Published in final edited form as:

Clin Neurophysiol. 2012 May ; 123(5): 1044–1052. doi:10.1016/j.clinph.2011.07.052.

Tremor Reduction and Modeled Neural Activity During Cycling Thalamic Deep Brain Stimulation

Alexis M. Kuncel¹, Merrill J. Birdno¹, Brandon D. Swan¹, and Warren M. Grill^{1,2,3}

¹Department of Biomedical Engineering, Duke University, Durham, NC

²Department of Neurobiology, Duke University, Durham, NC

³Department of Surgery, Duke University, Durham, NC

Abstract

Objective—The effectiveness of deep brain stimulation (DBS) depends on both the frequency and the temporal pattern of stimulation. We quantified responses to cycling DBS with constant frequency to determine if there was a critical *on* and/or *off* time for alleviating tremor.

Methods—We measured postural tremor in 10 subjects with thalamic DBS and quantified neuronal entropy in a network model of Vim thalamic DBS. We tested 12 combinations of cycling *on/off* times that maintained the same average frequency of 125 Hz, four constant frequency settings, and baseline.

Results—Tremor and neural firing pattern entropy decreased as the percent *on* time increased from 50% to 100%. Cycling with stimulation *on* for at least 60% of the time was as effective as regular stimulation. All cycling settings reduced the firing pattern entropy of model neurons from the no stimulation condition by regularizing pathological firing patterns, either through synaptically-mediated inhibition or axon excitation.

Conclusions—These results indicate that pauses present in cycling stimulation decreased its effectiveness in suppressing tremor, and that changes in the amount of tremor suppression were strongly correlated with changes in the firing pattern entropy of model neurons.

Significance—Cycling stimulation may reduce power consumption during clinical DBS, and thereby increase the battery life of the implanted pulse generator.

Keywords

essential tremor; movement disorders; thalamus; electrical stimulation; computational model

1. INTRODUCTION

Treatment of the motor symptoms of Parkinson's disease (PD) and essential tremor with deep brain stimulation (DBS) requires high frequency (≥ 90 Hz) stimulation (Kuncel et al. , 2006, Moro et al. , 2002). The efficacy of DBS also depends on the temporal pattern of

© 2011 International Federation of Clinical Neurophysiology. Published by Elsevier Ireland Ltd. All rights reserved.

Corresponding Author: Warren M. Grill, Department of Biomedical Engineering, Duke University, Box 90281, Durham, NC 27708, Fax: (919) 660-5276, warren.grill@duke.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

stimulation, and temporally irregular high frequency DBS is less effective than regular DBS with the same average frequency (Birdno et al., 2008, Dorval et al., 2010). Several lines of evidence suggest that temporally irregular stimulation may be less effective due to the presence of long interpulse intervals (pauses) in the stimulation trains, and the objective of the present study was to quantify the effects of pauses in thalamic DBS. Stimulation with patterns containing bursts and pauses degraded motor performance in healthy monkeys, while stimulation with irregular patterns at the same average frequency but without bursts and pauses had no effect (Ma and Wichmann, 2004). Recent computational (Babadi, 2005) and experimental (Person and Perkel, 2005) results indicate that pauses in trains of thalamic input led to burst responses and subsequent disruption of thalamic fidelity (Guo et al., 2008, Rubin and Terman, 2004). As well, bursts in the globus pallidus and subthalamic nucleus (STN) of primates were found consistently to be preceded by a long interspike interval (Wichmann and Soares, 2006). Long interspike intervals between thalamic inputs allow a release from inhibition and generation of a rebound burst mediated by the T-type Ca^{2+} current (Jahnsen and Llinas, 1984).

Pauses in DBS can be delivered clinically using the cycling setting in Kinetra neurostimulators (Model 7428, Medtronic Inc., Minneapolis, MN). STN DBS switched *on* and *off* for 1–60s intervals decreased the beneficial effects of DBS in a patient with PD, as compared to constant stimulation (Khandhar et al., 2005). Similarly, patients exhibited less bradykinesia with continuous STN DBS than when stimulation was cycled *on* and *off* for 100 or 500ms, although all patterns had the same average frequency (Montgomery, 2005). The goal of this study was to quantify the effects of cycling stimulation on tremor in human subjects and on the patterns of neuronal firing in a computational model.

2. METHODS

We measured the tremor response to cycling stimulation in human subjects with thalamic DBS in the ventral intermediate nucleus (Vim) and quantified the patterns of neuronal firing in a computational network model of the Vim thalamus.

Clinical Methods

We quantified tremor in 10 subjects with average age of 66.9 years (range 58–80 years) and thalamic deep brain stimulators implanted at least 3 months prior to participation in the study (range 4–51 months) (Table 1). Subjects were recruited from the Movement Disorders Clinic at Duke University. A neurologist specializing in movement disorders assessed potential subjects' tremor with DBS *off* and DBS *on*, using clinical stimulation parameters selected previously for tremor control. A decrease of one point on the tremor rating scale (Fahn et al., 1993) between the DBS *off* and DBS *on* conditions was an inclusion criterion for this study. Subjects provided informed written consent, and the Duke University Institutional Review Board approved the study. Subject 8 was diagnosed with tremor-dominant Parkinson's disease, and the other nine subjects were diagnosed with essential tremor. With the exception of one subject (Subject 6), all subjects had their deep brain stimulators implanted at Duke University Medical Center. The surgical procedure was performed under local anesthesia using the Leksell stereotactic frame and stereotactic MRI for AC/PC localization. Electrode targeting was confirmed using microelectrode recordings, electrode leads (Model 3387, Medtronic, Inc., Minneapolis, MN) were placed bilaterally in Vim, and a dual-channel pulse generator (Kinetra Model 7428, Medtronic, Inc., Minneapolis, MN) was connected to the leads and implanted subclavicularly.

