Stimulus features underlying reduced tremor suppression with temporally patterned deep brain stimulation

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DEEP BRAIN STIMULATION (DBS) is an established therapy for the treatment of movement disorders, including essential tremor (ET) and Parkinson’s disease (PD). Although the clinical benefits of DBS are well-documented, fundamental questions remain about the mechanisms of action. A hallmark of the effects of DBS on motor symptoms is the effect of stimulation frequency (Birdno and Grill 2008). Maximum reductions in symptoms are typically observed only when the frequency of stimulation is >90 Hz, and lower frequencies are ineffective or may exacerbate symptoms (Benabid et al. 1991; Kuncel et al. 2006; Ushe et al. 2004). The similarity of the clinical effects of ablative lesions and DBS (Vitek 2002) and the frequency-dependent effects of DBS gave rise to the hypothesis, termed the informational lesion, that effective DBS masks the intrinsic pattern of neural activity in the stimulated nucleus and replaces it with constant-rate firing time locked to the stimulus (Grill et al. 2004). Consistent with this hypothesis, stimulation with temporally random patterns, which did not regularize neural firing, was not effective in suppressing tremor by thalamic DBS in ET (Birdno et al. 2008) or in treating bradykinesia by subthalamic nucleus (STN) DBS in PD (Dorval et al. 2010). These results revealed that simply high-rate stimulation was not sufficient for symptom reduction, but it was not clear which characteristic(s) of temporally irregular DBS trains reduced their effectiveness. In the present study, we conducted measurements in human subjects with tremor and computer simulations in a model of thalamic DBS to determine the characteristic(s) of irregular stimulation trains that rendered them ineffective.

We used specific temporal patterns of stimulation to quantify the relative contributions of three characteristics to the loss of efficacy with high-rate irregular stimulation: pauses, bursts, and irregularity per se. The first hypothesis (\(H_{\text{pause}}\)) was that pauses (long interpulse intervals, IPIs) in stimulation enabled pathological activity to propagate through the thalamus. The source of the activity could be either physiological (i.e., intrinsic pathological activity returned during pauses in stimulus trains) or stimulus-generated (e.g., long periods of hyperpolarization during stimulation deinactivated membrane conductances to enable rebound bursts during pauses). The second hypothesis (\(H_{\text{burst}}\)) was that brief bursts of high-rate stimulation drove burstlike activity in the thalamus. The presence of thalamic bursts is correlated with the symptoms of motor disorders, and irregular trains with short bursts of high-frequency stimulus pulses may disrupt the fidelity of thalamic throughput (Rubin and Terman 2004). The third hypothesis (\(H_{\text{IR}}\)) was that the stimulus-train irregularity per se corrupted the effectiveness of the stimulus train. Even if irregular DBS is able to override intrinsic pathological patterns of activity, it does not drive regular firing patterns and thus is clinically ineffective.

Both experimental and computational results from this study indicate that the decreased effectiveness of irregular DBS trains is due to pauses between stimulus pulses and that temporally irregular DBS can indeed suppress tremor effectively if there are no long pauses. Furthermore, our findings indicate that the mechanism by which DBS suppresses tremor is by masking burst-driver inputs to the thalamus from the...
cerebellum. Importantly, these findings provide a mechanistic basis for correlative clinical studies, which indicate that the most effective electrode location for tremor suppression is near cerebellar fibers that terminate in the thalamus (Coenen et al. 2011; Hamel et al. 2007; Herzog et al. 2007; Jimenez et al. 2000; Kitagawa et al. 2005; Struppler et al. 1978), and recent preclinical studies suggesting that activation of presynaptic axons in the STN was necessary and sufficient to alleviate bradykinesia in a rodent model of PD (Gradinaru et al. 2009).

Although stimulation of other anatomic targets may provide tremor suppression, we propose that the most relevant neuronal targets for effective tremor suppression are the afferent cerebellar fibers that terminate in the thalamus.

MATERIALS AND METHODS

Ethical approval. Subjects participated on a volunteer basis with written informed consent, and the study protocol was approved by the Institutional Review Boards at Duke University and Emory University.

Human subjects and stimulation delivery. We conducted experiments on 8 subjects with tremor (7 ET and 1 multiple sclerosis) that was responsive to DBS of the ventral intermediate (Vim) nucleus of the thalamus and who were having their implantable pulse generator(s) (IPG) surgically replaced due to depleted batteries. Demographic characteristics and stimulation settings for each subject are shown in Table 1. Some subjects reported transient paresthesias for some stimulation settings, but there were no adverse events and no incidents of infection.

Irregular trains of stimulation cannot be delivered using the clinical IPG (Soleta Model 7426 or Kineta Model 7428; Medtronic, Minneapolis, MN); therefore, we used an external stimulator that was connected to the implanted DBS lead extension via a custom sterile extension cable at the time of IPG replacement. Stimuli were delivered with an isolated stimulator (bp Isolator; FHC, Bowdoinham, ME), and pulses were controlled by a high-speed digital-to-analog converter via LabVIEW software (National Instruments, Austin, TX). The regulated voltage stimulation waveform was an asymmetric, charge-balanced, biphasic pulse with a large-amplitude, short-duration primary phase followed by a low-amplitude, long-duration recharge phase similar to that used in the IPG. The amplitude of the recharge phase was 10% of the primary phase amplitude, and the duration of the recharge phase was 10 times the primary phase duration. Pulse width (PW) and stimulus amplitude were set to clinically programmed values (Table 1), and charge densities were below the manufacturer’s recommended limit of 30 μC/cm² per phase (using the conservative estimate that impedance = 500 Ω). In 2 cases where clinical settings included the IPG case as the anode, the electrode configuration was changed such that the contact farthest from the cathode(s) was selected as the anode (Table 1).

Intraoperative measurements of tremor. We measured tremor in the contralateral limb during unilateral stimulation with six different temporal patterns of stimulation and with stimulation off (controls) in single intraoperative sessions with each subject. Stimulation patterns were presented in a randomized block design, and the subject was blinded to the experimental condition. In each of three trial blocks, each of the seven experimental conditions was presented for 1 min in randomized order. Each trial began with 1 min of stimulation off; with baseline tremor measured for 20 s beginning ~30 s into these intervals, and ~30 s after each condition was initiated experimental tremor was measured for 20 s (Fig. 1A).

Tremor was measured using an accelerometer (5-V/4-g sensitivity; Crossbow CXL04LP3; San Jose, CA) taped to the dorsum of the hand. The amplitude of tremor recorded by an accelerometer correlates well with clinical tremor rating scales (Elble et al. 2006). To obtain a single quantitative measure of tremor for each trial, we first calculated the power spectral density for each of the three acceleration signals (AX, AY, and AZ; Fig. 1B) using the psd function [Welch’s averaged periodogram, Hanning window, fast Fourier transform (FFT) length = 5,000] in MATLAB (MathWorks, Natick, MA). Next, we integrated each spectrum from 2 to 20 Hz to get P_X, P_Y, and P_Z. Finally, we summed P_X, P_Y, and P_Z, the tremor power in the x-, y-, and z-dimensions, respectively. The frequency range of 2–20 Hz was chosen to include the primary and several harmonics of the tremor and to exclude steady-state acceleration due to gravity.

Table 1. Demographic characteristics and stimulation settings for each subject

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age, yr/Sex</th>
<th>Diagnosis</th>
<th>Arm Position During Tremor Trials</th>
<th>*Electrode Contacts</th>
<th>PW, μs</th>
<th>Amplitude, V</th>
<th>Medications Taken Morning of Experiment</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>57/M</td>
<td>ET</td>
<td>Elbow extended and unsupported, holding bottle (~20 oz)</td>
<td>0−1 2+</td>
<td>120</td>
<td>5.0</td>
<td>Ropinirole hydrochloride</td>
</tr>
<tr>
<td>B</td>
<td>31/M</td>
<td>MS</td>
<td>Elbow unsupported and extended (blocks A and B), elbow flexed (block C)</td>
<td>0−1 3+ [0−1 2− 3− 4−]†</td>
<td>120</td>
<td>5.4</td>
<td>None</td>
</tr>
<tr>
<td>C</td>
<td>78/M</td>
<td>ET</td>
<td>Elbow and wrist both supported and relaxed</td>
<td>0−1 2− 3+</td>
<td>150</td>
<td>4.9</td>
<td>None</td>
</tr>
<tr>
<td>D</td>
<td>65/F</td>
<td>ET</td>
<td>Elbow flexed and supported; wrist unsupported and straight</td>
<td>0−1 2+</td>
<td>90</td>
<td>3.1</td>
<td>Propranolol, midazolam for surgery</td>
</tr>
<tr>
<td>E</td>
<td>79/M</td>
<td>ET</td>
<td>Elbow flexed and supported; wrist unsupported and straight</td>
<td>1−2 3+ [1−2 4+]†</td>
<td>90</td>
<td>2.4</td>
<td>None</td>
</tr>
<tr>
<td>F</td>
<td>82/F</td>
<td>ET</td>
<td>Elbow and wrist both straight and unsupported</td>
<td>0−2+</td>
<td>90</td>
<td>4.0</td>
<td>None</td>
</tr>
<tr>
<td>G</td>
<td>75/M</td>
<td>ET</td>
<td>Elbow flexed and supported, wrist unsupported and straight (block A). Elbow straight and unsupported; wrist unsupported and extended (blocks B and C)</td>
<td>1−2+</td>
<td>60</td>
<td>3.3</td>
<td>Propofol during surgery</td>
</tr>
<tr>
<td>H</td>
<td>62/M</td>
<td>ET</td>
<td>Elbow flexed and supported, wrist unsupported and relaxed</td>
<td>1−2+</td>
<td>120</td>
<td>3.0†</td>
<td>None</td>
</tr>
</tbody>
</table>

*Deep brain stimulation (DBS) electrodes contain 4 contacts, with 0 being the most distal and 3 the most proximal. C, case of implantable pulse generator (IPG) used as anode. Contacts programmed as anodes are denoted by +, and contacts programmed as cathodes are denoted by −. †Experimental contact configurations differed from clinically programmed configurations (clinical configurations in brackets). ‡Amplitude decreased in subject H from clinical amplitude of 3.7 V due to strong stimulus onset paresthesias in this subject. M, male; F, female; PW, pulse width; ET, essential tremor; MS, multiple sclerosis.

