Deep brain stimulation alleviates parkinsonian bradykinesia by regularizing pallidal activity

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Running Head (≤55): DBS Regularity Alleviates Parkinsonism

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Abstract (≤250)

Deep brain stimulation (DBS) of the basal ganglia can alleviate the motor symptoms of Parkinson's disease, although the therapeutic mechanisms are unclear. We hypothesize that DBS relieves symptoms by minimizing pathologically disordered neuronal activity in the basal ganglia. In human participants with parkinsonism and clinically effective deep brain leads, regular (i.e., periodic) high frequency stimulation was replaced with irregular (i.e., aperiodic) stimulation at the same mean frequency (130 Hz). Bradykinesia, a symptomatic slowness of movement, was quantified via an objective finger tapping protocol in the absence and presence of regular and irregular DBS. Regular DBS relieved bradykinesia more effectively than irregular DBS. A computational model of the relevant neural structures revealed that output from the globus pallidus internus was more disordered and thalamic neurons made more transmission errors in the parkinsonian condition, compared to the healthy condition. Clinically therapeutic, regular DBS reduced firing pattern disorder in the computational basal ganglia and minimized model thalamic transmission errors, consistent with symptom alleviation by clinical DBS. However, non-therapeutic, irregular DBS neither reduced disorder in the computational basal ganglia nor lowered model thalamic transmission errors. Thus, we show that clinically useful DBS alleviates motor symptoms by regularizing basal ganglia activity and thereby improving thalamic relay fidelity. This work demonstrates that high frequency stimulation alone is insufficient to alleviate motor symptoms: DBS must be highly regular. Descriptive models of pathophysiology that ignore the fine temporal resolution of neuronal spiking in favor of average neural activity cannot explain the mechanisms of DBS-induced symptom alleviation.
Introduction

High frequency stimulation of the subthalamic nucleus or the internal segment of the globus pallidus is an effective treatment for persons with Parkinson's disease (PD) whose symptoms have become medically unmanageable. High-frequency deep brain stimulation (DBS) can alleviate tremor, bradykinesia, and rigidity, and can enable a reduction in medication dose, thereby reducing dyskinesias. The therapeutic benefits of high frequency DBS resemble those resulting from surgical lesions in the same locations. However, DBS has the advantages that it is adjustable (the electrode geometry and stimulation parameters are programmable), reversible (stimulation can be turned off and the electrodes can be removed), and DBS can be implanted bilaterally, while bilateral lesions are often associated with unacceptable side effects (Okun and Vitek, 2004). Although DBS has been implanted in over 40,000 patients, the mechanisms of action remain unclear.

Based on similarities in clinical outcomes, DBS was thought to share a physiological effect with a lesion: silencing or suppressing the neural activity in the stimulated tissue. Some experimental results support that DBS inhibits the neurons surrounding the electrode (Beurrier et al., 2001; Boraud et al., 1996; Filali et al., 2004). However, axons entering or leaving the stimulated nucleus may also fire synchronously with DBS, propagating increased activity to both afferent and efferent locations (McIntyre et al., 2004; Li et al., 2007; Gradinaru et al., 2009). Downstream changes in concentrations of neurotransmitters and related biochemicals (Windels et al., 2003; Stefani et al., 2005) and electrophysiological activity (Anderson et al., 2003; Hashimoto et al., 2003; Hershey et al., 2003; Degos et al., 2005; Phillips et al., 2006) support the claim that DBS excites axons entering and exiting the site of stimulation. Thus, while DBS and lesion may yield similar outcomes, the intuitive hypothesis that they both alleviate symptoms by silencing neural activity appears to be incorrect.

If neuronal firing rates were directly responsible for symptom severity, the emerging view that DBS increases widespread axonal activity could not be reconciled with the cessation of neural activity following surgical lesion. However, symptom severity may be less related to rates of neuronal activity than to patterns of neuronal activity, as suggested in: rodents (Degos et al., 2005), non-human primates (Hashimoto et al., 2003; Wichmann and DeLong, 2003; Bar-Gad et al., 2004; Meissner et al., 2005), humans with PD (Magnin et al., 2000;
Supporting this regularity assertion, high frequency stimulation overrode pathological firing patterns in computer models of DBS (Grill et al., 2004; Rubin and Terman, 2004; Terman et al., 2002). Tremor reduction by thalamic DBS with different frequencies, amplitudes (Kuncel et al., 2007) or patterns (Birdno et al., 2007) of stimulation was strongly correlated with the regularization of neuron firing patterns. Furthermore, high-frequency DBS that alleviated motor symptoms in a non-human primate model of parkinsonism also lowered the firing pattern entropy of neurons throughout the basal ganglia thalamic network (Dorval et al., 2008; Hashimoto et al., 2003). We hypothesize that the abolishment of pathological neuronal activity is the mechanism by which DBS alleviates the motor symptoms of PD.

We propose this specific test of causality: DBS that reduces the variability of synaptic inhibition from globus pallidus to thalamus will reduce bradykinesia in persons with PD, while DBS of the same amplitude and average frequency that does not reduce synaptic variability will not alleviate symptoms. In particular, masking the disease-induced pathological activity with regular (periodic) DBS-induced activity will alleviate parkinsonian symptoms, while masking the disease-induced pathological activity with irregular (aperiodic) DBS-induced activity will not alleviate symptoms. Indeed, in this study we found that periodic DBS patterns, which regularized activity (i.e., lowered neuronal firing pattern entropy) in a computational model of the basal ganglia thalamic circuit (Rubin and Terman, 2004), alleviated bradykinesia in human participants with PD. Conversely, aperiodic DBS patterns of the same amplitude and average frequency, which did not regularize neuronal activity in the computational model, did not alleviate bradykinesia in human participants. Thus we provide causal evidence for a mechanism of DBS: regularizing neuronal activity and thereby synaptic release in the basal ganglia thalamic network alleviates the motor symptoms of PD.
Methods

The efficacy of high-frequency deep brain stimulation (DBS) with increasing degrees of temporal variability was measured in both a computational model of the basal ganglia thalamic circuit and in human participants with Parkinson's disease (PD) and existing DBS electrodes under awake and behaving conditions during battery replacement surgery. These METHODS describe the types of DBS trains used in both cases, the computational model construction and simulation, the analysis of the computational data, and the human protocol and data analysis.