Postural tremor was quantified using accelerometry during 20 s trials (Figure 1), and the amplitude of tremor recorded by an accelerometer correlates well with clinical tremor rating scales (Elble et al., 2006). Patients were seated in an armchair while holding the arm

elevated at shoulder level in a wing-beat position with the elbow flexed and wrists extended in line with the elbow at the level of the subject's mouth. A triaxial accelerometer (CXL04LP3, Crossbow, San Jose, CA, USA) was attached to the dorsum of the hand, and the accelerometer output was sampled at 1000 Hz using Labview software (National Instruments, Austin, TX, USA). For each voltage output signal (V_x , V_y , V_z), we removed the DC offset, multiplied by 2g to convert voltage to acceleration (A_x , A_y , A_z) (Figure 1, top 3 rows), and performed spectral analysis (psd function, power spectral density, Welch's averaged periodogram, Hanning window, FFT length = 5,000) in Matlab (Mathworks Inc., Natick, MA, USA). The three power spectral densities (P_x , P_y , and P_z) were added together, and total tremor power was defined as the integral of the power spectral density from 1–20 Hz (Figure 1, bottom row). This bandwidth contained the dominant peak (~ 4 Hz) as well as the first several harmonics of the tremor power.

Computational Methods

We simulated the response of thalamic neurons to cycling stimulation using a computer-based network model of the Vim thalamus (Birdno, 2009). Details of the model can be found in the Supplementary Appendix A. The model contained 50 thalamocortical (TC) neurons (McIntyre et al., 2004), with morphology based on three-dimensional reconstruction of a dye-filled thalamic neuron from the rat (Destexhe et al., 1998), and terminating axons carrying inputs from cerebellum, cortex, reticular nucleus (RN), and local thalamic interneurons (TIN) (Darian-Smith et al., 1996, Tasker and Kiss, 1995). The inputs from cerebellum transmitted burst activity, similar to that recorded in the harmaline model of tremor in cat (de Montigny and Lamarre, 1973), with a burst frequency of 5.8 Hz, consistent with the predominant interburst frequency of Vim neurons in humans with ET (Hua and Lenz, 2005). Inputs from cortex were 20 Hz Poisson trains (Descheenes and Hu, 1990). Activity in the inputs from the RN resulted from synaptic excitation of the RN from both cortical inputs and feedback from the TC output (Ando et al., 1995, Steriade et al., 1997). The activity of inhibitory local TIN resulted from synaptic excitation of TIN by cortical and cerebellar inputs (Ando, et al., 1995).

We simulated 50 independent TC neurons positioned randomly within the Vim thalamus. The Vim thalamus was modeled as an oblique prism with a rectangular base. Contact 0 of the stimulating DBS electrode was positioned at the center of the Vim, and the electrode was angled 30° posterior to the coronal plane (Mobin et al., 1999) (Figure 2). The model TC cells' axons were oriented such that they made a straight trajectory from the center of the inferior base of Vim to the hand area of primary cortex (Hlustik et al., 2001). Cortical inputs were oriented inversely symmetrical to the TC axons, cerebellar axons were oriented 30° posterior to the coronal plane, and the RN and TIN axons extended in the lateral-medial and medial-lateral directions, respectively.

We used a finite element model representation (COMSOL, Burlington, MA) of a Medtronic DBS lead (Model 3387, Minneapolis, MN) to calculate the extracellular voltages resulting from stimulation. Simulations were performed with contact 0 set as the cathode, and the outside faces of a 20 cm × 20 cm × 20 cm cube set to ground to approximate using the implantable pulse generator as the return electrode. The conductivities of the homogenous isotropic tissue, electrode contacts, and insulating material between contacts were 2e-1, 1e7, and 1e-10 S/m, respectively. Boundary conditions on the face of contact 0 were set for constant voltage, while the continuity of current density normal to the face was imposed for the remaining components of the lead.

The model neurons were implemented in Neuron 6.1 (Hines and Carnevale, 1997), and the transmembrane potential in response to the extracellular stimulation was obtained by backward Euler integration with a time step of 0.01 ms. The simulation was run for 14

seconds: 2 seconds before stimulation, 10 seconds during stimulation, and 2 seconds after the stimulation was applied. The stimulation amplitude was set to 7.5 V, and this amplitude activated directly 32 of the 50 TC neurons in the absence of other inputs. The high amplitude, relative to typical clinical values, is a reflection of the relatively low density of modeled neurons distributed throughout the volume of the Vim, where some modeled neurons were quite far (> 5mm) from the electrode. 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).

Stimulation

We delivered 12 cycling stimulation trains (Table 2) to human subjects with thalamic DBS and to the computational model of Vim thalamic DBS. Cycling *on* times ranged from 100–500ms, and cycling *off* times ranged from 100–300ms, limited by the available settings of the implanted pulse generator. The stimulation frequency during the stimulation *on* times was varied such that the average frequency was held constant at 125 Hz. The maximum stimulation frequency available in the Kinetra neurostimulator is 250 Hz; cycling combinations where the *off* time was longer than the *on* time were not tested because we could not achieve an average frequency of 125 Hz. Regular DBS at 100, 125, 185, and 250 Hz, as well as stimulation *off*, were also tested. Each setting was tested 1–3 times in each subject in a randomized block design. For each setting, stimulation was turned on and after ~30 seconds, accelerometry was recorded for 20 seconds. Stimulation was then turned off for one minute before the next trial began. The contact configuration, pulse width, and voltage were set at the subjects' clinical settings (Table 1).