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Temporal patterns of stimulation. The patterns of stimulation were designed to isolate the characteristic(s) that may render irregular stimulus trains ineffective at suppressing tremor: pauses, bursts, and irregularity per se. The stimulus trains included three irregular patterns with large entropies ($H_1 = 5.2–5.6$ bits/pulse; Fig. 2, A–C), two periodic patterns with low entropy ($H_1 = 1$ bit/pulse) that consisted of constant-rate pulses interrupted by either long pauses (Fig. 2D) or short bursts of pulses at twice the base frequency (Fig. 2E), and regular stimulation at 185 Hz. All stimulus trains had a geometric mean of 185 Hz.

The stimulus-train distributions were created using entropy as the measure of irregularity and were computed in log space. Stimulus-train types were constructed in log space because distributions in log space have the same shape (e.g., uniform) and entropy regardless of whether the distribution is constructed with respect to frequencies or IPIs. This is because the nonlinear relationship between frequency and IPI, $F = 1/IPI$, becomes a linear relationship in log space: 

$$\log(F) = \log(1) - \log(IPI) = -\log(IPI).$$

Second, common measures used to compute the degree of irregularity in events drawn from a distribution include the coefficient of variation and the entropy of the distribution. The coefficient of variation is simple but ineffective in describing the variability of multimodal distributions (Holt et al. 1996). On the other hand, the entropy of a distribution provides an estimate on the maximum degree of irregularity present in the distribution and can be generalized to any type of distribution (Darbin et al. 2006; Dorval et al. 2008).

The first high-entropy train (Uniform; Fig. 2A) had instantaneous pulse frequencies (IPFs) drawn from a log-uniform distribution with a minimum at 90 Hz and a maximum at $\sim 380$ Hz. The Uniform train was highly irregular but contained no pauses or bursts (i.e., there were no IPIs outside of the established therapeutic frequency range of 90–380 Hz). The second high-entropy train (Unipeak; Fig. 2B) had IPFs also drawn from a log-uniform distribution but with wider frequency limits such that pauses (IPIs $> 20$ ms) arrived at a rate of 5.4 Hz (i.e., at least as fast as the dominant tremor frequency). The unipeak distribution had a sharp peak at 185 Hz to ensure that the entropies of the unipeak and Uniform distributions were equal. The third high-entropy train (Bimodal; Fig. 2C) had IPFs drawn from two log-uniform distributions and contained many pauses and bursts.

The first low-entropy periodic train (Absence; Fig. 2D) contained long pauses that came at a rate of 4.4 Hz, consistent with the predominant frequency of tremor in ET subjects (Deuschl et al. 1998). The second periodic train (Presence; Fig. 2E) contained brief increases in stimulus rate intended to drive bursting in thalamic neurons. These bursts of stimulus pulses occurred at 4.4 Hz (Deuschl et al. 1998) and lasted 52.57 ms, consistent with the burst duration observed in ET (Hua and Lenz 2005).

Computational model. We implemented and validated a biophysically based computational model of a thalamic neuronal network to simulate the responses of neurons in the Vim nucleus of the thalamus.

Fig. 1. Intraoperative measurements of tremor in response to different temporal patterns of thalamic deep brain stimulation (DBS). A: trial timeline that was followed to measure tremor suppression under experimental conditions. B: triaxial raw accelerometer signals ($A_x$, $A_y$, and $A_z$) recorded during 2 tremor trials in subject F. The raw traces illustrate the acceleration magnitude in each of the 3 dimensions during 20-s trials with DBS off (i) and during 185-Hz Regular DBS (ii). Scale bars in (ii) apply to both traces. C: power spectral density for the acceleration trial signals shown in B with DBS off (i) and during 185-Hz Regular DBS (ii).
population of neurons. Each input had an intrinsic pattern of activity, and the inputs were distributed across the compartments of the TC neuron based on reconstruction of synaptic inputs to cat ventral thalamic neurons (Sato et al. 1997). The intrinsic activity of CTX inputs was a 20-Hz Poisson train of spikes (Descheesens and Hu 1990), whereas the intrinsic activity of CER inputs was based on the burst activity recorded in the harmaline model of tremor in the cat (de Montigny and Lamarre 1973). The rate of harmaline burst activity was decreased from ~10 to 5.8 Hz [11 interspikes intervals (ISIs) at 7.0 ms followed by 1 ISI at 95 ms] so that the burst frequency of the model TC neurons was consistent with the predominant burst frequency of Vim neurons in humans with ET (Hua and Lenz 2005). The intrinsic activity of inhibitory RN inputs resulted from synaptic excitation of RN by CTX and synaptic excitation of RN via feedback from the TC output (Ando et al. 1995; Steriade et al. 1997), whereas the intrinsic activity of inhibitory TIN inputs resulted from synaptic excitation of TIN by CTX and CER (Ando et al. 1995).

Model geometry and extracellular stimulation. The Vim thalamus was modeled as an oblique prism with a rectangular base and parallelogram-shaped joining faces, and the center of the cell body of each model TC neuron and its input axons were positioned within this volume by generating uniformly distributed random coordinates (Fig. 3B). The bases of the prism had a lateral width of 4.0 mm in the coronal plane and a depth of 3.5 mm in the horizontal plane, and the perpendicular distance between bases was 10 mm (Benabid et al. 1998; Mobin et al. 1999). The TC axons were oriented along a straight trajectory from the center of the inferior base of Vim thalamus to the hand area of primary motor cortex, the orientation of CTX axons was inversely symmetric to the TC axons, the CER axons were oriented 30° posterior to the coronal plane, and the RN and TIN axons extended directly in the lateral-medial and medial-lateral directions, respectively (Fig. 3, C and D). These orientations were selected so that the output of the TC neurons was pointed directly toward the hand representations of the primary motor cortex (Hlustik et al. 2001). The length of TIN axons was half of that of other axons to account for the fact that these local axons originate much closer to the TC neuron of interest.

The extracellular voltages produced by DBS were calculated using a finite element model representation of a Medtronic DBS lead (Model 3387; Minneapolis, MN). The zero contact of the DBS electrode was positioned at the center of the oblique prism representing the Vim, and the electrode was angled 30° anterior to the coronal plane (Fig. 3, C and D; Mobin et al. 1999). The tissue was modeled as an isotropic homogeneous medium with conductivity $\sigma = 0.2$ S/m, and the conductivities of the metal electrode contacts and the insulating material between contacts were 1e7 and 1e−10 S/m, respectively (Wei and Grill 2005). The voltages in the modeled tissue volume were computed using COMSOL Multiphysics 3.4 (Burlington, MA) with ~55,000 tetrahedral elements, and this was sufficient density as doubling the number of elements changed the potentials by <6.0% (mean ± SD = 1.8 ± 1%). The modeled tissue volume extended throughout a 8,000-cm$^3$ cube centered on the origin, and this volume was sufficiently large because doubling the length of each side of the cube changed the potentials by <6.0% (mean ± SD = 0.28 ± 0.5%). All simulations were performed with the zero contact of the lead as the anode, and the outside faces of the cube were set to ground to approximate using the IPG as the return electrode. The boundary condition on the surface of the zero contact was constant voltage, whereas the tiny current density normal to the surface was imposed for the remaining components of the lead. Voltages outside of each compartment of each model TC neuron and each presynaptic axon were calculated using quadratic interpolation of the voltages at the grid points of the finite element mesh.

Simulation methods. The model neurons were implemented in NEURON 6.1 (Hines and Carnevale 1997), and the transmembrane potential ($V_m$) in response to DBS was obtained by backward Euler implicit integration with a time step of 0.01 ms. The population of

![Image](https://via.placeholder.com/150)

**Fig. 2.** Stimulus trains designed to test whether pauses, bursts, or irregularity per se are the causes of the ineffectiveness of temporally irregular DBS. A–C: high-entropy log-uniform distributions with various frequency limits. Example stimulus trains are shown in insets above corresponding distributions. A: Uniform stimulus distribution designed with a minimum at 90 Hz and a geometric mean of 185 Hz. B: Unipeak stimulus distribution with wider frequency limits than the Uniform stimulus. C: Bimodal stimulus distribution, where the frequency limits were adjusted such that interpulse intervals (IPIs) were either greater or less than the therapeutic frequency range. D: Absence trains had a geometric mean frequency of 185 Hz and pauses of 50.7 ms that came at a rate of 4.4 Hz. E: Presence trains had a geometric mean frequency of 185 Hz and brief bursts of stimulus pulses that lasted 52.57 ms and came at a rate of 4.4 Hz.

to DBS. The model of each of 50 thalamocortical relay (TC) neurons was taken from our previous work and is an anatomically and electrically accurate representation of mammalian TC neurons that reproduces a wide range of experimental electrophysiology ( McIntyre et al. 2004). Presynaptic axons were modeled using a double cable representation of mammalian axons, which we previously developed and validated (McIntyre et al. 2002). Subsequently, each element that was added to the model was based on biological data ( Detailed model description in APPENDIX), and the integrated network model was thoroughly validated against available data from brain slices, animals, and humans ( Model validation in APPENDIX). We used the model to calculate the combined effects of the intrinsic synaptic inputs and DBS on TC neurons. Thus the responses of each TC neuron depended on a combination of the intrinsic synaptic inputs, changes in the intrinsic synaptic activity evoked by stimulation of the input axons, and the direct effects of stimulation on the TC neuron.