Temporally Irregular DBS

Four classes of DBS trains were constructed and denoted by their degree of variability (Fig. 1a,b). One class had no variability consisting of periodic pulses at 130 Hz, identical to the DBS provided by the pulse generators used clinically (Kineta or Soletra, Medtronic Inc., Minneapolis MN). The other three classes were constructed as memoryless point processes, where the time from one pulse to the next was a random variable, found by drawing a random sample from a gamma distribution of instantaneous frequencies, $f_i$. The gamma distributions all had a mean of 130 Hz, with standard deviations of 13, 39 or 78 Hz for the 10%, 30% or 60% variability classes, respectively. Probability density functions of the instantaneous frequency, defined in terms of the gamma function ($\Gamma$), were described by: $p(f_i) = \left(\frac{f_i^{\kappa-1} e^{-f_i}}{\theta^\kappa \Gamma(\kappa)}\right) / \left(\theta^\kappa \Gamma(\kappa)\right)$ for $f_i > 0$ where the shape parameters ($\kappa = 100 \{1, 1/9, 1/36\}$) and scale parameters ($\theta = 13/10 \{1, 9, 36\}$) were set to yield a mean of 130 Hz and variabilities of 10%, 30% and 60%, respectively.

Computational Model Experiments

All computational experiments and analysis were performed on an x86 personal computer running the Ubuntu distribution (http://www.ubuntu.com, Canonical LTD, Isle of Man) of the GNU/Linux operating system (Free Software Foundation, Boston MA). All models and analysis code are available from the authors upon request.

The computational model was modified slightly from existing models of the basal ganglia thalamic network (Terman et al., 2002; Rubin and Terman, 2004). Sixteen point neurons in each of the four regions –
subthalamic nucleus (STN), globus pallidus externus (GPe), globus pallidus internus (GPI) and pallidal receiving
thalamic cells (TC) – comprised the model. Terman and colleagues (2002) categorized 3 anatomically distinct
connection schemes for the model, from which our connection scheme is somewhere between their *random* and
*structured-sparse* networks. In particular, our connections were structured and sparse, the scheme preferred by
others (Rubin and Terman, 2004; Feng et al., 2007), but included asymmetry present only in their random network
(Terman et al., 2002). We also introduced heterogeneity into the network by varying the striatal drive to GPe
behavior, and kept the network from highly regular, perfectly entrained activity in the presence of the intense
periodicity supplied by regular DBS of the STN cells.

The membrane potential ($V$) of neurons in basal ganglia was described by: $c_m \frac{dV}{dt} = I_{app} - I_{Na} - I_K - I_{Ca} -$ $I_T - I_{ahp} - I_L - I_{syn}$; where $c_m$ is the membrane capacitance and each $I$ variable denotes a current source: $I_{Na}, I_K, I_{Ca},$
$I_T, I_{ahp},$ and $I_L$ are the sodium, potassium, calcium, T-type calcium, after-hyperpolarizing, and leak currents,
respectively. The membrane potential of thalamic cells was described by $c_m \frac{dV}{dt} = I_{smc} - I_{Na} - I_K - I_T - I_L - I_{syn}$.
The ionic currents and gating variables, with parameter values, are detailed in the SUPPLEMENT. The applied ($I_{app}$,
$I_{smc}$) and synaptic ($I_{syn}$) currents are discussed below.

**Neuronal Inputs.** The neurons were connected in a sparse, structured fashion by repeating, with periodic boundary
conditions, the input scheme illustrating all inputs to the fourth neuron of each region in figure 1c: each $k^{th}$ neuron
in GPe and GPI received excitation from STN neurons $k-1$ and $k$ and inhibition from GPe neurons $k+1$ and $k+2$;
each $k^{th}$ STN neuron received inhibition from GPe neurons $k$ and $k+1$; and each TC neuron received inhibition
from GPe neurons $k-1$ and $k$. Every synaptic connection was described by a differential equation $dz/dt = \alpha(1 -$
z)z$\infty - \beta z$, where $z_\infty = [1 + \exp((V - \theta z)/\sigma_z)]^{-1}$. From each synaptic gating variable $z$, the synaptic current was found
as: $I_{syn} = G_{syn} z (V - V_{syn})$. Parameter values for the rate constants ($\alpha$ and $\beta$), shape parameters ($\theta$ and $\sigma$), maximal
conductance ($G_{syn}$) and reversal potential ($V_{syn}$) are defined for all synapses in the SUPPLEMENT. With the
neuronal parameters and synaptic connections established, the tonic drive currents to the basal ganglia neurons
were varied to yield firing rates and patterns as consistent as possible with published electrophysiological results
from in vivo models of parkinsonism.
The STN neurons were presented with a tonic applied current, unchanged from Rubin and Terman (2004), plus a stimulatory current during DBS, and only STN neurons received DBS. The patterns of stimulatory current pulses are described in Temporally Irregular DBS, and each monophasic pulse was depolarizing with an amplitude of 300 pA/μm² and a duration of 300 μs. Without DBS, the STN neurons exhibited mean firing rates of 16.4 ± 1.4 Hz (mean ± S.D.) in the parkinsonian state. Although those rates were lower than published values in humans, difficulties isolating STN neurons may lead to a reported firing rate bias toward higher frequencies (Magnin et al., 2000). More importantly however, the model firing rates in the parkinsonian state were 5-10 Hz higher than in their healthy-normal condition, and in the range of STN firing rates of some reported MPTP treated non-human primates (e.g., 26 ± 15 Hz (Bergman et al., 1994)), although slightly below others (e.g., 36.1 ± 10.7 Hz (Soares et al., 2004)).

The average 20 pA/μm² depolarizing current applied to the GPe neurons in control conditions was reduced to 5 pA/μm² in the parkinsonian state to simulate increased inhibition from striatum. These values were picked on the basis that they yielded inter-spike interval distributions – encompassing firing rate, burstiness and irregularity – similar to those recorded from non-human primates (Dorval et al., 2008). GPe firing rates fell from 77.0 ± 15.6 Hz in control to 32.2 ± 7.1 Hz in the parkinsonian state, within the ranges of neurons recorded from GPe in the non-human primate before (65.1 ± 23.6) and after (45.9 ± 18.9 Hz) MPTP exposure (Soares et al., 2004). While the parkinsonism-induced rate changes were greater in the model (44.7 ± 12.1 Hz) than in the non-human primate (19.2 ± 21.4), adjusting striatal drive to match rate more closely, eliminated the bursting and irregular firing patterns seen in vivo. Slight heterogeneity was introduced to the network by varying the striatal drive to GPe neurons: one-half of the GPe neurons (cells: 1, 3, 5, ..., 15) received the average current; one-quarter of GPe neurons (cells: 2, 8, 10, 14) received 2 pA/μm² above that average; and the final one-quarter (cells: 4, 6, 12, 16) received 2 pA/μm² below that average. The original model (Rubin and Terman, 2004; Terman et al., 2002) included parkinsonian-state modifications to the GPe to GPe synapses that were not incorporated here.