Data Analysis and Statistics

Tremor data were analyzed as $\log_{10}$ of the tremor power. Measurements made in different blocks within the same subject were considered replicates and were averaged to get a single measure for each experimental condition for each subject.

The patterns of model neuron firing were analyzed by calculating entropy of the log-transformed interspike intervals (ISIs) (Dorval, 2008). Entropy of the model TC-neuron spike times (H) was calculated as:

$$H = - \sum_{i=1}^{250} p(\log ISI_i) \log_2(\log ISI_i)$$

where $p(\log ISI_i)$ represents the proportion of the total ISIs that are within bin i , where bins range from ~1 – 10,000 ms in 250 bins evenly distributed in log space (bin width = 0.016 log ms).

Changes in tremor and neuron firing patterns across different patterns of stimulation were analyzed using repeated measures analysis of variance (ANOVA). Log-transformed tremor power for each experimental condition was the repeated measure in each subject. The entropy of the log-transformed interspike intervals was the repeated measure for the model neurons. Statistical models were implemented in JMP 8.0 (SAS Institute, Inc. Cary, NC). Tukey's Honestly Significant Difference (Tukey's HSD) test was used to make *post hoc* comparisons of tremor and entropy across experimental conditions with significance defined at $\alpha = 0.05$. The residuals of the log-transformed tremor and firing pattern entropy were normally distributed (visual inspection of residual normality (QQ) plot).

3. Results

Changes in Tremor across Cycling Patterns of DBS

We measured postural tremor in response to different frequencies and cycling patterns of stimulation in 10 subjects with Vim DBS. We measured baseline tremor during no stimulation and tremor during DBS with regular stimulation at 4 frequencies (100, 125, 185, and 250 Hz) (Figure 3). Tremor power was dependent on the stimulation frequency ($p < 0.0001$, ANOVA), and compared to no stimulation, tremor power was reduced significantly with all four stimulation frequencies ($p < 0.00001$, Tukey's HSD). Maximum tremor suppression was achieved with 185 Hz and tremor suppression was significantly less at 100 Hz than at 125, 185, and 250 Hz ($p = 0.03$, Tukey's HSD).

We measured tremor during 12 patterns of cycling DBS (Table 2) with different *on* (100, 200, 300, 400, 500 ms) and *off* (100, 200, 300 ms) times. The frequency during the *on* time was varied from 150 Hz to 250 Hz to maintain a constant average frequency of 125 Hz. Log-transformed tremor power was dependent on the stimulation type ($p < 0.0001$, ANOVA), and tremor was reduced significantly from the *no stimulation* setting with all cycling settings ($p < 0.0001$, Tukey's HSD) (Figure 4). Maximum tremor suppression was achieved with 125 Hz regular stimulation, and compared to regular 125 Hz stimulation, tremor suppression was significantly less with 4/12 cycling patterns: 100ms *on*/100ms *off*, 200ms *on*/200ms *off*, 300ms *on*/300ms *off*, and 400ms *on*/300ms *off* ($p < 0.0005$, Tukey's HSD).

We analyzed the frequency components of tremor across experimental conditions. The median frequency of tremor power between 1–20 Hz had a mean of 4.2 Hz (range 3.6–4.8 Hz) for DBS *off*, and was dependent on the stimulation setting ($p < 0.0001$, ANOVA) (Figure 5). The median frequency decreased significantly for all DBS *on* settings ($p < 0.0047$, Tukey's HSD) except regular 125 Hz ($p = 0.075$), 100ms *on*/100 ms *off* ($p = 0.14$), and 400ms *on*/300ms *off* ($p = 0.075$). Reduction in the median frequency of tremor power suggests the presence of low frequency aperiodic, irregular oscillations and/or mechanical reflex components (Duval et al., 2005) during cycling DBS.

Changes in Model Neuron Firing Patterns across Cycling Patterns of DBS

We used a computer model of Vim thalamic DBS to calculate the response of Vim thalamic neurons to stimulation with the same cycling patterns tested clinically. Across the population of 50 model thalamocortical (TC) neurons, we varied the strength of GABAergic synaptic conductance to produce regular-spiking (15 neurons), random-spiking (10 neurons), and bursting neurons (25) in the same proportions as observed in humans with ET (Molnar et al., 2005). The intrinsic patterns of activity in three representative regular spiking (rows 1–3), two representative random-spiking (rows 4–5), and five representative bursting (rows 6–10) model thalamic neurons in the baseline (no DBS) condition are shown in Figure 6a.

The response of the model neurons to regular 125 Hz stimulation was heterogeneous across the population of 50 model neurons (Figure 6b): 26 fired in synchrony with the stimulation pulses - 19 phase-locked to stimulation (e.g., rows 4, 8) and 7 fired every 4–8th stimulus pulse (e.g., rows 1, 6), 15 of the neurons were silent (e.g., rows 3, 7, 9, 10), and the remaining 9 neurons fired irregularly (e.g., rows 2, 5). We calculated the entropy of the log-transformed ISIs to quantify changes in neuronal firing patterns during DBS with different frequencies. The average firing pattern entropy is a measure of the irregularity of neuronal firing and correlates with the effectiveness of DBS in treating the symptoms of MPTP poisoning in non-human primates (Dorval et al., 2008). The entropy of the neuronal firing pattern was dependent on the stimulation frequency ($p < 0.0001$, ANOVA) (Figure 7). Compared with no stimulation, entropy was reduced significantly with all 4 stimulation

frequencies ($p < 0.00001$, Tukey's HSD), but the differences in entropy between the four stimulation frequencies did not reach statistical significance ($p \geq 0.18$, Tukey's HSD).