The fundamental unit of the model (Fig. 3) consisted of a TC neuron and 4 terminating axons carrying inputs from cerebellum (CER), cortex (CTX), reticular nucleus (RN), and local thalamic interneurons (TINs; Darian-Smith et al. 1996; Tasker and Kiss 1995) and was replicated 50 times to simulate the response of a distributed
where interpulse frequency (IPF) is the inverse of IPI, and provide the best estimate of the mean for each stimulus condition. Measurements from trials in incomplete blocks were included to single measure for each experimental condition within each subject. and the log-transformed tremor measurements were averaged to get a no-3-hydroxy-5-methylisoxazole-4-propionic acid.

These changes saturated above 7.5 V. Similarly, in the present model, stimulation-induced changes in neuronal activity were very strongly correlated with changes in the proportion of activated neurons, as changes in tremor suppression with changes in voltage are

32 of the 50 TC neurons in the absence of other inputs. The high-stimulation voltage, relative to the clinical values, is a reflection of the relatively low density (50) of modeled neurons that were distributed throughout the volume of the Vim (Fig. 3B). This amplitude was chosen to activate a sufficient number of neurons, as changes in tremor suppression with changes in voltage are very strongly correlated with changes in the proportion of activated neurons with changes in voltage (Kuncel et al. 2007). Similarly, in the present model, stimulation-induced changes in neuronal activity were strongly dependent on stimulation voltage (Fig. 14, A and C), and these changes saturated above 7.5 V.

Data analysis and statistics. Tremor during experimental conditions was analyzed as log10 of the tremor power. Measurements made in different blocks within the same subject were considered replicates, and the log-transformed tremor measurements were averaged to get a single measure for each experimental condition within each subject. Measurements from trials in incomplete blocks were included to provide the best estimate of the mean for each stimulus condition.

Stimulus-train entropy. The average entropy for the ISI distributions of model neuron spike trains was computed as:

where \( p(ISI) \) represents the proportion of the total ISIs that are within bin \( i \), where bins range from \( -0.6 \) to 14,000 Hz in 351 bins evenly distributed in log space (bin width = 0.0125 log Hz).

Spike-train entropy. The average entropy for the ISI distributions of model neuron spike trains was computed as:

where \( p(ISI) \) represents the proportion of the total ISIs that are within bin \( i \), where bins range from \( 0.6 \) to 14,000 ms, with the bin width = 0.0125 log ms.

Statistics. Experimental and computational data were analyzed using repeated-measures ANOVA with log-transformed tremor power for each experimental condition as the repeated measure in each subject. Repeated measures for the model neuron activity were the quantitative measures computed for the spike trains or \( V_m \). Statistical models were implemented in StatView 5.0 (SAS Institute, Cary, NC) for Mac OS X. Fisher protected least significant difference (PLSD) tests were used to make post hoc comparisons across experimental conditions. Paired \( t \)-tests were used to assess the effects of pauses,
bursts, and irregularity per se in data that were pooled across stimulus conditions. The residuals of the log-transformed tremor and model quantitative measurements were normally distributed [visual inspection of residual normality (Q-Q) plot]. Statistical significance was defined at \( \alpha = 0.05 \).

RESULTS

Tremor responses to patterns of stimulation. We conducted intraoperative measurements of tremor during six different temporal patterns of thalamic DBS and during DBS off in eight subjects with DBS-responsive tremor (Fig. 4A). Consistent with previous studies, Regular 185-Hz DBS reduced tremor compared with stimulation off \((P < 0.05, \text{post hoc Fisher PLSD})\). Although all stimulation trains had the same mean frequency, tremor reduction varied across stimulation patterns (repeated-measures ANOVA, \( F_{3,7} = 3.138, P < 0.015 \)). Compared with tremor with stimulation off, tremor was suppressed significantly during DBS with 185-Hz Regular, Uniform, Uni- peak, and Presence trains \((P < 0.05, \text{post hoc Fisher PLSD})\) but not during DBS with Bimodal or Absence trains \((P > 0.05, \text{post hoc Fisher PLSD})\).

We pooled data across stimulation trains that shared common characteristics to determine the contributions of pauses, bursts, or irregularity to the reduced efficacy of irregular DBS (Fig. 4B). To assess the effects of pauses, we pooled measurements made during Unipeak, Bimodal, and Absence DBS into a Pause group and measurements made during Regular, Uniform, and Presence DBS into a No Pause group [Fig. 4B (i)]. Similarly, to assess the effects of bursts, we pooled measurements made during Unipeak, Bimodal, and Presence DBS into a Burst group and measurements made during Regular, Uniform, and Absence DBS into a No Burst group [Fig. 4B (ii)]. Finally, to assess the effects of irregularity, we pooled measurements made during Unipeak, Bimodal, and Uniform DBS into an Irregular group and measurements made during Regular, Presence, and Absence DBS into a Periodic group [Fig. 4B (iii)]. Tremor during DBS with temporal patterns containing pauses or bursts was significantly larger than tremor during DBS with patterns containing no pauses \((P < 0.002, \text{paired } t\text{-test})\), and the median tremor power during DBS with patterns containing pauses was 1.60–3.46 times (95% confidence interval) the median tremor power during DBS with patterns without pauses. There was not a significant difference between tremor during DBS temporal patterns containing bursts compared with tremor during DBS without bursts \((P = 0.24)\), and median tremor power during DBS with bursts was 0.71–3.16 times the tremor power during DBS without bursts. There was also no significant difference between tremor measurements made during irregular DBS trains compared with periodic DBS trains \((P = 0.35)\), and median tremor power during irregular DBS was 0.58–3.87 times that during periodic DBS.

Subject responders were classified as having a change in tremor \(\geq 30\%\) between conditions. Seven out of eight subjects experienced tremor suppression \(\geq 30\%\) during Regular 185-Hz DBS compared with DBS off, and six of eight subjects experienced tremor suppression of \(\geq 80\%\) compared with DBS off. Tremor in subject \(G\) was not reduced by DBS during the experiment, and this may be due to propofol given to this subject who was unable to tolerate the surgery to access the IPG using only local anesthetic (Anderson et al. 1994).

Responders were also classified by comparing tremor suppression during Regular 185-Hz DBS to tremor suppression during stimulation with trains containing pauses, bursts, or irregularity per se. Tremor in 7/8 subjects was suppressed \(\geq 30\%\) more during DBS with no pauses than during DBS with pauses, tremor in only 4/8 subjects was suppressed by \(30\%\) more during DBS with no bursts than during DBS with bursts, and tremor in only 4/8 subjects was suppressed by \(\geq 30\%\) more during periodic than during irregular DBS. When considering only the trains that contained pauses, Regular DBS suppressed
tremor ≥30% more than Bimodal, Absence, and Unipeak DBS in 6/8, 5/8, and 6/8 subjects, respectively. Furthermore, the least effective stimulus train in each subject was a train that contained pauses. Bimodal trains performed worst in subjects F and H; Unipeak trains performed worst in subjects A, E, and G; and Absence trains performed worst in subjects B, C, and D.

We analyzed the frequency components of tremor across the different temporal patterns of DBS. The median frequency of tremor power between 2 and 20 Hz for DBS off was 4.17 ± 0.32 Hz (means ± SE, range 3.3–6.2 Hz). The median frequency of the tremor power varied nonsystematically across conditions, and there were no significant differences (repeated-measures ANOVA, $P = 0.59$).

Finally, we analyzed the data for carryover effects and correlations between tremor during stimulation and during the periods between stimulation and found that correlations were insignificant and nonsystematic (supplementary note b, available in the data supplement online at the Journal of Neurophysiology web site).

**Model responses to patterns of stimulation.** We used a validated model of the local Vim thalamic network to simulate the response of thalamic neurons to DBS with the same temporal patterns of stimulation used in the clinical experiments. Figure 5 illustrates responses of a single-model TC neuron across stimulation conditions, including somatic and axonal $V_{m}$, as well as rasters showing the times of action potentials in CER, CTX, RN, and TIN terminals, the times of the inputs to CER, the Poisson inputs to CTX, and the DBS stimulation pulses. With stimulation off (Fig. 5A), the TC neuron exhibited phasic bursting activity similar to that observed in human subjects with ET (Hua and Lenz 2005). The CER axon followed faithfully the phasic, harmaline-generated burst inputs, whereas the CTX axon followed faithfully the Poisson inputs. The TIN axon transmitted faithfully the combined inputs from CER and CTX, whereas the RN axon relayed the inputs from CTX and the TC neuron.

During Regular DBS (Fig. 5B), the presynaptic axons and the axon of the TC neuron followed the stimulus train and fired regularly at high rates due to stimulation-evoked action potentials in the axons (Baldissera et al. 1972), whereas the cell body of the TC neuron was silenced due to synaptic inhibition arising from stimulation of the TIN and RN axons (McIntyre et al. 2004). During DBS with temporal patterns that did not contain pauses (Uniform, Fig. 5C; Presence, Fig. 5G), the input axons and TC axon continued to follow closely the stimulus train, and the soma remained inhibited and silent. Conversely, during stimulation with trains containing pauses (Fig. 5, D–F), the TC soma responded with spikes or bursts. Specifically, during stimulation with Bimodal and Unipeak trains, the soma responded with rebound spikes at times when there were simultaneous pauses in both the DBS train and CER input (i.e., burst activity from cerebellum). Similarly, during DBS with the Absence pattern, somatic bursts occurred during simultaneous pauses in stimulation and the CER input. Thus the temporal patterns of DBS that were effective in suppressing tremor overrode the burst driver (harmaline-generated input from CER), whereas the temporal patterns of DBS that were ineffective (those with pauses) allowed the burst-driver input to generate rebound events in the TC neuron.