The 21 pA/μm² depolarizing current applied to the GPi neurons in control conditions was reduced to 12 pA/μm² in the parkinsonian state. This current was intentionally inhibitory in the parkinsonian relative to the control condition, because decreasing striatal inhibition to GPi led to physiologically unrealistic hyper-
pathological bursts of tens to hundreds of spikes followed by brief pauses in each neuron. Firing rates in model

GPi cells in the healthy (82.6 ± 3.2 Hz) and parkinsonian (70.1 ± 4.1Hz) states compared favorably with the
ranges recorded from non-human primates before (59.7 ± 16.8 Hz or 65.1 ± 20.8 Hz) and after (59.9 ± 26.9 Hz or
80.6 ± 19.6 Hz) MPTP exposure (Bergman et al., 1994; Soares et al., 2004) and to human participants with PD
(89.3 ± 11.2 Hz (Tang et al. 2005)).

Sensory-motor input to the thalamus ($I_{snc}$) was modeled as a gamma distributed pulse train, similar to the
trains used for irregular DBS stimulation. Each instantaneous frequency (i.e., the reciprocal of the time between
pulses) was drawn from a gamma distribution with shape parameter $\kappa = 25$ and scale parameter $\theta = 2/5$, which
had an average of 10 Hz with a standard deviation of 2 Hz. Each depolarizing monophasic sensory-motor input
pulse had an amplitude of 2 pA/µm² and a duration of 5 ms.

**Computer Simulations.** The computational model was used to quantify the effects of parkinsonism and
temporally regular and irregular DBS on neuronal activity. Changes to the bias current of neurons in the globus
pallidus shifted the model between healthy and parkinsonian conditions. The DBS and sensory-motor input pulse
trains were generated in Octave, the GNU numerical computing language (http://www.gnu.org/software/octave).
Simulations were run in XPP-AUT (http://www.math.pitt.edu/~bard/xpp/xpp.html), the nonlinear differential
equation simulation package, with the fourth order Runge-Kutta solver using a maximum time step of 50 µs. The
first 1.0 sec of simulation time was ignored to allow for initial conditions to settle. Simulations were run for 15
sec epochs, and summary results were calculated from 150 sec of simulation time (Figs. 2, 3 & 6).

**Computational Model Analysis**

All state variables and time varying signals generated in the computational simulations were exported to binary
files, and loaded into Octave. Membrane potential traces were converted to spike trains, where each spike time
corresponded to a moment at which the membrane potential crossed -20 mV with a positive slope. Inter-spike
intervals (ISIs) were sorted into histogram bins of equal size in logarithmic time at 50 bins per ISI decade. For
each cell, a histogram was constructed from 150 sec of simulation time and normalized to yield a probability
distribution of logarithmic ISIs. Distributions were averaged across all cells (Fig. 2b-d). Firing pattern entropy
(H) was estimated from the logarithmic ISI distributions to decouple changes in entropy from changes in firing rate (Dorval, 2008). The first order entropy estimate was found for each neuron, \[ H = - \sum P_k \log_2 P_k, \] where the sum is taken over all ISI bins and \( P_k \) is the probability associated with the \( k^{th} \) bin. Reported entropy values for each region are the mean and standard deviation across the 16 cells in that region (Fig. 2e). Higher order estimates and different entropy estimation techniques all yielded qualitatively similar results.

Model thalamic cell (TC) error rates (Guo et al., 2008; Rubin and Terman, 2004) were assessed by categorizing responses to the sensory-motor input current pulses into four types of events. A correct event was recorded when a TC fired a single spike within the response window, which began with a sensory-motor pulse and lasted 25 ms. Three types of errors were recorded: a miss event when a TC did not spike in a response window; a burst event when a TC spiked more than once in a response window; and an extraneous event when a TC spike was not in any response window. Error rates were calculated as the number of error events per 15 sec epoch, divided by the total number of events per epoch, normalized by 15 to yield errors per second. Reported values (Fig. 3) are the average and standard deviations of those error rates across all 16 TCs for 10 such epochs.

The synaptic conductance (\( G_{syn} \)) for each GPi to TC synapse was examined from 100 ms before to 50 ms after the initiation of each sensory-motor input pulse (Fig. 6a,b). Individual traces of the same condition (i.e., PD, PD with 130 Hz, etc.) and outcome event (i.e., correct, miss, burst or extraneous) were combined to yield the average time varying synaptic conductance for each event-condition (Guo et al., 2008). Autocorrelations of each 15 sec epoch spike train were found from the waveform generated by convolving each spike train with a normalized Gaussian function with a standard deviation of 1.0 ms. Autocorrelations were averaged across 10 epochs for each neuron, and each reported value is the mean across all 16 cells for that region (Fig. 6c). In addition, the average and standard deviation of each individual trace was calculated for each event, and those values were averaged together to yield overall conductance means and standard deviations (Fig. 6d,e).

**Measurements in Human Participants with Parkinson's Disease**

The human participants protocol was approved by the Institutional Review Board of Duke University, and all participants provided written informed consent. The battery of the implantable pulse generator (IPG) needs replacement every one to five years following implantation, depending on the parameters used for chronic...
stimulation. Participants were chosen for the study if 1) they had PD with bradykinesia that was treated effectively with DBS therapy through one or more existing leads, and 2) they were returning to the operating room for battery replacement surgery. Nine patients consented to participate in the study.

Data Collection. Participants entered the operating room, when possible having forgone dopaminergic therapy for at least 12 hours (6/9 subjects). Participants did not receive presurgical medications for analgesia or sedation. Individuals were resting on their backs but fully awake. Local anesthetic was applied above the IPG and a small incision opened the subcutaneous pocket housing the IPG. The IPG was removed and disconnected from the extension cable extending to the deep brain leads.

Signal generation was performed by custom software in LabView (National Instruments, Austin TX) on an x86 laptop computer (Latitude D810, Dell Inc., Round Rock TX) running Window XP (Microsoft, Redmond WA). Signals were trains of biphasic voltage pulses distributed in time as described in TEMPORALLY IRREGULAR DBS. Stimulation was presented on the electrical contacts used clinically (4/9 subjects) or a clinically unused contact on the DBS electrode was set as the current return (5/9 subjects) in participants whose clinical settings included the IPG case as a current return; there were no significant differences in the responses of those two groups. Typically, the stimulation amplitude was set to the clinically programmed values (6/9 subjects). The amplitude in one participant (#4) was reduced from 3.5 V to 3.0 V to minimize transient side effects associated with stimulation onset, and the amplitude in the two other participants was increased to compensate for changing the return electrode from the IPG case to a DBS lead: 4.0 V instead of 2.5 V (#8) and 3.5 V instead of 3.1 V (#6). The primary pulse duration was set to the clinically used value for each individual. The secondary pulses were one-tenth the amplitude of, ten times the duration of, and immediately following the primary pulses, similar to the waveforms generated by the IPG.