The firing pattern of the model neurons during cycling stimulation was dependent on the combination of *on/off* times (Figure 6c, d). For the same cycling *off* time, increasing the cycling *on* time resulted in neurons firing more regularly, and the number of neurons that fired synchronously with the stimulation (phase-locked or every 4–8th pulse) or that were silenced increased with the *on* time. The neuronal firing pattern entropy was dependent on the stimulation type ($p < 0.0001$, ANOVA) (Figure 8). Entropy was reduced significantly from the no stimulation case with all cycling settings ($p < 0.0001$, Tukey's HSD). However, the entropy of neuronal firing during regular 125 Hz stimulation was significantly less than the entropy during all the cycling settings ($p < 0.0001$, Tukey's HSD).

Correlation between Changes in Tremor and Changes in Neuronal Firing Pattern Entropy

Percent *on* times were calculated for each cycling setting as 100 times the cycle *on* time divided by the sum of the cycle *on* and *off* times (Table 2). Log-transformed tremor power was dependent on the percent *on* time ($p < 0.0001$, ANOVA), and as the percent *on* time increased the tremor power decreased (Figure 9a). Compared to 100% *on* (Regular 125 Hz), only 50 and 57% *on* were significantly less effective at reducing tremor ($p < 0.0003$, Tukey's HSD).

Similarly, the entropy of the model neuronal firing patterns was dependent on the percent *on* time ($p < 0.0001$, ANOVA). As the percent *on* time increased, the entropy decreased (Figure 9b). Compared to no stimulation, entropy was reduced significantly with all cycling settings ($p < 0.00001$, Tukey's HSD), but compared to 100% *on*, all percent *on* times $< 100\%$ exhibited significantly higher entropies ($p < 0.0001$, Tukey's HSD). There was a strong linear correlation between the log-transformed tremor power and the entropy of the model neuronal firing patterns across stimulation settings (Figure 9c) ($r = 0.91$).

4. Discussion

We measured changes in tremor in subjects with thalamic DBS and changes in neuronal firing patterns in a network model of thalamic DBS in response to cycling stimulation. Cycling stimulation was regular stimulation (*on* time) interrupted periodically by pauses in stimulation (*off* time), and we varied the cycling *on* and *off* times to determine if there was a critical *on* and/or *off* time for achieving tremor suppression. We maintained a constant average stimulation frequency by varying the frequency of stimulation during the cycle *on* times. DBS with constant, non-cycling stimulation at frequencies of 100, 125, 185, and 250 Hz revealed no significant difference in tremor suppression with frequencies of 125, 185, and 250 Hz. The frequency of stimulation was varied for the cycle *on* time from 125 Hz (Regular DBS) to 250 Hz (100ms *on*/100ms *off*, 200ms *on*/200ms *off*, or 300ms *on*/300ms *off*) and the results of the constant frequency tuning curve suggest that changes in the tremor response during cycling stimulation were not due to the changes in the frequency of stimulation during the cycle *on* time.

In the clinical experiments, tremor decreased as percent *on* time increased. All cycling stimulation patterns reduced tremor significantly from stimulation *off*. However, only cycling settings for which stimulation was *on* at least 60% of the time were as effective as constant (100% *on* time) 125 Hz stimulation. The results in this study are consistent with a previous study on cycling STN DBS. In human subjects with PD, cycling with 50 % *on* times (500 ms *on*/500 ms *off*, 100 ms *on*/100 ms *off*) was less effective at treating bradykinesia than regular stimulation at the same average frequency (Montgomery, 2005). As well, in the computational model, entropy decreased as percent *on* time increased.

Although all cycling stimulation reduced entropy significantly from no stimulation, the firing pattern entropies during cycling stimulation were higher than with regular (100% *on* time) 125 Hz stimulation.

Both tremor and entropy decreased with the percent *on* time, and this correlation supports the hypothesis that DBS alleviates motor symptoms by regularizing neuronal firing or masking pathological activity (Grill et al., 2004). Thalamic neurons that burst in synchrony with tremor in ET and Parkinson's disease are distributed throughout the Vim and ventralis oralis thalamic nuclei (Hua and Lenz, 2005, Kobayashi et al., 2003, Lee et al., 2003, Lenz et al., 1994, Molnar, Pilliar, 2005) and are thought to play a critical role in the generation and maintenance of tremor. Recordings in Vim in persons with ET demonstrated that 75% of neurons responding to active movements burst in synchrony with tremor (Hua and Lenz, 2005). The average interburst and intraburst frequencies of the pathological bursts were 5.8 Hz and 80–160 Hz (Hua and Lenz, 2005), respectively, and this burst pattern was consistent with the intrinsic activity of the computational model. The model results (Figure 6) indicate that DBS masks the pathological bursting patterns through both excitation, which regularized neural firing, and inhibition, mediated by activation of terminating axons presynaptic to inhibitory synapses, which eliminated neural firing (McIntyre et al., 2004). Both excitatory and inhibitory responses were observed in single thalamic neurons in cats in response to ventral lateral thalamic stimulation (Marco et al., 1967, Schlag and Villablanca, 1968), and DBS-like stimulation produced both activation and silencing of neuron in thalamic slices (Anderson et al., 2004, Lee et al., 2005). As well, STN DBS in persons with PD produced both excitation and inhibition of STN neurons (Filali et al., 2004). With clinically effective, high percent *on* stimulation, more neurons fired in regular patterns, either in synchrony (phase-locked or every 4–8th pulse) with stimulation or by being silenced, and this resulted in decreased entropy. There was a weak correlation between the entropy of the stimulation train and the entropy of the model neuron firing patterns ($R=0.58$) as well as between the entropy of the stimulation train and tremor ($R=0.33$). This indicated that the stimulation train alone did not determine the firing patterns of the neurons (and tremor), but rather it was the interaction of the stimulation train with the dynamics and intrinsic activity of the neural circuit, especially the burst driver input from the cerebellum, that determined the neural firing patterns and tremor.