The responses of 10 representative TC neurons (from the population of 50) to the same temporal patterns of stimulation used in the clinical experiments are shown in Fig. 6. The strengths of GABAergic conductances were varied across the population to produce regular-spiking, random-spiking, and bursting neurons in the proportions observed in humans with ET: ~50% bursting, ~30% regular spiking, and ~20% random spiking (Molnar et al. 2005; see Detailed model description in APPENDIX), and the model population included 15 regular-spiking TC neurons, 10 random-spiking neurons, and 25 bursting neurons. The times of axonal action potentials for 3 regular-spiking, 2 random-spiking, and 5 bursting model neurons are illustrated in Fig. 6.

The responses across neurons to Regular DBS were somewhat heterogeneous; however, the responses within each neuron were quite regular. From the population of 50 model neurons, 19 neurons responded with axonal action potentials that were phase-locked to the 185-Hz DBS (Fig. 6B, rows 2, 5, and 9), 5 neurons responded with axonal spikes at integer multiples of stimulus pulses (every 5th–8th pulse; Fig. 6B, rows 3 and 10), and 14 neurons were silenced due to activation of the TIN and RN presynaptic axons and subsequent synaptic inhibition (Fig. 6B, rows 7 and 8). The remaining 12 cells fired intermittently without a consistent pattern (Fig. 6B, rows 1, 4, and 6). The patterns of model neuron firing in response to Uniform, Unipeak, and Bimodal DBS were noticeably more irregular than the responses to Regular DBS. The rastergrams indicate more neuronal bursts during the Bimodal and Absence trains, where the bursts during the Bimodal train were brief and frequent, and the bursts during the Absence trains occurred during the long pauses in the stimulus train.

**Quantitative measures of TC neuron firing during stimulation.** We quantified the responses of model TC neurons to DBS using the average entropy of ISI distributions (Fig. 7A), the average entropy of log-transformed ISI distributions (Fig. 7B), and the fraction of power in the somatic $V_{m}$ within 1 Hz of the burst-driver frequency (5.8 ± 1 Hz; Fig. 8).

The average firing pattern entropy is correlated with the effectiveness of DBS in treating the motor symptoms of PD (Dorval et al. 2008) and is a valid measure of temporal irregularity that does not require normal distributions of ISIs. The average entropy of model neuron ISI distributions was well-correlated with the mean log-transformed tremor power across stimulus conditions ($r^{2} = 0.78$; Fig. 7A). The trends of ISI entropies followed closely those of tremor with one exception: Absence DBS was slightly, but not significantly, less effective than Unipeak DBS in suppressing tremor (Fig. 4A), but ISI entropies were significantly higher during Unipeak DBS than during Absence DBS (Fig. 7A).

The average entropy of the log-transformed ISI distributions was a measure of entropy that should be equivalent to the average entropy of the stimulus-train log-transformed IPIs if the model neuron spike trains followed faithfully the stimulus train (Fig. 7B). The median entropy of the log-transformed ISI distributions was approximately equal to the entropy of the stimulus-train log-transformed IPIs across conditions with one important exception (Fig. 7C). The median log-transformed ISI entropy for the Absence train was much higher than the log-transformed IPI entropy of the stimulus train (2.9 bits/spike compared with 0.18 bits/pulse), i.e., the low-entropy stimulus train that contained pauses generated high-entropy neural activity. The entropy of the log-transformed ISI distributions was...
also correlated with tremor responses across experimental conditions ($r^2 = 0.59$; Fig. 7B).

With stimulation off, the burst activity arising from CER inputs generated bursting activity in TC neurons at 5.8 Hz, the burst-driver frequency (Fig. 5A). The presence of fluctuations in somatic $V_m$ that were in the range of 5.8 ± 1.0 Hz (i.e., the burst-driver band) was computed as the proportion of the total $V_m$ power spectrum. This measure of the degree to which the
burst driver was represented in the output of the model neuron responses exhibited a very strong correlation with tremor across different temporal patterns of DBS ($r^2 = 0.81$; Fig. 8A).

The primary difference between this measure and tremor was the stimulation off condition, and when this point was not included, the correlation increased to $r^2 = 0.91$ (Fig. 8A, right inset).

Similarly, we quantified oscillations in the firing rates of TC axons within the burst-driver band by computing smoothed firing-rate histograms for each axonal spike train (Gaussian smoothing window, $\sigma = 50$ ms) and then calculating the cross-correlation between the smoothed firing rate of a neuron during a given stimulus condition and the smoothed firing rate of the same neuron during stimulation off. The mean power of these cross-correlations within the burst-driver band ($5.8 \pm 1$ Hz) is illustrated in Fig. 8B across all 50 model neurons. Trends in the mean power in the axonal spike rate cross-correlations also paralleled trends in mean tremor power across stimulus conditions ($r^2 = 0.59$; Fig. 8B, inset), with the most power in the

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**Fig. 6.** Responses of 10 model neurons to different temporal patterns of DBS. The times of action potentials for 10 of 50 TC neurons are shown as rasters during stimulation off (A) as well as during Regular (B), Uniform (C), Unipeak (D), Bimodal (E), Absence (F), and Presence (G) DBS. Rasters illustrate the times of action potentials in the distal axon of each TC neuron during 1 s of stimulation. The top 3 rows in each panel are the responses of regular spiking TC neurons, the next 2 rows are the response of random-spiking TC neurons, and the bottom 5 are bursting TC neurons. The time scale bar in A applies to all panels. These data are intended to provide an overview of the responses of the model neurons during the different stimulus conditions.
burst-driver band observed during stimulation with trains containing pauses.

As with the tremor measurements (see Fig. 4B), we pooled model data across stimulation trains that shared common characteristics to determine the contributions of pauses, bursts, or irregularity per se to the fraction of $V_m$ power in the burst-driver band. We computed the difference between the power in the burst-driver band for each neuron during stimulation with a given characteristic (pauses, bursts, or irregularity) and without a given characteristic (no pauses, no bursts, and periodic). The difference between the power with/without pauses was significantly larger than the difference between the power with/without bursts or with/without irregularity ($P < 0.0001$, Fisher PLSD after significant repeated-measures ANOVA; Fig. 8C). Thus the trends in the fraction of somatic $V_m$ power in the burst-driver band during stimulation with/without pauses, bursts, and irregularity paralleled remarkably well the trends we observed in tremor across the same stimulus characteristics (Fig. 4B).

Collectively, these results suggested that the mechanism by which DBS suppresses tremor is by masking burst-driver inputs to the thalamus from the cerebellum. Therefore, we implemented an additional version of the network model of thalamic DBS to determine the efficacy of stimulating selectively the cerebellar fiber inputs to the Vim thalamus. In this version of the model, we eliminated the effects of extracellular stimulation on all neuronal elements and replaced Regular 185-Hz extracellular stimulation with 185-Hz intracellular stimulation of only the cerebellar afferent terminals (CER). The burst-driver fluctuations in somatic $V_m$ during stimulation of cerebellar afferents was nearly identical to the burst-driver fluctuations in somatic $V_m$ observed during extracellular Vim DBS ($P = 0.89$, $T_{49} = 0.14$, paired $t$-test; Fig. 9).

**DISCUSSION**

We conducted measurements in human subjects with tremor and Vim thalamic DBS and simulations in a computational model of thalamic DBS to identify the characteristics of irregular stimulus trains that rendered them ineffective: pauses, bursts, or irregularity per se. Trains with pauses were the least effective at suppressing tremor, and when tremor responses were pooled across Pause/No Pause, Burst/No Burst, and Irregularity/Periodic groups, tremor was significantly different between groups only in the Pause/No Pause grouping. Furthermore, our results indicate that the mechanism by which DBS suppresses tremor was by masking burst-driver inputs to the thalamus from the cerebellum. Importantly, these findings provide a mechanistic basis for correlative clinical studies, which indicate that the most effective electrode locations for tremor suppression are near cerebellar fibers that terminate in the thalamus (Coenen et al. 2011; Hamel et al. 2007; Herzog et al. 2007; Jimenez et al. 2000; Kitagawa et al. 2005; Struppler et al. 1978).

Previous studies demonstrated that DBS with temporally random stimulation patterns, even when delivered at a high average frequency, was not effective at treating tremor or (Birdno et al. 2008) or bradykinesia (Dorval et al. 2010), and we evaluated three potential hypotheses for the decreased effectiveness of irregular DBS: $H_{Pause}$, $H_{Burst}$, and $H_{IR}$. We tested $H_{IR}$ by comparing the relative effectiveness of the
Uniform, Bimodal, and Absence trains, all of which had high entropy (i.e., were highly irregular). The Uniform train was effective, but the Bimodal and Absence trains were not, and therefore we rejected HIR. We tested HBurst by comparing the effectiveness of the Absence and Presence trains. The Presence train, which contained burstlike patterns of pulses, suppressed tremor significantly compared with stimulation off, whereas the Absence train did not; therefore, we rejected HBurst. We concluded that the ineffectiveness of the Absence and Bimodal trains was due to pauses in the trains enabling pathological activity to propagate through the thalamus (HPause), and the least effective train in all subjects was one that contained pauses.

