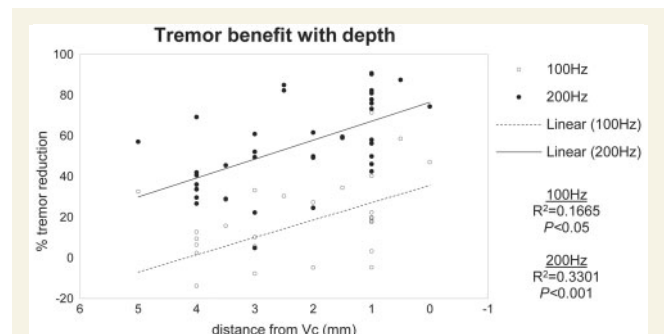
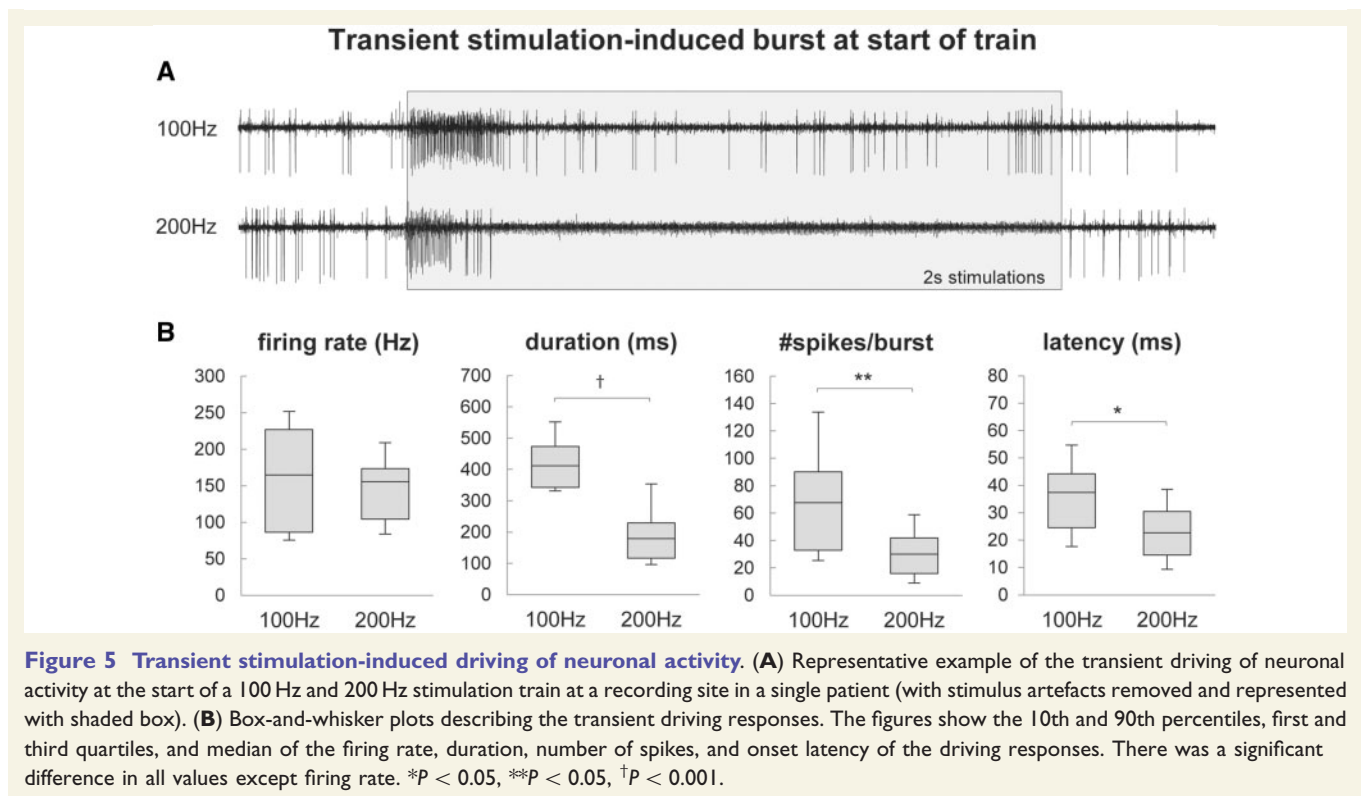