After the computer generated the condition-specific signal, a multifunction data acquisition card (PXI-6052e, National Instruments, Austin TX) converted that digital signal into an analog output. That output signal was passed through an optical isolator (BP-Isolator, Frederic Haer Corporation, Bowdoin ME) and into a custom passive switch box that was configured uniquely for each participant to tie the signal and return paths to the appropriate leads. The switch box, which housed an extra high-pass filter to remove any constant charge flow, fed
the signal into a sterilized custom cable designed to interface with the DBS lead extension cable (Medtronic Inc., Minneapolis MN). This custom cable was strung into the sterile field and connected to the lead extension cable.

The hand contralateral to the stimulated brain hemisphere was placed on a two-button computer mouse on a flat surface. In each trial, participants were prompted to click alternately the two buttons with their index and middle finger as rapidly as possible. The laptop recorded time stamps for each press and release action of the mouse (Fig. 4a). Each trial lasted for approximately 2 minutes: ~100 sec of rest followed by 20 or 30 sec of prompted mouse button clicking. Each participant began with two to five baseline trials without DBS.

Subsequently, the four classes of DBS were presented in random order for four minutes each, with four minutes of no stimulation between DBS trains (Fig. 4b). Thus, each participant performed two 20 or 30 sec clicking trials during each DBS and each no stimulation epoch. After completing the experimental protocol, the extension lead was disconnected from the custom stimulation system and the generator replacement surgery continued.

Although many participants could identify when some DBS was being presented, participants were blinded to the stimulation conditions and none expressed any discrimination between the types of DBS.

**Data Analysis.** Finger tap rate and tap variability are correlated with the symptom severities measured clinically (Tavares et al., 2005). The tap rate for each trial was found as the number of button depressions divided by the trial duration. To pool data, each trial of a given participant was shifted by subtracting the mean tap rate of the baseline conditions for that participant. Post hoc analysis revealed that data from the first of the two trials in each condition were more correlated with data from the previous trial than from the subsequent trial. In other words, the symptomatic effects of the DBS condition became evident with a time course greater than 2 minutes, consistent with previous studies of the time course of effects of DBS (Lopiano et al., 2003; Temperli et al., 2003). To minimize the effects of this nonstationarity, data from the first trial in each condition were not included in this analysis. Summary results are plotted as the mean ± S.E. rates across participants (Fig. 4c).

Tap variabilities were also found for each condition. Since the first trials are not included in this analysis, all data presented were collected ~210-240 seconds into their respective conditions. Although this 210 s delay approaches the time constant of DBS onset effects, it is too short for symptoms to return to baseline following DBS offset. Thus, the finger tap variabilities of interest are not the absolute variabilities, but the change in variability from the previous condition. These measures will naturally underestimate the absolute changes, but
because condition order was randomized across subjects, these measures will not introduce any biases for on or off DBS conditions. The durations of all button tap depressions $\{T_{dur}\}$ and the intervals between button taps $\{T_{int}\}$ were found to range over two orders of magnitude for most participants. For example, the tap durations of the example participant (Fig. 4b, left) ranged from substantially less than one-tenth of a second to substantially more than ten seconds. To accommodate this change of scales, the base ten logarithm was taken of each tap duration $\{\log_{10} T_{dur}\}$ and interval $\{\log_{10} T_{int}\}$ (e.g., Fig. 4b, right). The standard deviations of these logarithmic transforms of tap duration ($\sigma_{dur} = \text{STD}\{\log_{10} T_{dur}\}$) and interval ($\sigma_{int} = \text{STD}\{\log_{10} T_{int}\}$) were found for each finger of each participant in each trial. To accommodate slow nonstationarities – due to changes in alertness, effort, or enduring effects from the previous DBS condition – the standard deviation from each condition was subtracted from that of the subsequent condition to yield shifts in the variability of duration ($\Delta \sigma_{dur}^{k+1} = \sigma_{dur}^{k+1} - \sigma_{dur}^k$) and interval ($\Delta \sigma_{int}^{k+1} = \sigma_{int}^{k+1} - \sigma_{int}^k$).

Statistical analysis was performed on those normally distributed variability shifts (i.e., $\{\Delta \sigma_{dur}\}$ and $\{\Delta \sigma_{int}\}$) pooled together by condition across all participants. Because all measures are changes from the previous condition, the absolute severity of the baseline bradykinesia has minimal effect on the statistics; whether subjects were on (3/9) or off (6/9) dopaminergic medication did not affect subsequent results. The reported values were found as the inverse base 10 logarithm of the variability shifts, to use the more intuitive units of variability gains, $\xi_{dur} = \log_{10}^{-1} \Delta \sigma_{dur}$ and $\xi_{int} = \log_{10}^{-1} \Delta \sigma_{int}$, but are presented on logarithmically graduated axes to highlight their underlying logarithmic nature (Fig. 5). A bootstrap procedure was used to estimate the median and confidence intervals of the mean. The mean of a population of random samples drawn with replacement from the equally numerous population of variability shifts was found 10,000 times for each condition, and sorted to yield confidence intervals (Figs. 5, 7).

Results

We measured the effects of temporally regular and temporally irregular high-frequency DBS on motor symptoms in persons with Parkinson's disease (PD) and on neuronal activity in a computational model of the basal ganglia thalamic circuit. Four patterns of DBS were constructed to have the same average instantaneous frequency, but differing degrees of regularity. A temporally regular pattern consisted of identically spaced pulses at 130 Hz. For
the other three temporally irregular patterns, the instantaneous frequencies were drawn from a gamma distribution
with a mean of 130 Hz and a standard deviation equal to 10%, 30% or 60% of the mean (Fig. 1a,b).

Error Rates in Model Thalamic Cells Track DBS Irregularity. A computational model of the basal ganglia
thalamic network (Fig. 1c) containing 64 point neurons with voltage-dependent conductances was used to
quantify the effects of temporally regular and irregular DBS on neuronal activity. Changes to the bias current of
neurons in the globus pallidus shifted the model between healthy and parkinsonian states. In the parkinsonian
state, four patterns of DBS were used to activate neurons in the subthalamic nucleus (STN).

Changing the model from the healthy to the parkinsonian state increased the firing rate of neurons in the
STN. Regular DBS (130 Hz) further increased the average firing rate but also regularized the inter-spike intervals
(ISIs, Fig. 2b). Increasingly irregular DBS had the same effect on firing rate as regular DBS, but decreased the
ISI regularity, broadening the ISI distributions (Fig. 2b).

In contrast to disease-induced rate changes in STN, neuronal firing rates in the external globus pallidus (GPe)
dramatically decreased from the healthy to the parkinsonian condition (Fig. 2c). Similar to changes observed in
STN however, the firing rates of GPe neurons increased in response to all patterns of DBS. During regular DBS,
GPe firing patterns became more regular, exhibiting fewer bursts and fewer long pauses. Also similar to STN, the
ISIs in GPe became increasingly irregular with increasingly irregular DBS (Fig. 2c).