Results from simulations in the validated biophysical model of thalamic DBS provided a mechanistic basis for the conclusion that the ineffectiveness of the irregular stimulus trains was due to pauses. When pauses in the stimulus train coincided with pauses in the input from CER, the thalamic neurons were prone to burst (Fig. 5F). The fraction of power in TC somatic Vm and in the TC axon spike train within the burst-driver band (5.8 ± 1 Hz) correlated well with tremor across stimulation patterns (Fig. 8). Thus, to be effective, DBS must mask or override the input from the cerebellum (i.e., the pathological burst driver). Furthermore, stimulation that is temporally irregular, provided that it effectively overrides this driver (e.g., Uniform train), can also suppress tremor.

Correlative clinical data indicate the importance of activating the cerebellar inputs for effective tremor suppression (Cohen et al. 2011; Hamel et al. 2007; Herzog et al. 2007; Jimenez et al. 2000; Kitagawa et al. 2005; Struppler et al. 2006).

Fig. 8. Fraction of somatic Vm power in the burst-driver band. A: power in somatic Vm in the burst-driver band (5.8 ± 1 Hz) across stimulation conditions. Data are shown as means ± SE. Markers not containing the same letters are significantly different from one another (P < 0.05, post hoc comparisons with Fisher PLSD). The 2 insets illustrate the fraction of somatic Vm in the burst-driver band as a function of mean tremor across 8 subjects. The left inset includes all experimental conditions, and the right inset includes only the conditions with stimulation on. B: power in the burst-driver band of the cross-correlation between the smoothed axonal spike rates during a given condition and stimulation off. Data are shown as means ± SE. Markers not containing the same letters are significantly different from one another (P < 0.05, post hoc comparisons with Fisher PLSD). The inset illustrates the correlation between the axonal spike rate cross-correlations and the mean tremor in 8 subjects across conditions with stimulation on. C: difference between the somatic Vm power in the burst-driver band for each neuron during stimulation with a given characteristic [Power (with): pauses, bursts, or irregularity] and the power in the burst-driver band for each neuron during stimulation without a given characteristic [Power (without): no pause, no bursts, periodic], respectively. *P < 0.0001, Fisher PLSD.
shown as the means of power in the burst-driver band rather than the proportion of power. Data are intracellular cerebellar and extracellular DBS, we compared the absolute value amus are the primary target of therapeutic thalamic DBS. Furthermore, the hypothesis that cortical afferents to the thalamic DBS facilitated the cerebellothalamocortical pathway, indicating activation of this pathway during thera- et al. 2011). These results are consistent with our conclusion that effective thalamic DBS stimulates CER inputs, thereby masking the burst-driver activity.

The effects of thalamic DBS on motor-evoked potentials support our finding that thalamic DBS activates the cerebello-thalamocortical pathway (Molnar et al. 2004; Pinto et al. 2003), however, activation of corticothalamic afferents might also contribute to the reduction in tremor by thalamic DBS in ET. Thalamic DBS facilitated the cerebellothalamocortical pathway, indicating activation of this pathway during therapeu-tic DBS (Molnar et al. 2004). Pinto and colleagues (2003) concluded that thalamic DBS does not work by inhibiting an overactive cerebellothalamocortical pathway, and their findings were “consistent with an oscillating source feeding into the cerebellum (Ugawa et al. 1997), and the inferior olive has been implicated in this role (Deuschl and Bergman 2002).” Furthermore, the hypothesis that cortical afferents to the thalamus are the primary target of therapeutic thalamic DBS contradicts the findings that stimulation of the subthalamic area is more beneficial than stimulation in the thalamus proper (Hamel et al. 2007; Herzog et al. 2007). Finally, a very recent clinical study implicated transient changes in pallidal input to the cortical/cerebellar/thalamic loop in parkinsonian resting tremor (Helmich et al. 2011). Specifically, they found that activity in the cerebellothalamic pathway correlated well with tremor amplitude and concluded that resting tremor in PD is produced by the cerebellothalamic circuit.

Although the present results are restricted to thalamic DBS to treat tremor, previous findings suggests that pauses also corrupt the effectiveness of STN DBS in PD. DBS of the STN in a healthy monkey with a stimulation pattern containing pauses and bursts disrupted motor performance, whereas stimulation with the same IPIs shuffled to eliminate the presence of pauses and bursts did not disrupt motor performance (Ma and Wichmann 2004). In human subjects with PD, movement times were shorter (i.e., better effect) during continuous STN DBS when DBS was cycled on and off for either 0.1 or 0.5 s, although all patterns had the same average rate (Montgomery 2005). This finding is consistent with our conclusion that pauses (off cycles in their experiments) disrupt the effectiveness of stimulation. Finally, computational (Babadi 2005) and experimental (Person and Perkel 2005) results also indicate that pauses between spikes in trains of thalamic input led to burst responses in thalamus.

The range of stimuli that can be generated with the clinically implanted IPG is limited, and we used an innovative setting to make these measurements, during surgery to replace the IPG, which allowed us to establish a direct connection to implanted DBS leads under stable conditions (i.e., months to years after the original implant, with stable lead function). In contrast to investigations conducted using externalized leads between the implant of the DBS lead and subsequent implantation of the IPG (Birdno et al. 2007), this approach eliminated the confounding effects of focal acute brain edema (i.e., microlesion) caused by the insertion of the lead. However, the intraoperative setting imposed several experimental limitations.

The duration of DBS before assessment of tremor and the interval between trials were short, but longer trials would result in the experiment becoming too long to conduct during an operative procedure. Similarly short trial lengths have been used in studies of parameter settings (Kuncel et al. 2006; Moro et al. 2002; O’Suilleabhain et al. 2003), and the effects of short stimulus trials were mitigated partially by the fact that tremor reduction following onset of DBS occurs “within a few seconds” (Beuter and Ticotme 2003). Furthermore, the potential impact of the short trial length was minimized by randomizing the trial order and by making comparisons of tremor relative to baseline. The amount of baseline tremor was variable across subjects. However, repeated-measures ANOVA models allowed each subject to act as their own control, thus increasing the statistical power to reveal significant effects on tremor across experimental conditions.

It should be noted that synapses are unreliable and that the current model neglects many details in this regard. However, during electrical stimulation, there are a large number of axon terminals stimulated simultaneously, and it is reasonable to assume that the overall impact of stimulation on the receptors can be modeled by reliable transmission. Indeed, in vivo recordings in globus pallidus internus (GPI) during STN DBS
(Hashimoto et al. 2003) and in thalamus during GPi DBS (Anderson et al. 2003) suggest that postsynaptic activity is reliably generated, even during long trains of stimulation. The synapses in the current model were not intended to represent individual cell-to-cell transmission, but rather they represent the aggregate input from one group of cells to another group of cells.

The bursts in the thalamic network model were driven by oscillations in the cerebellar afferents, premised on activity recorded in the harmaline model of ET. Although the etiology of ET is not well-understood (Rothwell 1998), the harmaline model is the most commonly accepted animal model of ET (de Montigny and Lamarre 1973; Deuschl and Elble 2000; Miwa 2007), and it has even been suggested that the harmaline model should be used to screen pharmaceutical interventions (Martin et al. 2005). Thus we chose to implement the model with thalamic bursts driven by harmaline-induced activity in the cerebellar afferents.

Conclusions. The decreased effectiveness of temporally irregular DBS trains is due to the pauses in the stimulus trains and not to temporal irregularity alone. Thus temporally irregular DBS can suppress tremor effectively if there are no long pauses. The ability of DBS to control tremor was correlated most strongly with the ability of DBS to override burst-driver inputs from the cerebellum. Both clinical and computational data support the hypothesis that the most relevant neuronal elements to stimulate for effective tremor suppression are the afferent cerebellar fibers that terminate in Vim thalamus and that the mechanism by which DBS suppresses tremor is masking cerebellar burst-driver input to the thalamus.

APPENDIX: MODEL DEVELOPMENT AND VALIDATION

Detailed model description. This APPENDIX includes a detailed description of the computational model that we developed and simulated for this study. Source code files for the model can be downloaded from the NEURON ModelDB database (http://senselab.med.yale.edu/modeldb).

TC neuron. We used computer-based models of TC neurons and their synaptic inputs to simulate the response of Vim thalamic neurons to DBS. The TC neuron included a cell body, 251 dendritic compartments, and a double-cable axon with 30 nodes of Ranvier. The thalamocortical cell geometry was derived from a 3-dimensional reconstruction of a filled thalamocortical cell from rat (Destexhe et al. 1998), and the axon diameter was selected as representative of those in ventrolateral thalamus (Kultz-Ilinsky et al. 2003). The resting $V_m$ of the TC neuron cell body was $-69 \text{ mV}$, and the resting membrane potential of all axons was $-70 \text{ mV}$. Noise was introduced into the TC neuron via a somatic current injection that followed a normal distribution ($\mu = 0, \sigma^2 = 5 \text{ nA}$). The noise current changed amplitudes every time step and resulted in fluctuations in somatic transmembrane voltage that paralleled those observed in vivo (Destexhe et al. 2001).