Figure 4 Tremor reduction with respect to distance from ventral caudal nucleus. The correlation suggests that clinical benefit was maximal at recording sites closest to the Vim-Vc border. The 0-mm mark is the first location with patient-reported paraesthesia. This does not imply that the recorded neuron at that site was in Vc, but rather that the stimulation has begun to spread into Vc.

was effective at completely silencing neuronal firing in the STN, while SNr and GPi could be silenced with an even lower frequency of 50 Hz. Furthermore, neither transient nor tonic excitatory responses occurred in those structures, unlike in Vim. This suggests that the mechanism of action of electrical stimulation is dependent on the underlying microcircuit anatomy of the target structure.

Initial burst and subsequent inhibition during high frequency stimulation

A modelling study by Kuncel *et al.* (2012) predicted that with 125 Hz Vim-DBS, neuronal firing is either entirely inhibited, or exhibits a sustained entrainment. However, our findings showed that there is a bimodal response, and appear to support the theory by Dittman *et al.* (2000) that there may be interplay between facilitation and



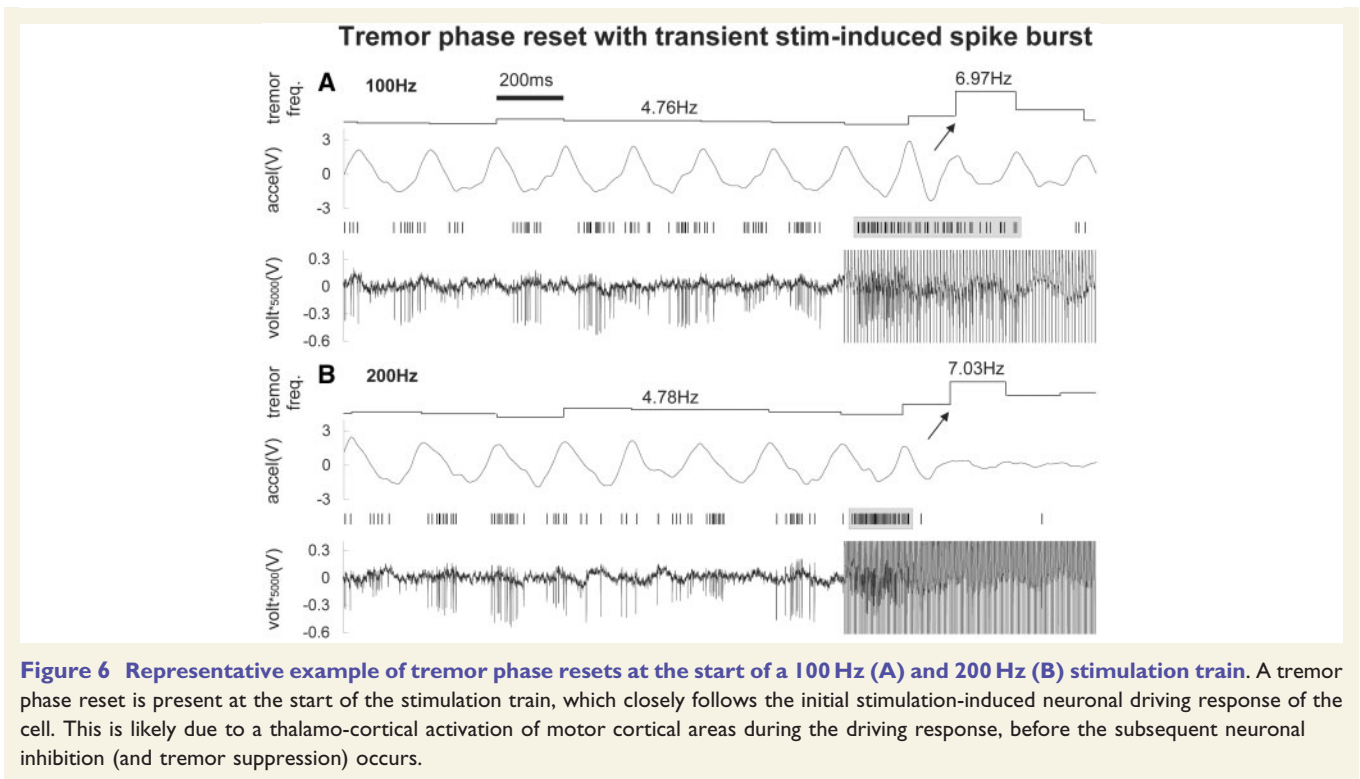
depression. In many synapses (especially glutamatergic, due to their lower probabilities of neurotransmitter release) there is a ‘short-lived’ synaptic facilitation that occurs at the onset of repeated stimulation, believed to occur by increased presynaptic calcium (Katz and Miledi, 1968). The facilitation is followed in short order by synaptic depression (Katz, 1966; Malenka and Siegelbaum, 2001; Fioravante and Regehr, 2011), believed to occur by vesicle depletion and/or decreased presynaptic calcium (Zucker and Regehr, 2002; Fioravante and Regehr, 2011). When a rapid stimulus results in release of a readily releasable pool of neurotransmitter vesicles, subsequent stimuli delivered before replenishment will release fewer vesicles, eventually depleting the pool (Zucker, 1989; Rosenmund and Stevens, 1996). Modelling studies have shown that synaptic depression increases when the initial release probability and/or frequency of activation are increased (Dittman and Regehr, 1998; Zucker and Regehr, 2002; Rizzoli and Betz, 2005; Fioravante and Regehr, 2011). Indeed, these findings have been found to hold true in glutamatergic cortico-thalamic synapses in a rat brain slices (Ran *et al.*, 2009).