Shifting from the healthy to the parkinsonian state did not have a large effect on the average firing rate of
neurons in the internal globus pallidus (GPi), but substantially altered the firing patterns. The ISI distribution
shifted from primarily unimodal centered around 15 ms in the healthy condition, to bimodal in the parkinsonian
condition, with a broad intra-burst mode centered around 8 ms and a broad inter-burst mode centered around 25
ms (Fig. 2d). All patterns of DBS increased the firing rate of GPi model neurons, but had different effects on the
patterns of neuronal activity. Regular DBS converted the two broad modes into three relatively narrow modes,
representing the GPi neurons firing phase-locked to the DBS pulses in ratios of 1:1, 2:3 or 1:2 (Fig. 2d). Irregular
DBS generated broad ISI distributions more similar to the parkinsonian state than to the regular DBS state.

In summary, firing rate changes between the healthy and parkinsonian states were different across all three
regions: increasing, decreasing, and nearly constant in STN, GPe and GPi, respectively. The rate changes
generated by DBS amplified those of parkinsonism in STN, counter-acted them in GPe, and simply increased the rate in GPi, regardless of DBS regularity. However, irregular DBS produced ISI distributions that were qualitatively similar to the parkinsonian state, whereas regular DBS produced ISI distributions qualitatively similar to the healthy state. To quantify these similarities, the firing pattern entropy was calculated from each ISI distribution. In all regions, firing pattern entropy increased between the healthy and parkinsonian conditions (Fig. 2e). Regular DBS decreased firing pattern entropy to below the levels observed in the healthy condition. Increasingly irregular DBS increased the firing pattern entropy, which returned to or exceeded the unstimulated parkinsonian level in response to the most irregular pattern, 130±60%.

The fidelity of thalamic transmission was quantified to estimate the functional impact of different patterns of DBS. Thalamic cells (TC), in addition to receiving inhibitory synaptic input from GPi cells, received excitatory current pulses that represented motor information passing through the thalamus. Responses were counted as correct when a thalamic cell spiked once in response to one excitatory input, and responses were counted as errors when a thalamic cell did not spike in response to an input (miss), spiked more than once in response to an input (burst), or spiked in the absence of an input. While errors were rare in the healthy condition (Fig. 3), they were commonplace in the parkinsonian condition (DBS Off). Regular DBS reduced the error rate to almost the healthy level. Increasingly irregular DBS increased the thalamic error rate, and with 130±60% DBS, errors were more common than with no stimulation. Thus, thalamic errors were not corrected by high frequency DBS unless the pulse train was highly regular.

Human Bradykinesia Tracks DBS Irregularity. We tested the same four patterns of DBS in human participants to determine whether high frequency DBS also had to be highly regular for therapeutic effectiveness. The implanted pulse generator used for clinical DBS can only generate regular pulse patterns. Therefore, we connected an external pulse generator to the DBS brain leads of participants with PD whose motor symptoms were managed effectively by DBS therapy during battery replacement surgery. Four patterns of DBS were delivered through their previously implanted DBS leads for four minute epochs using a randomized block design. At regular intervals during and between epochs, bradykinesia was quantified by instructing participants to tap alternately the two buttons of a computer mouse as quickly as possible for 20- or 30-second trials.
Example trials depict the raw tap durations collected from three different stimulation conditions in one participant (Fig. 4a). Data summaries for that participant in all conditions are presented in the order in which the data were collected (Fig. 4b, left). Tap durations for each condition were approximately log-normally distributed (Fig. 4b, right). Changes in tap rate, from the patient-specific mean baseline, were found for each trial and data from all participants were combined by condition (N = 42, 54, 18, 18, 16 and 18 for baseline, recovery, 130 Hz, 130±10%, 130±30% and 130±60%, respectively). Omnibus van der Waerden testing (data not normally distributed) yielded a significant effect of therapy condition (p=0.041) when the stimulation off conditions (i.e., baseline and recovery) were combined into a single group.

The eight pairwise comparisons between the two hypothesized asymptomatic conditions (130 Hz and 130±10%) and the other four conditions were evaluated with the Mann-Whitney U test. Five hypotheses were significant (α=0.05, uncorrected): 130 Hz increased the tap rate over baseline (p=0.0024), recovery (p=0.012), 130±30% (p=0.038) and 130±60% (p=0.044); and 130±10% increased the tap rate over baseline (p=0.031). In other words, regular 130 Hz DBS increased the finger tap rate over the four hypothesized symptomatic conditions, and nearly regular 130±10% DBS increased finger tap rate over baseline. Employing the Holm-Bonferroni method to account for multiple comparisons with eight hypotheses and the same statistical criterion (m=8, α=0.05), one hypothesis was highly significant: 130 Hz increased tap rate from baseline.

Changes in the tap duration variability (the standard deviation of the logarithms of finger tap durations) and the tap interval variability (the standard deviation of the logarithms of the intervals between finger taps) were calculated for each trial (Fig. 5), and data from all participants were combined by condition. Analyses of variance showed that changes in variability of both tap duration (p=0.0080) and tap interval (p=0.028) were dependent upon stimulation condition. Regular and nearly regular (130±10%) DBS decreased tap duration variability and tap interval variability relative to the DBS Off and the highly irregular DBS conditions, while neither of the highly irregular conditions changed either the tap duration or tap interval variability relative to DBS Off.

Specifically, the data support three of the six hypotheses regarding tap duration: that the two hypothesized asymptomatic conditions decreased tap duration variability shifts with respect to the other three conditions. DBS Off increased duration variability from 130 Hz (p=0.00074) and 130±10% (p=0.0063); and 130±60% increased duration variability from 130 Hz (p=0.033). After correcting for multiple comparisons (m=6, α=0.05), the first
two hypotheses remained highly significant: DBS Off increased duration variability over 130 Hz and 130±10%.

Additionally, the data support all six hypotheses regarding tap intervals: that the two hypothesized asymptomatic conditions decreased tap interval variability shifts with respect to the other three conditions. Regular DBS decreased interval variability from DBS Off (p=0.00050), 130±30% (p=0.012) and 130±60% (p=0.0043); and 130±10% decreased interval variability from DBS Off (p=0.0081), 130±30% (p=0.040) and 130±60% (p=0.016).

After correcting for multiple comparisons (m=6, \( \alpha \)=0.05), all six hypotheses remained highly significant.