Inputs to TC neuron. Each input axon had an intrinsic pattern of activity subject to modification by DBS. The CTX input consisted of a 20-Hz Poisson train of suprathreshold pulses (Descheennes and Hu 1990; Person and Perkel 2005). Intrinsic activity of CER inputs was based on the burst activity recorded in the harmaline model of tremor in the cat (de Montigny and Lamarre 1973). The rate of harmaline burst activity was decreased from $\sim 10$ to $5.8 \text{ Hz}$ (11 IP1s at 7 ms followed by 1 IP1 at 95 ms) so that the interburst frequency of the model TC neurons was consistent with the predominant interburst frequency of Vim neurons in humans with ET (Hua and Lenz 2005). Inhibitory input from RN resulted from synaptic excitation of RN from the CTX input and excitation of RN via feedback connections from the TC output (Ando et al. 1995; Steriade et al. 1997). Finally, input from TINs resulted from synaptic excitation of TINs by CTX and CER inputs (Ando et al. 1995).

This model configuration assumed that the harmaline-induced bursting in the CER fibers comprised the primary source of tremor-related oscillations in the thalamus. The etiology of ET is not well-understood; however, “disturbance of olivocerebellar rhythmicity” is the most prominent hypothesis for the pathology underlying ET (Deuschl and Elble 2000; Haslinger et al. 2003; Koster et al. 2002). Supporting evidence for the role of the cerebellum in ET comes from a recent postmortem histological study that identified a decrease in the number of Purkinje cells in the cerebellum of subjects with ET (and without Lewy bodies) compared with healthy controls (Louis et al. 2007). Louis et al. (2007) also saw a sevenfold increase in “torpedoes” (fusiform swellings of Purkinje cell axons) in the same ET subjects compared with healthy controls. Additionally, an ischemic cerebellar lesion due to stroke produced ipsilateral tremor suppression in a subject with ET, suggesting a role of the cerebellum in the development of ET (Dupuis et al. 1989). Finally, positron-emission tomographic studies revealed bilateral increases in olivary glucose metabolism as well as increases in blood flow in the cerebellum, red nucleus, and thalamus of patients with ET (Boecker and Brooks 1998). Hence, the CER fibers were assumed to be the source of tremor-related oscillations in our computational model.

Activation of input synapses on the TC neuron was evoked not only by the intrinsic activity of the input axons, but also by the effects of stimulation on the biophysically modeled input axons. The input axons were modeled as having the same morphological and conductance properties as the axon of the TC neuron with a slight adjustment made to the nodal slow potassium conductance from 0.07 to 0.08 $\text{S/cm}^2$. In addition, because TINs are local cells, the TIN axons consisted of only 15 nodes of Ranvier. Hence, the responses of the TC neuron depended on a combination of the intrinsic synaptic inputs, changes in the intrinsic synaptic activity evoked by stimulation of the input axons, and the direct effects of stimulation on the TC neuron.

The synaptic effects on TC neurons were modeled by applying either excitatory or inhibitory synaptic conductances to each of the dendritic and somatic compartments of each TC neuron, with the distribution of synapses based on electron microscopic reconstructions of glutamatergic and GABAergic terminals on cat ventral thalamic neurons (Table 2; Sato et al. 1997).

The CER input axon drove $\mathrm{DL}-\alpha$-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA)-dominated glutamatergic synapses that were located near the soma and for which the effect was large in amplitude but brief in duration (Miyata 2007; Schwarz and Schmitz 1997). The CTX input axon drove longer-lasting, but weaker, $\mathrm{N}$-methyl-$\mathrm{D}$-aspartate (NMDA)-dominated glutamatergic synapses that were...
Table 3. Synaptic conductance values

<table>
<thead>
<tr>
<th>Origin</th>
<th>Synapse Type</th>
<th>Regular, Random, or Bursting Cells</th>
<th>Conductance, nS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortical</td>
<td>NMDA</td>
<td>All</td>
<td>0.0164</td>
</tr>
<tr>
<td>Cerebellar</td>
<td>NMDA</td>
<td>All</td>
<td>0.0006</td>
</tr>
<tr>
<td>Cortical</td>
<td>AMPA</td>
<td>All</td>
<td>0.00082</td>
</tr>
<tr>
<td>Cerebellar</td>
<td>AMPA</td>
<td>All</td>
<td>0.000456</td>
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<td>RN</td>
<td>GABA_A</td>
<td>Regular</td>
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</tr>
<tr>
<td>TIN</td>
<td>GABA_A</td>
<td>Regular</td>
<td>0.001</td>
</tr>
<tr>
<td>RN</td>
<td>GABA_A</td>
<td>Random</td>
<td>0.01</td>
</tr>
<tr>
<td>TIN</td>
<td>GABA_A</td>
<td>Random</td>
<td>0.01</td>
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<td>Bursting</td>
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<tr>
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<tr>
<td>TIN</td>
<td>GABA_B</td>
<td>Bursting</td>
<td>0.0005</td>
</tr>
</tbody>
</table>

RN, reticular nucleus; TIN, thalamic interneuron; NMDA, N-methyl-D-aspartate; AMPA, dl-α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid.

Table 4. Parameters altered from model published previously (McIntyre et al. 2004)

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Compartments Affected</th>
<th>Channel</th>
<th>Parameter</th>
<th>Previous Value [or Equation]</th>
<th>New Value [or Equation]</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>Soma/dendrites</td>
<td>T-type Ca^{2+}</td>
<td>P_{Ca,T}</td>
<td>0.0001 cm/s</td>
<td>0.000075 cm/s*</td>
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<tr>
<td>TC</td>
<td>Soma/dendrites</td>
<td>T-type Ca^{2+}</td>
<td>\tau_{e} for \ V_{m} &gt; -80</td>
<td>9.33 + 0.333e^{-\left(V_{m} + 25\right)/10.5}</td>
<td>1.6147[8.91 + 0.318e^{-\left(V_{m} + 25\right)/10.5}]†</td>
</tr>
<tr>
<td>TC</td>
<td>Soma/dendrites</td>
<td>T-type Ca^{2+}</td>
<td>\tau_{m} for \ V_{m} ≤ -80</td>
<td>0.333e^{-\left(V_{m} + 470\right)/66.6}</td>
<td>0.318e^{-\left(V_{m} + 470\right)/66.6}</td>
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<tr>
<td>TC</td>
<td>Soma/dendrites</td>
<td>T-type Ca^{2+}</td>
<td>m_{s}</td>
<td>0.204 + e^{-\left(V_{m} + 135\right)/6.7} + e^{-\left(V_{m} + 158\right)/82}</td>
<td>0.195 + e^{-\left(V_{m} + 135\right)/6.7} + e^{-\left(V_{m} + 158\right)/82}</td>
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<tr>
<td>TC</td>
<td>Soma/dendrites</td>
<td>T-type Ca^{2+}</td>
<td>\ m_{m} = 1/\left[1 + e^{-\left(V_{m} + 60\right)/6.2}\right]</td>
<td>m_{m} = 1/\left[1 + e^{-\left(V_{m} + 60\right)/6.2}\right]^*</td>
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</tr>
<tr>
<td>TC</td>
<td>Soma/dendrites</td>
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<td>g_{Na}</td>
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<td>0.0000305 S/cm^{2}§</td>
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<tr>
<td>TC</td>
<td>Soma/dendrites/initial segment</td>
<td>Slow K^{+}</td>
<td>\ I_{ks}</td>
<td>g_{K}(0.4 * h_{1} + 0.6 * h_{2})(V_{m} - E_{K})</td>
<td>g_{K}(0.6 * h_{1} + 0.4 * h_{2})(V_{m} - E_{K})§</td>
</tr>
<tr>
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<td>Nodes</td>
<td>Slow K^{+}</td>
<td>\beta_{s}</td>
<td>0.03/[1 + \exp((V_{m} + 80)/-1)]</td>
<td>0.03/[1 + \exp((V_{m} + 40)/10)]‡</td>
</tr>
<tr>
<td>All</td>
<td>Nodes</td>
<td>Slow K^{+}</td>
<td>\ g_{ks}</td>
<td>0.07 S/cm^{2} TC axon, 0.08 S/cm^{2} input axons</td>
<td>0.07 S/cm^{2} TC axon, 0.08 S/cm^{2} input axons</td>
</tr>
<tr>
<td>All</td>
<td>Nodes</td>
<td>Leak</td>
<td>g_{KL}</td>
<td>0.005 S/cm^{2}</td>
<td>0.007 S/cm^{2}*</td>
</tr>
<tr>
<td>All</td>
<td>All</td>
<td>All K^{+}</td>
<td>\epsilon_{s}</td>
<td>-95 mV</td>
<td>Approximately -95 mV, [K^-]_i = 106 and [K^-]_o = 3 mM</td>
</tr>
</tbody>
</table>

*Adjusted to facilitate tonic bursting during direct current hyperpolarization (Fig. 11C) (McCormick and Pape 1990) and poststimulus inhibition (Fig. 13D; Dostrovsky and Lozano 2002). †Equation updated to ensure that decay time constant \tau_{e} of the state parameter \ m, which decreases with activation of muscarinic, \alpha_{1}, and/or H_{1}-receptors, curves for transmembrane potential (\ V_{m} ≤ -80 mV and \ V_{m} > -80 mV meet at \ V_{m} = -80 mV. §Equation updated with correct proportions from earlier study (Huguenard and McCormick 1992). ‡Equation updated to correct \tau_{s} and \ s_{c} curves (\alpha_{s} and \beta_{s} were previously both monotonic in the same direction). This was equal to the conductance used in the tonically active version of the previous model, \ g_{KL}, conductance of the leak current; \ k, kinetic rate constant; \ P_{Ca,T}, maximum T-type Ca^{2+} permeability; \ e, mathematical constant; \epsilon_{s}, K^{+} reversal potential; \ s, seconds; \alpha_{s}, and \beta_{s}, activation and inactivation parameters of slow K^{+} channel; \ I, current; \ i, intracellular; \ o, extracellular.
mine, acetylcholine, serotonin, and noradrenaline (McCormick 1992b; Steriade et al. 1997). The role of neuromodulators in the effects of DBS are being investigated, and a recent paper highlights the influence of adenosine. Adenosine levels increased during intervals of high-frequency stimulation in thalamic slices and intrathalamic infusion of adenosine suppressed tremor in the harmaline mouse model of tremor even in the absence of stimulation (Bekar et al. 2008).