With lower stimulation frequencies, which would allow sufficient time for vesicle replenishment, the driving response should be sustained (Supplementary Fig. 1). Although we were not able to measure synaptic field potentials, previous studies from our group (Liu *et al.*, 2012; Milosevic *et al.*, 2017) have shown that the rate of attenuation of extracellular inhibitory postsynaptic potentials in SNr and GPi increases as stimulation frequency is

increased, indicative of frequency-dependent neurotransmitter depletion/synaptic depression as a mechanism of HFS.

An intracellular sensorimotor thalamic rat brain slice study by Anderson *et al.* (2004) has indeed shown that HFS leads to an initial transient depolarization, characterized by a burst of action potentials. Following the initial burst, the neurons were either quickly repolarized and returned to a quiescent baseline, or maintained some level of membrane depolarization, with or without spike firing. Reduction in the initial depolarization was achieved with application of kynurenic acid, a non-specific antagonist of ionotropic glutamate receptors, as well as with application of NMDA receptor blocker, and sodium channel blocker. This suggests that the HFS-induced depolarization was primarily mediated by glutamate. Furthermore, blockade of voltage-dependent calcium channels, which reversibly inhibited the depolarization, suggested that the depolarization was mediated primarily through pre-synaptic calcium channels (Anderson *et al.*, 2004), which are known to facilitate transmitter release (Zucker and Regehr, 2002). Thus, Anderson *et al.* (2004) hypothesize that HFS in the ventral thalamus disrupts local synaptic function and neuronal firing thereby leading to a ‘functional deafferentation’.

Alternatively, other postsynaptic mechanisms may underlie the stimulation-induced burst at the onset of HFS. When thalamic neurons are hyperpolarized for 50–100 ms, incoming excitatory synaptic potentials trigger activation of T-type Ca^{2+} currents (Jahnsen and Llinas, 1984a), which causes the cell to fire a burst of action potentials. This leads to further calcium channel