There was a strong linear correlation between the log-transformed tremor power and the entropy of model neuron firing patterns across stimulation settings, but there were two notable differences. All cycling stimulation settings with greater than 60% *on* times resulted in tremor suppression that was statistically equivalent to the tremor suppression achieved with regular 125 Hz stimulation. However, the entropy of neuronal firing patterns during cycling stimulation was consistently higher than during constant 125 Hz stimulation, although reduced significantly relative to the no stimulation condition. Also, as the percent *on* time increased, there was a non-linear decrease in the tremor, with a sharp decrease in tremor occurring at patterns with greater than 60% *on* time. The decrease in neuronal firing entropy, however, was steady and linear with increasing *on* time. Our model did not account for the slow dynamics of changes in excitability that may occur as a result of changes in extracellular ion concentrations or release of neuromodulators, and this may account for the difference between the entropy and tremor response. For example, adenosine is released by thalamic DBS and suppresses tremor by neuronal inhibition (Bekar et al., 2008). If the *on* time was sufficiently long, then tremor was reduced to a level equivalent to regular stimulation, suggesting a potential carryover effect within the *off* interval. However, because slow dynamics were not included in the model there was no carry-over effect of stimulation from the cycle *on* times to the cycle *off* times, allowing pathological firing patterns to continue during even short *off* times.

Temporally irregular high-frequency DBS is less effective than regular high-frequency DBS at relieving tremor (Birdno et al., 2008), and related studies suggest that the decline of efficacy is due to generation of rebound bursts during long pauses (Person and Perkel, 2005, Wichmann and Soares, 2006). The cycle *off* times in this study ranged from 100–500ms in duration, sufficiently long to enable generation of rebound bursts, but all cycling settings suppressed tremor from the stimulation *off* case. The modeling results indicated that pauses enabled generation of rebound bursts and provided an opportunity for the transmission of pathological bursting from presynaptic (cerebellar) axons to thalamic neurons. Rebound bursts were only generated during pauses in which the burst driver was not firing. Cycling with a sufficiently high percent *on* time minimized the number of transmitted bursts by masking the intrinsic activity either through synaptically mediated inhibition (Dostrovsky et al., 2000) or regular firing synchronized with the stimulation (Grill et al., 2004). Also with a high percent *on* time, there were fewer pauses, and therefore fewer opportunities for a rebound burst to occur.

Cycling stimulation is not presently used to treat movement disorders, but it may provide a means to reduce the average stimulation frequency and therefore possibly extend the battery life of the implanted pulse generator (IPG). The IPG requires surgical replacement on average every 3–5 years, and these surgeries have associated risks and expense. A reduction in the average stimulation frequency would decrease energy consumption, and extend the battery life of the IPG (Medtronic, 2010). We compared, in a subset of 5 subjects, the effects on tremor of 3 cycling settings (500ms *on*/100ms *off*, 300ms *on*/100ms *off*, 100ms *on*/100ms *off*) with either a constant average frequency of 125 Hz (cycling *on* frequency = 150 Hz, 167 Hz, 250 Hz, respectively, i.e., as in the primary experiments) or a constant cycle *on* frequency of 125 Hz (i.e., a reduced average frequency of 104 Hz, 94 Hz, or 63 Hz, respectively). The difference between cycling with an average frequency of 125 Hz and cycling with an *on* frequency of 125 Hz was statistically significant for the 3 cycling settings tested (paired t-test, one-sided $p = 0.00013$, $p = 0.00025$, $p = .00066$, respectively). However, tremor power was reduced by at least 90% from baseline with cycling settings of 300 ms *on*/100ms *off* and 500ms *on*/100ms *off* for both an average frequency of 125 Hz and a cycle *on* frequency of 125 Hz. Reducing the average frequency by decreasing the cycling *on* frequency to 125 Hz could therefore decrease power consumption by up to 40% and potentially add several years of battery life to the IPG.

Highlights

- Tremor and firing pattern entropy of model neurons decreased from baseline levels with cycling stimulation.
- Cycling with stimulation on for at least 60% of the time was as effective as continuous 125 Hz stimulation at reducing tremor.
- Cycling stimulation decreased the firing pattern entropy of model neurons by regularizing pathological bursting, while pauses in stimulation generated rebound bursts and allowed transmission of pathological bursts.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Supported by NIH R01 NS040894.