The neuromodulators activated a pertussis toxin-sensitive potassium current (\(I_{KG}\); McCormick and Prince 1987a,b), inhibited a nonpertussis toxin-sensitive leak potassium current (\(I_{KL}\); McCormick 1992a), and shifted the activation curve of the hyperpolarization-activated cation current (\(I_{H}\); McCormick and Williamson 1991; Pape 1992).

\(I_{KG}\): potassium channel activated by GABA\(_B\) and putative neurotransmitters. First, we included a potassium current known as \(I_{KG}\), which is modulated by a pertussis toxin-sensitive protein G that can be activated by GABA\(_B\), muscarinic, or A\(_1\)-adenosine receptors (McCormick 1992b). To implement this channel, we started with a GABA\(_B\) mechanism that allowed the release of GABA to summate when multiple presynaptic action potentials arrived within a short period of time to enhance the postsynaptic response to presynaptic bursting (Destexhe et al. 1996; Otis et al. 1993). The kinetic scheme for the GABA\(_B\) mechanism was taken from Destexhe et al. (1996), and the effects of activating A\(_1\)-adenosine and muscarinic receptors was modeled by adding a new equation to the kinetic scheme for this channel. The modified kinetic scheme was as follows:

\[
R = k_1[[C](1 - R) - k_2R] \\
S = k_3M(1 - S) - k_4S \\
\left[G\right] = k_5[R + 2\psi S] - k_6\left[G\right],
\]

where \(R\) is the fraction of activated \(GABA_{B}R\) receptor, \(S\) is the fraction of activated A\(_1\)- and/or muscarinic receptor, \([G]\) is the concentration of activated protein G, \([C]\) is the concentration of GABA in the synaptic cleft, \(M\) represents a unitless time course of adenosine and/or

![Fig. 10. Response of M (a unitless time course of adenosine and/or acetylcholine in the synaptic cleft) to stimulation. A: time course of M in response to a single-stimulus pulse (arrowhead) follows an \(\alpha\)-function. B: time course of M in response to a 10-s epoch of DBS at 10 and 185 Hz. In these cases, the \(\alpha\)-function responses to individual stimulus pulses summate temporally and stabilize at different steady-state amplitudes (au = arbitrary units, unitless).](http://jn.physiology.org/)

![Fig. 11. Comparison of responses of model and in vitro TC neurons. A: Responses to 60-ms depolarizing pulses were similar to those recorded in in vitro thalamic slices under various levels of direct current (DC) polarization. (i): Responses from thalamic neurons recorded from guinea pig slices in a hyperpolarized cell (left), a cell at rest potential (middle), and a depolarized cell (right; Jahnsen and Linas 1984). (ii): Responses of model thalamic neuron to a depolarizing pulse of 0.55 nA for 60 ms at hyperpolarized (left), rest (middle), and depolarized (right) potentials. B: model rebound responses to 45-ms hyperpolarizing pulses was similar to those of the same thalamic slice neurons. (i): Responses of in vitro neurons (Jahnsen and Linas 1984). (ii): Responses of the model TC neuron. C: model responded to DC hyperpolarization with rhythmic bursting. (i): Responses of in vitro neurons (McCormick and Pape 1990). (ii): Responses of the model TC neuron.](http://jn.physiology.org/)

![Fig. 12. Comparison of thalamic model activity with data recorded in human Vim. A: \(V_m\) recordings from model regular- (i), random- (ii), and burst-spiking (iii) neurons. B: (i): action potential raster recorded from Vim of human with essential tremor (ET; Hua and Lenz 2005). (ii): Action potential raster recorded from model burst-spiking neuron. C: firing rates in the Vim and ventral caudal (Vc) thalamus in subjects with ET (Ohara et al. 2007) along with the firing rates of the model Vim neurons (means ± SE = 23.4 ± 1.8 Hz). The human Vc data are shown to demonstrate that the internuclear difference is much larger than the difference between the model and human Vim. Model firing-rate estimates were averaged across all 50 neurons during the time period from 2 to 12 s with stimulation off.](http://jn.physiology.org/)
acetylcholine in the synaptic cleft, and dot indicates derivative. When GABA$_h$ receptors are activated, [C] changes instantaneously from 0 to 1 and then returns to 0 after 0.3 ms (Destexhe et al. 1996). In a similar fashion, when A$_r$- and/or muscarinic receptors are activated, $M$ follows an $\alpha$-function (Fig. 10):

$$a = \frac{a}{\tau_1} + w$$  
$$b = -\frac{b}{\tau_2} + w$$  
$$M = b - a,$$

where $a$ and $b$ are dummy variables used to construct the $\alpha$-function, $w = 0.0035/\text{ms}$ is a constant weight added to both $a$ and $b$ on the arrival of each stimulus pulse, and $\tau_1$ and $\tau_2$ are the decay time constants associated with $a$ and $b$, respectively ($\tau_1 = 500 \text{ ms}, \tau_2 = 510 \text{ ms}$).

In Eqs. A1–A3, the $k$'s are the kinetic rate constants for activating (odd) and deactivating (even) the receptors or G proteins and were set to the following values: $k_1 = 0.52 \text{ mM}^{-1}\text{ms}^{-1}, k_2 = 0.0013 \text{ mM}^{-1}\text{ms}^{-1}, k_3 = 0.098 \text{ mM}^{-1}\text{ms}^{-1}, k_4 = 0.033 \text{ mM}^{-1}\text{ms}^{-1}, k_5 = 0.1 \text{ mM}^{-1}\text{ms}^{-1},$ and $k_6 = 0.0003 \text{ mM}^{-1}\text{ms}^{-1}$.

In Eq. A3, $\phi_i$ is a unitless constant that represents the magnitude of the response of adenosine and/or acetylcholine terminals to extracellular stimulation in the volume near the $i$th TC neuron. The value of $\phi_i$ was set equal to the extracellular potential generated at the soma of cell $i$ during stimulation at 1 V. $\phi_i$ has a theoretical maximum of 1; however, the random population used in this study had a maximum of 0.52.

**Linear leak potassium current ($I_{KL}$) inhibited by putative neurotransmitters.** Activation of muscarinic acetylcholine, $\alpha_1$-adrenergic, and/or $H_1$-histaminergic receptors results in the suppression of a relatively linear leak potassium current, $I_{KL}$, leading to slow depolarization of the TC neuron (McCormick 1992a,b). $I_{KL}$ suppression was modeled by altering the leak current in McIntyre et al. (2004) as follows:

$$I_{KL} = g_{KL}(V_m - E_K)$$  
$$m = \frac{m_e - m}{\tau_m} - \phi_i M_w$$

where $g_{KL} = 0.00016 \text{ S/cm}^2$ is the maximal conductance of the leak current, $E_K$ is the reversal potential of $K^+$, and $m$ is a state parameter that decreases with activation of muscarinic, $\alpha_1$-, and/or $H_1$-receptors following Eq. A8. In Eq. A8, $\phi_i$ and $M$ have the same meaning and values as in Eqs. A2–A6, $w = 0.2/\text{ms}$ is a constant weight added on the arrival of each stimulus pulse, and $\tau_m = 400 \text{ ms}$ is the decay time constant of $m$. Because of the linearity of this current, a simple scaling of the maximal conductance by $m$ was sufficient to produce lasting depolarization in the soma of the TC neuron.

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**Fig. 13.** Comparison of firing patterns in model and human thalamic neurons. A: mean normalized autopower computed for tremor-related neurons in human thalamus during postural tremor exhibits a strong peak at ~5 Hz (Hua and Lenz 2005). B: mean normalized autopower computed for the population of 50 model neurons shows a similar peak at ~5 Hz. Normalized autopower was averaged across all 50 neurons during the time period from 2 to 12 s with stimulation off. C: preburst ISIs in the Vim and Vc thalamus in subjects with ET (Ohara et al. 2007) along with the preburst ISIs of the model Vim neurons. The human Vc data are shown to demonstrate that the internuclear difference is much larger than the difference between the model and human Vim. Model preburst ISI estimates were made by combining all averaged across the 25 bursting neurons during the same time period (means ± SE = 173 ± 2 ms). D: poststimulus inhibition seen after 0.5 s of stimulation at 200 Hz observed in human thalamus (top; Dostrovsky and Lozano 2002) and in the model Vim neuron (bottom). Time scale bar applies to both traces. $V_{m}$ (20 mV) scale bar applies only to the bottom trace, as the top trace is an extracellular recording. Thick gray bar represents simulation on in both the human and model.
Shifts in activation curve of \( I_h \) driven by putative neurotransmitters. Activation of \( \beta \)-adrenergic, serotoninergic and \( H_2 \)-histaminergic receptors enhances \( I_h \) (Steriade et al. 1997), whereas activation of \( A_1 \)-adenosine receptors inhibits \( I_h \) (McCormick 1992b; Pape 1992). Enhancement and inhibition of \( I_h \) are driven by rightward and leftward shifts in the activation curve of this current, respectively (McCormick and Williamson 1991; Pape 1992). \( I_h \) was modeled as:

\[
I_h = g_h m^3(V_m + 43)
\]

\[
\tau_m = \frac{1}{e^{[-14.599 \cdot (V_m + V_{shift})] + e^{[-1.877 \cdot (V_m + V_{shift})]}}}
\]

\[
m_{\text{shift}} = \frac{1}{1 + e^{\left(\frac{(V_m + V_{\text{shift}} + 75)}{5.5}\right)}}
\]

\[
V_{\text{shift}} = \frac{V_{m_{\text{off}}}}{\tau_{V_{\text{shift}}}} - \varphi_\text{Mw},
\]

where \( V_{\text{shift}} \) determines the left/right shifts in the activation curve, \( g_h = 0.0015 \text{ S/cm}^2 \) is the maximal conductance, and \( V_{m_{\text{off}}} = 5 \text{ mV} \) is the baseline shift used previously (McIntyre et al. 2004). In Eq. A12, \( \varphi_h \) and \( M \) have the same meaning and values as in Eqs. A2–A6, \( w = 0.5 \text{ mV/ ms} \) is a constant weight added on the arrival of each stimulus pulse, and \( \tau_{V_{\text{shift}}} = 400 \text{ ms} \) is the decay time constant of \( V_{\text{shift}} \).