openings, which eventually trigger calcium-activated potassium currents, which quickly hyperpolarize the cell and reset it for another cycle of bursting. While these mechanisms may explain the generation of rhythmic bursts (i.e. tremor cells), they are less likely to explain the lack of continued bursting (sustained inhibition) that we have shown here occurs during HFS. The more likely involvement of the T-current is that the initial excitatory response (via glutamate release) leads to inactivation of T-type Ca^{2+} channels, thereby preventing bursting activity. Beurrier *et al.* (2001) have shown that in the STN of rat brain slices, there is an inhibition of neuronal activity that outlasts a 1-min train of HFS. They found that (L- and) T-type Ca^{2+} currents were indeed transiently depressed during the HFS-induced silence. Additionally, they found that the HFS-induced inhibition was persistent in the presence of blockers of ionotropic GABA and glutamate receptors, and suggest that the inhibition was non-synaptic. However, they did not study the synaptic function during HFS. Thus, neurotransmitter blockers would not affect the persistent inhibition if synaptic function was already depressed due to the HFS.

Furthermore, thalamic inhibition has been linked to the activity of neuromodulators. Bekar *et al.* (2008) found that in rodent thalamic slices, DBS caused increased levels of adenosine, which they hypothesized led to neuronal inhibition that was necessary for suppression of tremor. Additionally, Dirx *et al.* (2017) showed that the treatment of Parkinson's tremor with levopoda was associated with increased thalamic self-inhibition, which may be a physiological mechanism that protects the thalamus from a permanent oscillatory state.

Thalamic gating

This study offers mechanistic insight on the gating properties of the Vim and its thalamo-cortical projection. The Vim sends excitatory glutamatergic projections to cortical motor regions in order to modulate movements (Rouiller *et al.*, 1994). In this study, we have identified five different types of Vim firing patterns that corresponded to different motor states. First, there were three described previously in the literature that occurred in the absence of electrical stimulation, exemplified in Fig. 7. When the patient was at rest with no tremor, the neurons exhibited (i) tonic irregular firing. Both passive and voluntary manipulations of the limb led to (ii) kinaesthetic movement-related responses (Ohye and Narabayashi, 1979; Lenz *et al.*, 1990). When the patient had tremor, the neuron exhibited (iii) tremor-related (4–6 Hz) bursting (Albe-Fessard *et al.*, 1963). The significance of these classifications is the potential to use this real-time information in an application of closed-loop DBS (Priori *et al.*, 2013; Arlotti *et al.*, 2016) for the control of tremor. A novel finding of this study was the stimulation-induced (iv) transient driving of Vim neurons that reset the regular periodic rhythmicity of the tremor (Fig. 6). The most likely explanation of this is that the transient neuronal driving response leads to an activation of thalamo-cortical motor neurons either in the primary or supplementary motor cortical areas (Rouiller *et al.*, 1994) via collaterals that give rise to the transcortical reflex that then quickly activate the forearm muscles. Our EMG results showed a fast latency muscle activation that is consistent with thalamo-cortical activation of the transcortical reflex. In many

simple laboratory models of central pattern generators, such as the locust thoracic ganglion motor neuron recordings, a very similar phenomenon of rhythmic reset is observed with short train out-of-phase stimulation of the isolated proprio-sensory input from the wing to the central pattern generator (Pearson, 1991; Marder and Bucher, 2001). In fictive locomotion induced by mesencephalic locomotor region stimulation in the decerebrate paralysed cat, a prominent reset of the step cycle is produced by brief out-of-phase 100 Hz stimulation of the Group I muscle spindle afferents (Guertin *et al.*, 1995; Hiebert *et al.*, 1996). This would suggest that tremor reset and tremor reduction is due to interruption of the pacing of proprioceptive input in human thalamus, which is found near the Vim-Vc border that receives input from deep muscles (Tasker *et al.*, 1987; Vitek *et al.*, 1994). Indeed, our results show that more efficacious tremor reduction was at stimulation sites closest to the Vim-Vc border.