References

- Anderson T, Hu B, Pittman Q, Kiss ZH. Mechanisms of deep brain stimulation: an intracellular study in rat thalamus. *J Physiol.* 2004; 559:301–313. [PubMed: 15218068]
- Ando N, Izawa Y, Shinoda Y. Relative contributions of thalamic reticular nucleus neurons and intrinsic interneurons to inhibition of thalamic neurons projecting to the motor cortex. *J Neurophysiol.* 1995; 73:2470–2485. [PubMed: 7666153]
- Babadi B. Bursting as an effective relay mode in a minimal thalamic model. *J Comput Neurosci.* 2005; 18:229–243. [PubMed: 15714271]
- Bekar L, Libionka W, Tian G-F, Xu Q, Torres A, Wang X, et al. Adenosine is crucial for deep brain stimulation-mediated attenuation of tremor. *Nat Med.* 2008; 14:75–80. [PubMed: 18157140]
- Birdno, MJ. Analyzing the mechanisms of thalamic deep brain stimulation: computational and clinical studies. Durham, NC: Duke University; 2009.
- Birdno MJ, Kuncel AM, Dorval AD, Turner DA, Grill WM. Tremor varies as a function of the temporal regularity of deep brain stimulation. *Neuroreport.* 2008; 19:599–602. [PubMed: 18388746]
- Darian-Smith I, Galea MP, Darian-Smith C, Sugitani M, Tan A, Burman K. The anatomy of manual dexterity. The new connectivity of primate sensorimotor thalamus and cerebral cortex. *Adv Anat Embryol Cell Biol.* 1996; 133:1–140.
- de Montigny C, Lamarre Y. Rhythmic activity induced by harmaline in the olivo-cerebello-bulbar system of the cat. *Brain Res.* 1973; 53:81–95. [PubMed: 4697252]
- Descheenes M, Hu B. Electrophysiology and Pharmacology of the Corticothalamic Input to Lateral Thalamic Nuclei: an Intracellular Study in the Cat. *Eur J Neurosci.* 1990; 2:140–152. [PubMed: 12106057]
- Destexhe A, Neubig M, Ulrich D, Huguenard J. Dendritic Low-Threshold Calcium Currents in Thalamic Relay Cells. *J Neurosci.* 1998; 18:3574–3588. [PubMed: 9570789]
- Dorval A. Probability distributions of the logarithm of inter-spike intervals yield accurate entropy estimates from small datasets. *J Neurosci Methods.* 2008; 173:129–139. [PubMed: 18620755]
- Dorval AD, Kuncel AM, Birdno MJ, Turner DA, Grill WM. Deep brain stimulation alleviates parkinsonian bradykinesia by regularizing pallidal activity. *J Neurophysiol.* 2010; 104:911–921. [PubMed: 20505125]
- Dorval AD, Russo GS, Hashimoto T, Xu W, Grill WM, Vitek JL. Deep brain stimulation reduces neuronal entropy in the MPTP-primate model of Parkinson's disease. *J Neurophysiol.* 2008; 100:2807–2818. [PubMed: 18784271]
- Dostrovsky JO, Levy R, Wu JP, Hutchison WD, Tasker RR, Lozano AM. Microstimulation-Induced Inhibition of Neuronal Firing in Human Globus Pallidus. *J Neurophysiol.* 2000; 84:570–574. [PubMed: 10899228]
- Duval C, Strafella AP, Sadikot AF. The impact of ventrolateral thalamotomy on high-frequency components of tremor. *Clin Neurophysiol.* 2005; 116:1391–1399. [PubMed: 15978501]
- Elble RJ, Pullman SL, Matsumoto JY, Rauthjen J, Deuschl G, Tinter R. Tremor amplitude is logarithmically related to 4- and 5-point tremor rating scales. *Brain.* 2006; 129:2660–2666. [PubMed: 16891320]
- Fahn, S.; Tolosa, E.; Marin, C. Clinical rating scale for tremor. In: J, J.; E, T., editors. *Parkinson's disease and movement disorders*. Baltimore: Williams & Wilkins; 1993. p. 225–234.
- Filali M, Hutchison W, Palter V, Lozano A, Dostrovsky J. Stimulation-induced inhibition of neuronal firing in human subthalamic nucleus. *Exp Brain Res.* 2004; 156:274–281. [PubMed: 14745464]
- Grill WM, Snyder AN, Miocinovic S. Deep brain stimulation creates an informational lesion of the stimulated nucleus. *Neuroreport.* 2004; 15:1137–1140. [PubMed: 15129161]
- Guo Y, Rubin JE, McIntyre CC, Vitek JL, Terman D. Thalamocortical Relay Fidelity Varies Across Subthalamic Nucleus Deep Brain Stimulation Protocols in a Data-Driven Computational Model. *J Neurophysiol.* 2008; 99:1477–1492. [PubMed: 18171706]
- Hines ML, Carnevale NT. The NEURON simulation environment. *Neural Comput.* 1997; 9:1179–1209. [PubMed: 9248061]