**Pallidal Variability Determines Error Rate in Model Thalamic Cells.** To examine the cause of irregular-DBS-induced bradykinesia in the human participants and thalamic errors in the model, the inhibitory synaptic conductances from model GPi cells to TCs were measured between 100 ms before and 50 ms after each excitatory input. Thalamic miss errors were associated with a prolonged (100 – 10 ms before the input pulse) weaker-than-average inhibitory conductance, followed by increased inhibition coincident with the excitatory input (Fig. 6a). Thalamic burst errors were associated with a prolonged (100 – 10 ms before the input pulse) stronger-than-average inhibitory conductance, followed by decreased inhibition coincident with the excitatory input (Fig. 6b). Averaged across all similar events, the amplitudes of these changes in inhibitory conductance were larger in both the unstimulated parkinsonian and irregular DBS states than for either the healthy or regular DBS states.

While the inhibitory conductance profile around error events explained why a TC may have made a particular type of error, it did not explain why different conditions yielded different error rates. To explore the statistical behavior of the inhibitory synaptic inputs, the GPi neuron spike-time autocorrelations were calculated (Fig. 6c). Autocorrelations in the healthy condition were similar to those in the parkinsonian condition and during irregular DBS: small rapidly decaying oscillations that reflect primarily the neuronal refractory period. However, autocorrelations during regular DBS differed dramatically, exhibiting long lasting oscillations reflecting the DBS periodicity. Thus, thalamic error rates could not be predicted from GPi spike-time autocorrelations.

The mean and standard deviation of the inhibitory synaptic conductance were calculated for each thalamic neuron in response to each excitatory input. While the mean conductance across all conditions was roughly equivalent (Fig. 6d), the standard deviation of the inhibitory conductance differed dramatically across conditions (Fig. 6e). Highly variable conductances yielded high thalamic error rates, while minimally variable conductances
yielded low thalamic error rates. Additionally, the condition specific ranges of the standard deviations were so small that essentially no cases overlapped between the high error rate (i.e., symptomatic) and low error rate (i.e., asymptomatic) conditions.

In summary, GPi cell autocorrelations were poor predictors of thalamic errors. The swings in inhibitory conductance that lead to misses and bursts were relatively independent of the average synaptic input, which varied widely within all conditions but not systematically across conditions. Rather, the temporal profile and variability of the synaptic conductance, while consistent within each condition, changed dramatically across conditions and were correlated strongly with the thalamic error rate.

**Discussion**

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) or globus pallidus internus (GPi) is an effective therapy for the motor symptoms of Parkinson's disease (PD), but the mechanisms of symptom alleviation are not fully understood. Work over the past decades has suggested that symptom progression in PD is the behavioral manifestation of increasingly pathological neuronal activity in the basal ganglia. In addition to changes in neuronal firing rates, changes in the firing patterns of neurons and neural assemblies accompany the onset of parkinsonism in non-human primates (Legényd and Salcman, 1985; Bergman et al., 1994; Wichmann and DeLong, 2003; Wichmann and Soares, 2006) and persons with PD (Lenz et al. 1994; Magnin et al. 2000; Tang et al. 2005). In this study we provide evidence for causality of the relationship between neuronal firing pattern variability and symptom severity by showing that for a fixed frequency of DBS, reducing the output variability of basal ganglia neurons is necessary for symptom alleviation in human participants with PD.

*Irregular stimulation and symptom severity.* We hypothesized that 1) masking the parkinsonism-related pathological activity with *regular* DBS-induced activity would alleviate the motor symptoms of human participants with PD, and that 2) masking the pathological activity with *irregular* DBS-induced activity would fail to alleviate the same motor symptoms. We tested these hypotheses by substituting clinically-effective temporally regular DBS with temporally irregular DBS during previously scheduled surgery to replace the depleted pulse generator. Highly irregular DBS, even when delivered at an effective average frequency, did not improve
bradykinesia. However, regular DBS at the same frequency lead to faster (Fig. 4c) and more regular (Fig. 5) motor control.

In a related study, Tavares and colleagues (2005) showed that the logarithms of both the mean and the coefficient of variation of the button hold duration were correlated with the Unified Parkinson's Disease Rating Scale, Section III subscore (UPDRS$_{III}$). Since the logarithm of the coefficient of variation of tap duration had been mapped to UPDRS$_{III}$ scores directly, and was the mostly highly correlated measure found (Tavares et al., 2005), we calculated that measure for the nine participants in our study. Multiplying those values by the reported correlation coefficient (R=0.66) and scaling by the gain (80 UPDRS$_{III}$ points per log unit), we calculated predicted UPDRS$_{III}$ score shifts from the unstimulated case (DBS Off) for all DBS conditions (Fig. 7). The estimated improvements in UPDRS$_{III}$ scores diminished with increasingly irregular DBS.

These findings extend previous work highlighting the effects of DBS pattern regularity, as opposed to DBS rate, on motor symptom severity. In particular, rapidly cycling DBS on and off, thereby creating DBS patterns that were less regular on short time scales, alleviated motor symptoms less effectively than regular DBS (Montgomery, 2005). Also, in a population of human participants with heterogeneous tremor disorders, regular DBS alleviated tremor while irregular DBS did not (Birdno et al., 2008). Thus, independent of the type of irregular DBS or the particular neurological disorders, symptoms may be maximally alleviated when stimulation is maximally regular.

*Irregular neuronal activity and thalamic errors.* The symptoms of parkinsonism are accompanied by a transition to irregular and burst-like firing patterns in rodents (Degos et al., 2005), non-human primates (Hashimoto et al., 2003; Wichmann and DeLong, 2003; Bar-Gad et al., 2004; Meissner et al., 2005) and human participants with PD (Brown et al., 2004). We used a computational model of the basal ganglia thalamic network, which captured this transition, to quantify the effects of different temporal patterns of DBS on neuronal firing patterns. The computational network did not exhibit the highly regular bursting described in previous implementations of the model, but did yield burst-like events mixed with non-bursting irregular activity (Fig. 2), similar to that recorded from basal ganglia output neurons in parkinsonian models in rodents (Degos et al., 2005; Shi et al., 2006), non-
human primates (Bergman et al., 1994; Hashimoto et al., 2003; Wichmann and DeLong, 2003; Dorval et al., 2008) and humans with PD (Tang et al. 2005).

Because all activity within the model basal ganglia was funneled to the thalamus via the GPi, we focused on the spiking and synaptic activity of GPi neurons (Fig. 6). The average synaptic outputs of GPi neurons to TCs were not changed substantially between control, parkinsonian, and any DBS conditions. However, the variability of these outputs varied markedly between conditions. The importance of firing patterns revealed by this model reinforces experimental studies that found average changes in GPi firing rates to be negligible (Bergman et al., 1994) or overshadowed by large variability across cells in any given condition (Hashimoto et al., 2003; Soares et al., 2004).