While the phase reset demonstrates that a transient excitatory neuronal response in Vim would facilitate a brief movement, the subsequent (v) inhibition of neuronal activity was associated with a reduction of tremor. This finding supports the hypothesis (Anderson *et al.*, 2004) that DBS at a high frequency may in effect function as a reversible lesion, which disrupts the pathological tremor-genic rhythmicity of Vim (Fig. 2B). Indeed, we have found that at a lower stimulation frequency (100 Hz) that is less effective at inhibiting the firing of Vim neurons, the tremor and tremor-related bursting persists (Fig. 2A). These findings support recent functional MRI findings by Dirkx *et al.* (2017), which suggest that efficacious treatment of tremor with levodopa may act by increasing thalamic self-inhibition. However, it is unlikely that the stimulation-induced inhibition of Vim only effects tremor, but may also be associated with a more widespread inhibition of movements. The continuous inhibition of neuronal activity in this area may explain the commonly reported adverse effects on other motor functions such as gait disturbances and ataxia (Cury *et al.*, 2017), or less commonly weakness/uncertainty of the treated limbs (Takahashi *et al.*, 1998). With respect to the gating function of Vim, it supports the notion that inhibition of neuronal activity has a role in downregulation of movements, including perhaps non-pathological (Strafella *et al.*, 1997). This would further justify the need for a closed-loop system to selectively control tremor, in order to offset the chronic adverse effects of unnecessary continuous stimulation.

Taken together, these observations support the theory that the Vim acts as a gate for incoming information required to trigger movements. Depending on the input it receives (inhibitory, excitatory, rhythmic, etc.), its thalamocortical projection gives rise to an appropriate motor action. It also shows that the Vim can be selectively modulated by external stimuli. This likely explains why HFS relieves tremor, low frequency stimulation has been shown to induce or worsen tremor (Hassler *et al.*, 1960; Barnikol *et al.*, 2008; Pedrosa *et al.*, 2013) likely due to

persistent driving/entrainment of neuronal activity (Supplementary Fig. 1), and also why additional incoming proprioceptive information may desynchronize tremor-related activity (Naros *et al.*, 2018). It may also explain why anti-phasic rhythmic stimulation has been reported to be efficacious for suppressing tremor (Cagnan *et al.*, 2013), which likely works by regularizing the overall neuronal firing in Vim by producing short excitations between tremor bursts, rather than by overall inhibition which we have shown here appears to be the mechanism of continuous HFS.

Clinical utility

We found that the degree of cell inhibition was correlated to the degree of tremor reduction, suggesting that suppression of neuronal firing in the Vim is likely an important mechanism of DBS for the control of tremor. Our finding of better tremor suppression with 200 Hz supports clinical studies (Blomstedt *et al.*, 2007; Earhart *et al.*, 2007; Kuncel *et al.*, 2012), which suggest that Vim-DBS produces better tremor benefit with higher programmed stimulation frequencies than typically used for STN (~185 Hz versus ~130 Hz). Single and multicentre studies have reported an average tremor reduction of ~80% with Vim-DBS in essential tremor patients (Ondo *et al.*, 1998; Koller *et al.*, 1999; Rehnrona *et al.*, 2003). We found a reduction of $53 \pm 5\%$ with microstimulation at 200 Hz, which is likely due to stimulating a much smaller population of neurons as well as testing less effective sites dorso-anterior to the tentative target site. The most effective sites for tremor reduction were in close proximity to the Vim-Vc border. At stimulation sites within 1 mm of the Vim-Vc border, 200 Hz microstimulation led to a tremor reduction of $70 \pm 4\%$, comparable to that of the reported benefit of DBS macro-stimulation. This finding is important in informing surgical electrode placement, which can be accounted for intraoperatively with micro-recording and stimulation. It also supports neurosurgical observations that the ideal location for a Vim thalamotomy is the small section of Vim near Vc that receives proprioceptive input (Tasker *et al.*, 1987). A recent study identified that more posterior DBS electrode placements were associated with failure of benefit, and more anterior placements were optimal (Sandoe *et al.*, 2018). Our study shows that microstimulation of the ventroposterior region of Vim (i.e. as close to Vc as possible, without inducing paraesthesia) yielded the best tremor reduction, within the standard Vim-DBS trajectory. This is likely due to the larger size of DBS electrodes and the contacts being too close to Vc, producing paraesthesias that limit the current density required for tremor reduction. In the advent of novel 'current-steering' electrodes, this finding may be able to inform stimulation delivery, i.e. placement of the DBS electrode near the Vim/Vc border, but directing the current away from Vc.