- Hlustik P, Solodkin A, Gullapalli RP, Noll DC, Small SL. Somatotopy in human primary motor and somatosensory hand representations revisited. *Cereb Cortex*. 2001; 11:312–321. [PubMed: 11278194]
- Hua SE, Lenz FA. Posture-Related Oscillations in Human Cerebellar Thalamus in Essential Tremor Are Enabled by Voluntary Motor Circuits. *J Neurophysiol*. 2005; 93:117–127. [PubMed: 15317839]
- Jahnsen H, Llinas R. Voltage-dependent burst-to-tonic switching of thalamic cell activity: an in vitro study. *Arch Ital Biol*. 1984; 122:73–82. [PubMed: 6087765]
- Khandhar, SM.; Heath, SL.; Ostrem, JL.; Marks, WJ, Jr. Efficacy and tolerability of rapid cyclical stimulation of the subthalamic nucleus in Parkinson's disease. 9th International Congress of Parkinson's Disease and Movement Disorders; New Orleans, LA. 2005.
- Kobayashi K, Katayama Y, Kasai M, Oshima H, Fukaya C, Yamamoto T. Localization of thalamic cells with tremor-frequency activity in Parkinson's disease and essential tremor. *Acta Neurochir Suppl*. 2003; 87:137–139. [PubMed: 14518541]
- Kuncel AM, Cooper SE, Wolgamuth BR, Clyde MA, Snyder SA, Montgomery EB Jr, et al. Clinical response to varying the stimulus parameters in deep brain stimulation for essential tremor. *Mov Disord*. 2006; 21:1920–1928. [PubMed: 16972236]
- Lee BH, Lee KH, Chung SS, Chang JW. Neurophysiological identification and characterization of thalamic neurons with single unit recording in essential tremor patients. *Acta Neurochir Suppl*. 2003; 87:133–136. [PubMed: 14518540]
- Lee KH, Hitti FL, Shalinsky MH, Kim U, Leiter JC, Roberts DW. Abolition of spindle oscillations and 3-Hz absence seizure-like activity in the thalamus by using high-frequency stimulation: potential mechanisms of action. *J Neurosurg*. 2005; 103:538–545. [PubMed: 16235687]
- Lenz FA, Kwan HC, Martin RL, Tasker RR, Dostrovsky JO, Lenz YE. Single unit analysis of the human ventral thalamic nuclear group. Tremor-related activity in functionally identified cells. *Brain*. 1994; 117(Pt 3):531–543. [PubMed: 8032863]
- Ma, Y.; Wichmann, T. Society for Neuroscience. San Diego, CA: 2004. Disruption of Motor Performance by Basal Ganglia Stimulation.
- Marco LA, Brown TS, Rouse ME. Unitary response in ventrolateral thalamus upon intranuclear stimulation. *J Neurophysiol*. 1967; 30:482–493. [PubMed: 6037589]
- McIntyre CC, Grill WM, Sherman DL, Thakor NV. Cellular Effects of Deep Brain Stimulation: Model-Based Analysis of Activation and Inhibition. *J Neurophysiol*. 2004; 91:1457–1469. [PubMed: 14668299]
- Medtronic I. System eligibility, Battery longevity: Neurostimulation systems for deep brain stimulation. 2010
- Mobin F, De Salles AA, Behnke EJ, Frysinger R. Correlation between MRI-based stereotactic thalamic deep brain stimulation electrode placement, macroelectrode stimulation and clinical response to tremor control. *Stereotact Funct Neurosurg*. 1999; 72:225–232. [PubMed: 10853082]
- Molnar GF, Pilliar A, Lozano AM, Dostrovsky JO. Differences in Neuronal Firing Rates in Pallidal and Cerebellar Receiving Areas of Thalamus in Patients With Parkinson's Disease, Essential Tremor, and Pain. *J Neurophysiol*. 2005; 93:3094–3101. [PubMed: 15703231]
- Montgomery EB Jr. Effect of subthalamic nucleus stimulation patterns on motor performance in Parkinson's disease. *Parkinsonism Relat Disord*. 2005; 11:167–171. [PubMed: 15823481]
- Moro E, Esselink RJA, Xie J, Hommel M, Benabid AL, Pollak P. The impact on Parkinson's disease of electrical parameter settings in STN stimulation. *Neurology*. 2002; 59:706–713. [PubMed: 12221161]
- Person AL, Perkel DJ. Unitary IPSPs Drive Precise Thalamic Spiking in a Circuit Required for Learning. *Neuron*. 2005; 46:129–140. [PubMed: 15820699]
- Rubin JE, Terman D. High Frequency Stimulation of the Subthalamic Nucleus Eliminates Pathological Thalamic Rhythmicity in a Computational Model. *J Comput Neurosci*. 2004; 16:211–235. [PubMed: 15114047]
- Schlag J, Villablanca J. A quantitative study of temporal and spatial response patterns in a thalamic cell population electrically stimulated. *Brain Res*. 1968; 8:255–270. [PubMed: 5652719]
- Steriade, M.; Jones, EG.; McCormick, DA. *Thalamus*. Oxford: Elsevier Science Ltd; 1997.

- Tasker RR, Kiss ZH. The role of the thalamus in functional neurosurgery. *Neurosurg Clin N Am*. 1995; 6:73–104. [PubMed: 7696876]
- Wichmann T, Soares J. Neuronal Firing Before and After Burst Discharges in the Monkey Basal Ganglia Is Predictably Patterned in the Normal State and Altered in Parkinsonism. *J Neurophysiol*. 2006; 95:2120–2133. [PubMed: 16371459]

Figure 1.

Tremor response. Triaxial acceleration (A_x , A_y , A_z) (rows 1–3) and power spectral density (row 4) for one subject in response to no stimulation (column 1), regular 125 Hz stimulation (column 2), cycling 100ms *on*, 100ms *off* stimulation (column 3), and cycling 500ms *on*, 100ms *off* stimulation (column 4). Power spectral densities for the x-, y-, and z- axes were added, and tremor was quantified as the integral of tremor power ($m^2/s^4/Hz$) from 1–20 Hz.

Figure 2. Computational model of thalamic deep brain stimulation. A population of fifty 3-dimensional cable models of thalamocortical (TC) neurons and four terminating axons providing input to each modeled thalamic neuron were distributed within a prism representation of the Vim thalamus and DBS electrode.