Model validation. The computational model of Vim TC neurons and their inputs reproduced a variety of experimental results without changing biophysical parameters or ionic conductances across validation or experimental simulations.

**Single-cell responses to various polarizations.** First, a single-cell version of the TC neuron, with no synaptic inputs, demonstrated responses to 60-ms depolarizing pulses that were similar to in vitro recordings of guinea pig thalamic slices (Jahnsen and Llinas 1984) under various levels of direct current (DC) polarization (Fig. 11A). The responses of the single-cell TC neuron to 45-ms hyperpolarizing pulses was also similar to those of the same thalamic slice neurons (Fig. 11B; Jahnsen and Llinas 1984). Finally, the model reproduced well the tonic bursts that occur in thalamic neurons during DC hyperpolarization (Fig. 11C; McCormick and Pape 1990).

**Full model replicates responses recorded in Vim of subjects with ET.** More important than comparing the responses of the model to in vitro preparations was comparing the responses of the model to spike activity recorded in the Vim of humans with ET, and the model neuron replicated well several behaviors observed in human recordings.

We set the strength of GABAergic conductances to obtain three classes of TC neuron response types: regular-spiking, random-spiking, and bursting neurons (Table 3) in the proportions observed in human ET [\( \sim 50\% \) bursting, \( \sim 30\% \) regular spiking, and \( \sim 20\% \) random spiking (Molnar et al. 2005)]. Other channel dynamics and conductances remained constant across regular-spiking, random-spiking, and bursting TC neurons. Responses during stimulation off are shown for each of the three classes of model neurons in Fig. 12A.

Action potential rasters from the bursting model neuron were qualitatively similar to rasters recorded from humans with ET during epochs of tremor (Fig. 12B; Hua and Lenz 2005). Furthermore, the mean \( \pm \) SE firing rates across the population of 25 bursting, 15 regular-spiking, and 10 random-spiking neurons \( (23.4 \pm 1.9 \text{ Hz}) \) was very close the firing rate observed in Vim thalamus of human subjects with ET (Fig. 12C; Ohara et al. 2007).

We computed the mean normalized autopower spectra of the model neuron by calculating the autocorrelation of the spike times for each...
neuron and then taking the power spectrum of the autocorrelation
(autopower spectrum). We normalized the autopower for each neuron
and then computed the mean and SE of the autopower spectra across
the population of 50 model neurons. The mean normalized autopower
of the model neuron spike times paralleled closely the mean normalized
autopower spectra of neurons in the Vim of human subjects with ET
(Fig. 13, A and B; Hua and Lenz 2005). The length of preburst ISIs
were also very similar between human subjects with ET and model
TC neuron (Fig. 13C) ET (Ohara et al. 2007).
We also compared the responses of the model with the response of
a low-threshold spike (LTS) bursting neuron in human thalamus in the
period immediately after 200-Hz stimulation delivered for 0.5 s. The
human LTS bursting neuron responded immediately after cessation of
stimulation with a short epoch of burst activity followed by a pro-
longed period of inhibition before a return to LTS bursting (Fig. 13D,
top; Dostrovsky and Lozano 2002). The model replicated well the measured
poststimulus burst, inhibition, and recovery (Fig. 13D, bottom).

Finally, we examined the responses of the model to DBS with constant
IPs (i.e., Regular DBS) at various amplitudes and frequencies (Fig. 14).
As the amplitude of stimulation increased, the ability to regularize
neuronal firing and suppress fluctuations at the burst-driver frequency
improved (Fig. 14, A and C). Likewise, as the frequency of stimulation
increased, the ability to regularize neuronal firing and suppress fluctua-
tions at the burst-driver frequency improved (Fig. 14, B and D).

We observed a small increase in entropy of ISIs during stimulation
at very low frequencies; however, we did not observe an increase in
burst-driver power during stimulation at low frequencies. This is a
limitation of the model, as it departs slightly from clinical studies that
demonstrate exacerbation of tremor during stimulation at very low
frequencies (Grill et al. 2004; Kuncel et al. 2007). This finding
indicates that the mechanism by which low-frequency stimulation
exacerbates tremor is not solely due to the pauses in the low-
frequency stimulus train. The mechanisms of tremor exacerbation at
low-stimulus frequencies is not addressed in the current study, but this
question warrants future examination.

REFERENCES
Andersen BJ, Marks PV, Futter ME. Propofol—contrasting effects in move-
Andersen ME, Postupna N, Rufio M. Effects of high-frequency stimulation
in the internal globus pallidus on the activity of thalamic neurons in the
Anderson TR, Hu B, Iremonger K, Kiss ZH. Selective attenuation of
afferent synaptic transmission as a mechanism of thalamic deep brain

Ando N, Iwata Y, Shinoda Y. Relative contributions of thalamic reticular
nucleus neurons and intrinsic interneurons to inhibition of thalamic neurons

Baradari B. Bursting as an effective relay mode in a minimal thalamic model.

Baldessara F, Lundberg A, Udo M. Stimulation of pre- and postsynaptic

Bekar L, Libionka W, Tian GF, Xu Q, Torres A, Wang X, Lovatt D,
Williams E, Takano T, Schnerrmann J, Bakos R, Nedergaard M. Aden-
osine is crucial for deep brain stimulation-mediated attenuation of tremor.

Benabid AL, Pollak P, Gervason C, Hoffmann D, Gao DM, Hommel M,
Perret JE, de Rougemont J. Long-term suppression of tremor by chronic
stimulation of the ventral intermediate thalamic nucleus. Lancet 337: 403–406,

Benabid AL, Pollak P, Hoffmann D, Limousin P, Gao DM, Le Bas JF,
Benazzouz A, Segebarth C, Grand S. Chronic stimulation for Parkinson’s
disease and other movement disorders. In: Textbook of Stereotactic and
Functional Neurosurgery, edited by Gildenberg PL and Tasker RR. New

Birdno MJ, Cendes F, Andermann E, Titcome MS. Modulation of tremor amplitude during deep brain

Birdno MJ, Cooper SE, Rezai AR, Grill WM. Pulse-to-pulse changes in the frequency of deep brain stimulation affect tremor and modeled neuronal activity.

Birdno MJ, Grill WM. Mechanisms of deep brain stimulation in movement
disorders as revealed by changes in stimulus frequency. Neurotherapeutics

Birdno MJ, Kuncel AM, Dorval AD, Turner DA, Grill WM. Tremor varies
as a function of the temporal regularity of deep brain stimulation. Neurore-

Boecker H, Brooks DJ. Functional imaging of tremor. Mov Disord 13,

Coenen VA, Mödder B, Schiiffbauer H, Urbach H, Allert N. Individual fiber
anatomy of the subthalamic region revealed with diffusion tensor imaging:
a concept to identify the deep brain stimulation target for tremor suppres-

Darbin O, Soares J, Wichmann T. Nonlinear analysis of discharge patterns

Darian-Smith I, Galea MP, Darian-Smith C, Sugitani M, Tan A, Burman K. The
anatomy of manual dexterity. The new connectivity of the primate sensorimotor

de Montigny C, Laromar Y. Rhythmic activity induced by harmaline in the

Descheunes M, Hu B. Electrophysiology and pharmacology of the cortico-
thalamic input to lateral thalamic nuclei: an intracellular study in the cat. Eur

Destexhe A, Bal T, McCormick DA, Sejnowski TJ. Ionic mechanisms
underlying synchronized oscillations and propagating waves in a model of

Destexhe A, Neubig M, Ulrich D, Huguenard J. Dendritic low-threshold

Destexhe A, Rudolph M, Fellous JM, Sejnowski TJ. Fluctuating synaptic
conductances reiterate in vivo-like activity in neocortical neurons. Neuro-

Deuschl G, Bain P, Brin M. Consensus statement of the Movement Disorder
Society on Tremor. Adv Hoc Scientific Committee. Mov Disord 13, Suppl 3:

Deuschl G, Bergman H. Pathophysiology of nonparkinsonian tremors. Mov

Deuschl G, Elble RJ. The pathophysiology of essential tremor. Neurology 54:

Dorval AD. Probability distributions of the logarithm of inter-spike intervals
yield accurate entropy estimates from small datasets. J Neurosci Methods

Dorval AD, Kuncel AM, Birdno MJ, Turner DA, Grill WM. Deep brain
stimulation alleviates parkinsonian bradykinesia by regularizing pallidal

Dorval AD, Russo GS, Hashimoto T, Xu W, Grill WM, Vitek JL. Deep
brain stimulation reduces neuronal entropy in the MPTP-primated model of

Dostrovsky JO, Lozano AM. Mechanisms of deep brain stimulation. Mov

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