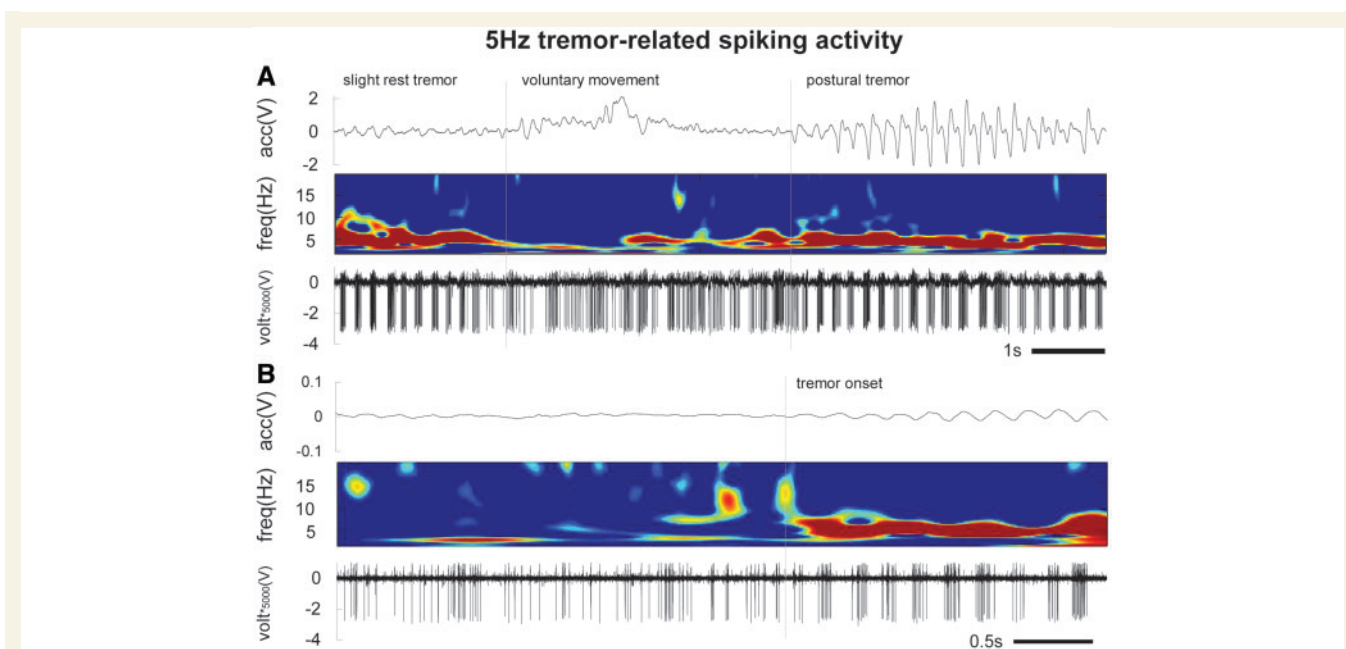


Figure 7 Tremor and movement-related spiking in Vim in a single neuron. (A) 5 Hz spiking activity is present during a slight rest tremor. When the patient was asked to raise their arm (to begin our experimental protocol), there is a voluntary movement-related kinaesthetic response and an interruption in the 5 Hz tremor-related activity. This is followed by a re-emergence of tremor bursting with the maintenance of a tremorgenic posture (postural tremor). (B) At rest with no tremor, the neuron had irregular tonic firing, and the emergence of 5 Hz bursting was robustly measurable even with the slightest tremor onset.

Functional implications

Additionally, suboptimal electrode placement can be clinically compensated for by increasing the volume of tissue activation. However, this increases the risk of stimulating different neuro-circuits that lack relevance to the patient pathology, which likely gives rise to side-effects such as paraesthesia and dysarthria (Cury *et al.*, 2017). Our study confirms the existence of an optimal site within the standard Vim trajectory, just anterior to the Vim-Vc border. At sites within 1 mm of the Vim-Vc border, 200 Hz microstimulation led to comparable long-term benefit of previously reported DBS macro-stimulation, despite stimulating a smaller population of neurons. This demonstrates the potential for improving therapeutic window by (i) minimizing the volume of tissue activation (reduces risk of side-effects); and (ii) minimizing the size of the stimulating electrode to have a more focal target (reduces risk of oedema, haemorrhage, micro-lesion, etc.).