The parallel between symptom alleviation in human participants and DBS-induced firing pattern changes in the model is consistent with previous computational findings (Rubin and Terman, 2004), symptom-correlated changes in bursting activity in the 6-OHDA-rat (Shi et al., 2006) and firing pattern entropy changes in the MPTP-primate (Dorval et al., 2008) in response to DBS. In a computational model similar to the one used here, thalamic neurons presented with parkinsonian firing patterns exhibited reduced fidelity, whereas model neurons presented with regular DBS-induced firing patterns exhibited improved fidelity (Guo et al., 2008). Similarly, in a preliminary study on healthy non-human primates, replacing normal firing patterns with firing patterns recorded from animals in the parkinsonian state induced parkinsonian motor symptoms (Ma Y & Wichmann T, Society for Neuroscience Abstracts 2004).

Summary. Collectively, these data suggest that irregular activity is somehow responsible for parkinsonian symptoms. Furthermore, effective therapy must alleviate those symptoms either by adding some new activity or by removing the existing irregular activity. Surgical history indicates that lesion and DBS are similarly effective, implicating the removal of irregular activity as a mechanism of symptom alleviation. Therapeutic lesion removes the pathological activity by eliminating the neural substrate in which it resides; therapeutic DBS merely masks the pathological activity with periodic pulse trains. Indeed, DBS that masks the activity with aperiodic pulse trains does not alleviate symptoms. However, any means of eliminating irregular activity in GPi should reduce information processing errors by thalamic neurons, and alleviate symptoms. Indeed, Tass and colleagues have
proposed one such alternative approach – using well timed stimulus bursts to desynchronize pathological network activity – and shown that it can be effective in computational models of PD (Hauptmann et al., 2005; Tass, 2003) and in vitro models of pathological synchronization (Tass et al., 2009).

The present results demonstrate that for a fixed frequency of DBS, the pattern of stimulation has dramatic effects on parkinsonian bradykinesia, highlighting the importance of neuronal firing patterns independent of firing rate. While regular DBS regularized firing patterns, reduced synaptic variability and increased thalamic fidelity, irregular stimulation at the same average frequency simply replaced the pathological disease-induced patterns with pathological stimulation-induced patterns. Irregular DBS was unable to reduce the rate of errors made by thalamic cells in the model, and was unable to alleviate bradykinesia in human participants with PD. Four potential mechanisms have been offered to explain symptom relief by DBS (Grill and McIntyre, 2001; Garcia et al., 2005): 1) depolarization blockade of neurons around the electrode by activation or inactivation of voltage-gated currents (Beurrier et al., 2001), 2) depression or failure of synaptic transmission resulting in blockade of output from the stimulated neurons (Anderson et al. 2006), 3) synaptic inhibition of the neurons around the electrode by activation of local inhibitory (GABAergic) axon terminals (Filali et al., 2004), and 4) alteration or “jamming” of pathological patterns of activity (Rubin and Terman, 2004; Vitek, 2002). The data presented here strongly support the fourth potential mechanism of regularization of pathological patterns of activity in the basal ganglia (Birdno and Grill, 2008), and argue against the first three potential mechanisms, as it is not clear how such mechanisms would depend on the fine temporal structure of the stimulation train.

Understanding the time scales that divide DBS patterning from DBS rate is important to this work and to our conclusion that fine temporal structure matters. During irregular DBS, the time between any two DBS pulses often deviated beyond the therapeutic range. However, the average rate over many consecutive pulses rarely left the therapeutic range. As an example, the time between any two pulses in the 30% irregular DBS case was highly variable, ranging from less than 2.5 ms to greater than 25 ms (Fig. 1). In contrast to this pattern variability, the DBS rate was fairly constant. In particular, the probability that one second elapsed during which DBS was outside of the clinically accepted therapeutic range (i.e., DBS rate was below 100 Hz), was less than 0.001. In other words, for every 1000 seconds of 30% irregular DBS, only one second was outside of the therapeutic range comprising fewer than 100 pulses. And yet, even though the DBS rate was in the therapeutic range 99.9% of the
time, symptoms were not alleviated. Thus, while DBS rate may play a therapeutic role, we have shown that high frequency alone is insufficient: DBS patterning is a critical component of symptom alleviation.

Recent work suggests that effective DBS of the STN may be mediated via activation of afferents projecting from layer V of motor cortex (Li et al., 2007; Gradinaru et al., 2009), a possibility that our computational model does not address. However, when participants with STN electrodes were stimulated with irregular DBS, their bradykinetic symptoms were not alleviated. Thus, whether the electrophysiological mechanisms of DBS therapy are orthodromic through the basal ganglia thalamic cortical loop, or antidromic directly to motor cortex, regularizing neuronal activity is a necessity for symptom alleviation. Incorporating our model, we provide causal evidence that DBS of the STN alleviates the symptoms of Parkinson's disease by regularizing the firing patterns of basal ganglia neurons, enabling motor thalamic neurons to process what residual streams of information remain in the parkinsonian state.

Applying this understanding to other disorders, electrical stimulation may be beneficial to disorders accompanied by aberrant firing patterns within identified brain regions (Llinás et al., 1999). However, each brain region will require a different minimum stimulation frequency to mask the pathological pattern of neuronal activity (Grill et al., 2004). Regular DBS eliminates pathological firing patterns, but does not reintroduce the healthy firing patterns present in the absence of disease. The high frequency tonic firing imposed on the basal ganglia by DBS masks the information that those neurons would otherwise convey, eliminating all normal output messages to thalamus. While motor symptoms were better treated by regular DBS than irregular DBS at the same high frequency, there is no reason to believe that regular DBS trains are optimal (Feng et al., 2007). The most desirable interventions would eliminate the pathological firing patterns associated with PD, without imposing new firing patterns, thereby allowing the healthy normal firing patterns to reemerge.
† If the coefficient of variation and the mean both increase then their product, the standard deviation, will increase more robustly. Additionally, because the variability of tap duration scales with the mean (Fig. 4b, right), the distribution of tap durations (and intervals) are log-normally distributed. Thus we used the standard deviation of the logarithmic transform of the tap durations and intervals.
Acknowledgments

This work supported by the National Institutes of Health, K25-NS053544 (A.D.D.) & R01-NS040894 (W.M.G.).
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Tavares ALT, Jefferis GSXE, Koop M, Hill BC, Hastie T, Heit G, Bronte-Stewart HM. Quantitative measurements of alternating finger tapping in Parkinson's disease correlate with UPDRS motor disability and reveal the improvement in fine motor control from medication and deep brain stimulation. *Mov. Disord* 20:


Table 1. Participant Population. Relevant conditions and parameters for the nine subjects with Parkinson's disease who participated in this study.
Figure Captions

**Figure 1. Experimental Paradigm.** Four classes of DBS were presented to human participants with Parkinson's disease and to a computational model. 