Figure 3.

Log-transformed tremor power as a function of stimulation frequency. Mean and standard error are shown for $n = 10$ (0, 125, 250 Hz) or $n = 8$ (100, 185 Hz) subjects.

Figure 4.

Log-transformed tremor power as a function of cycling *on* times (100–500 ms). Results for cycling *off* times of 100ms are shown in the top panel, 200ms in the middle, and 300ms in the bottom panel. The cycling *on* times in ms are listed on the x-axis. Stimulation *off* (Stim off) and regular 125 Hz (Reg) stimulation are also shown on each graph. Mean and standard error of log-transformed tremor power are shown for $n = 8$ (300ms *on*/300 ms *off*) or $n=10$ (all other settings) subjects.

Figure 5.

Median frequency of tremor power spectral density from 1–20 Hz as a function of cycling *on* times (100–500 ms). Results for cycling *off* times of 100 ms are shown in the top panel, 200 ms in the middle, and 300 ms in the bottom panel. The cycling *on* times in ms are listed on the x-axis. Stimulation *off* (Stim off) and regular 125 Hz (Reg) stimulation are also shown on each graph. Mean and standard error of median frequency of tremor PSD are shown for $n = 8$ (300ms *on*/300ms *off*) or $n=10$ (all other settings) subjects.

Figure 6.

The firing times of action potentials for 10 of 50 model thalamo-cortical neurons. Rasters are shown for a) Stimulation *off*, b) Regular 125 Hz stimulation, c) Cycling stimulation 100 ms *on*/100 ms *off*, and d) Cycling stimulation 500 ms *on*/100 ms *off*. The times of action potentials in the distal axon of each TC neuron during the final 2 seconds of stimulation are shown. The top 3 rows represent the regular spiking thalamo-cortical cells, the next 2 rows represent the random-spiking cells, and the bottom 5 rows represent the bursting thalamo-cortical neurons.

Figure 7. Entropy of log-transformed interspike intervals (ISIs) of computational model thalamo-cortical neurons as a function of stimulation frequency. Mean and standard error are shown for $n=50$ model neurons.

Figure 8.

Entropy of log-transformed interspike intervals (ISIs) as a function of cycling *on* times (100–500 ms). Results for cycling *off* times of 100 ms are shown in the top row, 200 ms in the middle, and 300 ms in the bottom row. The cycling *on* times in ms are listed on the x-axis. Stimulation *off* (Stim off) and regular 125 Hz (Reg) stimulation are also shown on each graph. The mean and standard error are shown for 50 model neurons.

Figure 9.

Log-transformed tremor and entropy of the log-transformed interspike intervals (ISIs) of the model thalamo-cortical neurons as a function of percent cycle *on* time. a) Mean and standard error are shown for $n = 28$ (50% *on* time including $n = 10$ 100ms *on*/100 ms *off*, $n = 10$ 200ms *on*/200ms *off*, and $n = 8$ 300ms *on*, 300ms *off*), $n = 20$ (67% *on* time including $n = 10$ 200ms *on*/100ms *off* and $n = 10$ 400ms *on*/200ms *off*) and $n = 10$ (all other settings) subjects. b) Mean and standard error are shown for $n = 150$ (50% *on* time including $n = 50$ 100ms *on*/100 ms *off*, $n = 50$ 200ms *on*/200ms *off*, and $n = 50$ 300ms *on*, 300ms *off*), $n = 100$ (67% *on* time including $n = 50$ 200ms *on*/100ms *off* and $n = 50$ 400ms *on*/200ms *off*) and $n = 50$ (all

other settings) model neurons. c) Entropy of log-transformed ISIs as a function of log-transformed tremor-power.

Table 1

Subject Characteristics. Postural tremor rating on a scale of 0–4, where 0 is no tremor.

Subject	Age/Gender	Months since implant	Tremor Rating DBS ON/OFF	Clinical DBS Settings			
				Contacts	Pulse Width (µs)	Frequency (Hz)	Amplitude (V)
1	67/M	25	1/4	6-7+	90	170	3.9
2	79/M	44	NA	1-2-C+	90	185	2.4
3	65/F	51	2/3	0-1-2+3+	60	130	3.5 (2.5)*
4	80/M	16	1/4	0-1+	90	130	6.8 (6.0)*
5	60/F	5	0/4	6-C+	90	130	3.2
6	62/M	25	0/4	0-1-2+	90	135	3.7
7	58/M	44	0/3	5-6-7+	120	185	3.6
8	60/F	33	1/2	0-1+	60	185	4.8
9	65/M	23	NA	0-1+	60	150	3.3
10	73/M	4	NA	0-1-C+	60	135	4

* Values in parentheses are stimulation amplitudes used during the study. Amplitudes were reduced in Subjects 3 and 4 to minimize side effects.

Cycling stimulation parameters. The top number in each cell is the stimulation frequency during cycle *on* times. Stimulation frequency was varied to keep average frequency constant at 125 Hz. The bottom number in each cell is the percent *on* time, calculated as 100 times the cycle *on* time divided by the sum of the cycle *on* and *off* times.

Table 2

		Cycle ON time (ms)				
		100	200	300	400	500
Cycle OFF time (ms)	100	250 Hz 50%	190 Hz 67%	167 Hz 75%	157 Hz 80%	150 Hz 83%
	200	X	250 Hz 50%	210 Hz 60%	190 Hz 67%	175 Hz 71%
	300	X	X	250 Hz 50%	220 Hz 57%	200 Hz 63%