Additionally, having an embedded electrode with a significantly smaller effective contact size can allow for the possibility to chronically record single neurons (DBS macroelectrodes are limited to local field potentials). Although ambitious, DBS technologies are evolving more rapidly than ever (Arlotti *et al.*, 2016). This would allow for measurement of tremor-related neuronal activity to be used as a control parameter for adaptive DBS systems. Since tremor amplitude and prevalence can fluctuate over time, within seconds or minutes (Beuter and Vasilakos,

1995*a, b*), continuous open-loop strategies present an inefficient solution. Closed-loop DBS has been explored in Parkinson's disease using beta (12–35 Hz) oscillations (Little and Brown, 2012; Little *et al.*, 2013), but tremor-related activity in Vim may be a more robust and promising symptomatic correlate (Fig. 7).

Finally, we have shown that HFS can downregulate activity, which is important in essential tremor (where Vim receives pathophysiological input from cerebellum) and Parkinson's disease (where the STN is believed to be overactive; Delong, 1990). However, we propose that stimulation at lower frequencies (conductive to excitation, but insufficient for neuronal inhibition) may be able to persistently drive/entrain neuronal firing in a target structure with predominantly glutamatergic inputs (Supplementary Fig. 1). This could have implications for upregulating activity in pathologies where structures may be underactive.

Limitations

One limitation of human intraoperative studies is the inability to use pharmacological agents to elucidate specific synaptic mechanisms. In contrast, these studies have the advantage over animal studies in that it is not known how well animal models correspond to human conditions, or anatomy. Furthermore, DBS is delivered chronically over a long period of time, while the time course of our intraoperative stimulation is limited. DBS macroelectrodes also stimulate a much larger population of neurons, with a

current density that is capable of spreading up to 2 mm from the centre of a contact (Wu *et al.*, 2001; Erez *et al.*, 2009). Despite the short durations of stimulation and smaller volume of tissue activation with a microelectrode, we were still able to produce marked therapeutic symptomatic benefit, especially when delivered to the optimal location. Thus, our findings should be applicable to understanding the mechanisms that might be involved in Vim-DBS. A future study to validate our findings within the Vim would be the demonstration of tremor reduction in response to direct activation of the afferent dentatothalamic tracts (Coenen *et al.*, 2014). While our results suggest that HFS of the Vim, and in particular ventroposterior Vim/Vc border region, does lead to marked tremor reduction, it would also be of interest to compare our results to other targets implicated in tremor suppression, such as caudal zona incerta, prelemniscal radiations, or subthalamic nucleus, as outlined in Elble and Deuschl (2011), which may have stronger effects. Another interesting prospective study would be the investigation of the effect of low frequency stimulation on Vim neuronal activity, and the potential relationship with the purported worsening of tremor.

Conclusions

Our study shows that the degree of neuronal inhibition in the Vim is associated with the degree of tremor suppression. The predominance of glutamatergic boutons located on somas of Vim neurons may explain why Vim was more resistant to neuronal inhibition than structures such as STN, SNr and GPi, which have predominantly GABAergic inputs. Hence, the mechanism of action of electrical stimulation is dependent on the underlying anatomical and physiological properties of the stimulated target structures. The transient excitatory responses at the onset of stimulation likely reflect those glutamatergic inputs, whereas the subsequent inhibition may be due to synaptic fatigue. Furthermore, we have shown that the location for maximal tremor suppression within the Vim is the ventroposterior region proximal to the Vim-Vc border. Finally, some of the response properties described in this study can help guide advancement of DBS therapy. First, the potential for using Vim tremor-related spike bursting as a robust, real time predictor of tremor onset and occurrence, and second, the potential for using electrical stimulation to upregulate neuronal activity.

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Conflict of interest

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Supplementary material

Supplementary material is available at *Brain* online.

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