- **a)** Example pattern rastergrams of the DBS pulse timings.
- **b)** Probability densities of the four distributions; all with a mean of 130 Hz. See METHODS: TEMPORALLY IRREGULAR DBS for details.
- **c)** Connectivity diagram of the computational model of the basal ganglia thalamic circuit, including: the subthalamic nucleus (STN), globus pallidus externus (GPe) and internus (GPi), and thalamic cells (TC). Red connections are excitatory. Blue connections are inhibitory. Shown are all of the input connections going to the fourth neuron of each region. Connections to all other cells were parallel, with wrap-around boundary conditions. See METHODS: COMPUTATIONAL MODEL EXPERIMENTS for implementation details.

**Figure 2. Changes in model neuron activity.** Patterns of neuronal firing activity varied across conditions and basal ganglia. 

- **a)** Rastergrams depicting representative firing patterns of three connected computational neurons,
in the identified basal ganglia (labels left), in three conditions (labels above). Note the visually correlated activity across connected basal ganglia neurons in the 130±30% condition (right). b-d) Inter-spike interval (ISI) probability distributions, found by normalizing the histogram of all ISIs of all neurons in each ganglion in each condition, of the three high error rate (symptomatic, left) and the three low error rate (asymptomatic, right) conditions, in the STN (b), GPe (c) and GPi (d). Note that while changes are evident for all comparisons, the symptomatic distributions are generally broader with lower peak probabilities than the asymptomatic distributions in the same ganglion. e) Firing pattern entropies were calculated from the ISI distributions constructed from 150 sec of data for each neuron. Bar graphs depict the mean ± S.D. across the population of 16 neurons in each ganglion. Entropy always increased from healthy to parkinsonian states, decreased during regular DBS, and increased again with increasingly irregular DBS.

**Figure 3. Thalamic errors increase with DBS irregularity.** Thalamic errors were identified when a model neuron failed to spike or spiked more than once to a single excitatory input, or spiked in the absence of an input.
Example membrane potential traces (left) from a thalamic neuron in the six conditions depict the responses to excitatory input pulses (bottom). Errors are highlighted with thick colored lines. Error rates are presented as the mean ± S.D. across all 16 neurons from 150 sec of simulation data (right). Error rate increased from healthy to parkinsonian states, decreased during regular DBS, and increased again with increasingly irregular DBS.

**Figure 4. Human Protocol.** Human participants were tasked with tapping alternately left and right computer mouse buttons with their index and middle fingers, during presentation of the four patterns of DBS.  

a) Representative examples of finger tapping from one participant in three conditions. The horizontal tape indicates when the mouse button corresponding to the index (front) or middle (back) finger was depressed.  

b) From the same participant, the duration of each button press is plotted as a function of protocol time (left) and condition (right). The left plot shows the experimental protocol, with horizontal bars at the bottom indicating when the different patterns of DBS were applied. The right plot shows the same data on a logarithmic ordinate to provide a more meaningful depiction of the tap duration variability.  

c) Across nine participants, the change in the average
tap rate as a function of stimulation condition. Reported values are means ± S.E. Van der Waerden testing found a significant effect of therapy condition (p=0.041). Grey lines indicate significant differences (p<0.05) on an uncorrected single-sided Mann-Whitney U test. The black line indicates that 130 Hz increased the finger tap rate over baseline after accounting for multiple comparisons with the Holm-Bonferroni method.

Figure 5. Regular DBS reduces tapping variability. The variability of finger tap times was quantified for each participant in each condition, as tap duration variability (\( \xi_{\text{dur}} \)) or tap interval variability (\( \xi_{\text{int}} \)). See METHODS: MEASUREMENTS IN HUMAN PARTICIPANTS WITH PARKINSON'S DISEASE for a more detailed description. Pooled by condition across nine participants, the boxes represent the 25-75% confidence intervals on the mean, split by the median. Error bars cover the 95% confidence intervals. One way analyses of variance found there were effects of stimulation condition in the tap duration (p=0.0080) and tap interval (p=0.028) variabilities. Statistically significant (p<0.05) pairwise comparisons from a single-sided Student's T test (grey and black lines) were confirmed with the Holm-Bonferroni method (black lines only). In particular, regular and nearly regular DBS
(130 Hz and 130±10%) reduced tap interval variability from the control (DBS Off) and highly irregular DBS
(130±30% and 130±60%) conditions.

**Figure 6. Changes in synaptic input to thalamic cells.** Model GPi cells provide inhibitory synaptic input to
thalamic cells (TCs). *a-b*) The average synaptic conductance experienced by a TC, in a window ranging from 100
ms before to 50 ms after the onset (*dashed line*) of each excitatory current pulse (*Input*), when that TC (*a*) failed
to spike, or (*b*) spiked more than once. Conditions are all on the same conductance scale (*scale bar, bottom*) but
are offset to ease viewing. The dotted lines denote the mean value of the synaptic conductance in each condition.
Below the dotted line denotes weaker than average inhibition; above the dotted line denotes stronger than average
inhibition. The larger swings in conductance are associated with the conditions yielding higher error rates (Fig.
3). *c*) Autocorrelations of the GPi spike times, convolved with a Gaussian window with a 1.0 ms S.D., in all
conditions. *d*) The conductance means from the same 150 ms around the excitatory input as above, for all miss,
burst and correct events in each condition. Data are presented as mean ±50% and ±90% distribution intervals. *e*)
The conductance standard deviations from the same 150 ms around the excitatory input as above, for all input events in each condition. Data are presented as mean ±90% distribution intervals.

**Figure 7.** Expected improvements in UPDRSⅢ induced by different DBS trains. The logarithm of the coefficient of variation of the finger tap durations correlates with changes in the clinically used UPDRSⅢ motor scores (Tavares et al., 2005). Across nine participants, the boxes represent the 25-75% confidence intervals on the mean, split by the median. Error bars cover the 95% confidence intervals. Regular DBS improved the motor score estimates more than irregular DBS.
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<th>Age / Sex</th>
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<th>Implant Target(s)</th>
<th>Hemisphere Tested</th>
<th>Active Contacts</th>
<th>DBS Parameters on Tested Side</th>
<th>Carbidopa/Levodopa* mg:dose x doses:day</th>
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* CR = Controlled Release
Example Button Taps of Both Fingers in 3 Conditions

(a)

DBS Off

130 Hz

130 ±30%

(b)

Tap Duration vs Time

(c)

Tap Rate Across Population, Shifted from Baseline
Miss Event Inhibition

Normal

130 Hz

130±10%

130±30%

130±60%

DBS Off

Burst Event Inhibition

Normal

130 Hz

130±10%

130±30%

130±60%

DBS Off

25 ms

10 pS/µm²

Autocorrelations

Normal

130 Hz

130±10%

130±30%

130±60%

DBS Off

τ = 0

20 ms

Conductance Mean

Normal

DBS Off

130 Hz

130±10%

130±30%

130±60%

Mean, pS/µm²

Conductance STD

Normal

DBS Off

130 Hz

130±10%

130±30%

130±60%