Network effects of subththalamic deep brain stimulation drive a unique mixture of responses in basal ganglia output

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Abstract

Deep brain stimulation (DBS) is a remarkably successful treatment for the motor symptoms of Parkinson’s disease. High-frequency stimulation of the subthalamic nucleus (STN) within the basal ganglia is a main clinical target, but the physiological mechanisms of therapeutic STN DBS at the cellular and network level are unclear. We set out to begin to address the hypothesis that a mixture of responses in the basal ganglia output nuclei, combining regularized firing and inhibition, is a key contributor to the effectiveness of STN DBS. We used our computational model of the complete basal ganglia circuit to show how such a mixture of responses in basal ganglia output naturally arises from the network effects of STN DBS. We replicated the diversification of responses recorded in a primate STN DBS study to show that the model’s predicted mixture of responses is consistent with therapeutic STN DBS. We then showed how this ‘mixture of response’ perspective suggests new ideas for DBS mechanisms: first, that the therapeutic frequency of STN DBS is above 100 Hz because the diversification of responses exhibits a step change above this frequency; and second, that optogenetic models of direct STN stimulation during DBS have proven therapeutically ineffective because they do not replicate the mixture of basal ganglia output responses evoked by electrical DBS.

Introduction

Deep brain stimulation (DBS) has proved to be a remarkably successful treatment for the motor symptoms of Parkinson’s disease (Limousin et al., 1995; Deep Brain Stimulation for Parkinson’s Disease Study Group, 2001). High-frequency stimulation of the subthalamic nucleus (STN) within the basal ganglia has emerged as the main clinical target (Deep Brain Stimulation for Parkinson’s Disease Study Group, 2001). The physiological mechanisms of therapeutic STN DBS at the cellular and network level are unclear (McIntyre et al., 2004; McIntyre & Hahn, 2010).

One potential explanation is that high-frequency stimulation inhibits STN neuron firing (Beurrier et al., 2001). However, although somatic inhibition of many STN neurons may occur (Beurrier et al., 2001; Tai et al., 2003; Moran et al., 2011), their axons are probably stimulated to spike (Nowak & Bullier, 1998; Miocinovic et al., 2006), others may fire somatically-generated spikes locked to the stimulation frequencies (Garcia et al., 2003, 2005) and the firing patterns of others are modified (Moran et al., 2011). Correspondingly, the basal ganglia output nuclei show elevated glutamate (Windels et al., 2000) and firing rates (Hashimoto et al., 2003; Bosch et al., 2011; Moran et al., 2011) during STN high-frequency stimulation. Subsequently, a theory has emerged that the key therapeutic action of DBS is regularization overwriting pathological activity (Perlmutter & Mink, 2006; Birdno et al., 2007; Birdno & Grill, 2008). Previous theoretical work has shown how high-frequency stimulation of the STN could overwrite the pathological activity of basal ganglia output neurons by entraining their firing (Rubin & Terman, 2004; Hahn & McIntyre, 2010), and consequently return the target structures of the basal ganglia to normal operation by removing the deleterious effect of their pathological output (Rubin & Terman, 2004; Guo et al., 2008; Dorval et al., 2010).

A common result from studies of therapeutically effective STN DBS has received comparatively little attention: that STN DBS does not just overwrite, but rather causes a diversification of basal ganglia output. In the simplest manifestation, and consistent across species [human, Reese et al. (2011); primate, Hashimoto et al. (2003); rat, Shi et al. (2006)], the onset of therapeutic STN DBS causes a mixture of increased and decreased firing rates in the basal ganglia output nuclei. A plausible hypothesis is that this diversification of basal ganglia output, mixing regularized firing and inhibited neurons, underlies the effectiveness of STN DBS.

We set out to begin to address this hypothesis by extending our established computational model of the basal ganglia (Humphries et al., 2006) to incorporate a simple model of DBS effects on STN neurons. Our first goal was to use the model to establish how such a mixture of responses can arise from the basal ganglia network, and whether the mixture of responses predicted by the model accurately reflected those found under therapeutic STN DBS in parkinsonian primates (Hashimoto et al., 2003; Hahn et al., 2008). Our second goal...
was to seek whether, from the ‘mixture of responses’ perspective, the model could provide suggested resolutions to two DBS puzzles: why the clinically therapeutic frequency is above 100 Hz (Deep Brain Stimulation for Parkinson’s Disease Study Group, 2001); and why optogenetic models of DBS failed to find a therapeutic effect when mimicking the direct activation of STN neurons (Gradinaru et al., 2009).

Materials and methods
We first outline our computational model of the basal ganglia. A complete description is given in Humphries et al. (2006) – here we outline the pertinent features. Our model was explicitly of the rat basal ganglia, hence parameters such as transmission delays and neuron time constants were taken from the literature on the rat, and the tonic firing rates of the basal ganglia nuclei were fitted to those found in the rat.

Basal ganglia circuitry
The basal ganglia are a group of inter-connected subcortical nuclei, which receive massive convergent input from most regions of the cortex, and output to targets in the thalamus and brainstem. Figure 1A illustrates the macro-architecture of the basal ganglia, showing the connections between the input nuclei (striatum and STN), output nuclei (substantia nigra pars reticulata and globus pallidus pars internus (GPI)), and internally-projecting globus pallidus pars externus (GPe). Figure 1B illustrates the corresponding micro-architecture of the basal ganglia, implemented in the computational models (for detailed discussion, see Gurney et al., 2001; Humphries et al., 2006). In this model, the projections between the neural populations are topographically arranged to form a series of parallel loops (channels) running through the basal ganglia from input to output stages (Alexander & Crutcher, 1990; Hoover & Strick, 1993; Romanelli et al., 2005).

For studying DBS effects, we used our basal ganglia model with 3 channels and 72 neurons per channel in each separate structure (striatum D1, striatum D2, STN, GPe and GPI), giving 1080 neurons in total. The connection probability between nuclei was set at $P = 0.25$ for connections within a channel, and $P = 0.25/3$ for diffuse connections across channels (STN projections to the GPI and GPe; local collaterals in the GPe and GPI). The massively convergent input from the striatum to its targets was accounted for by assigning the striatal connections a synaptic weight four times larger than all others.

Model neurons
The model used current-based integrate-and-fire neurons. The change in membrane potential $V$ of each neuron was given by

$$\tau_m \frac{dV}{dt} = -V + R[I_{syn} + I_{ion} + I_{DBS}], \quad (1)$$

with resistance $R$, membrane time constant $\tau_m$, and driven by contributions from synaptic $I_{syn}$, ionic $I_{ion}$, and extrinsic $I_{DBS}$ current.

![Diagram of basal ganglia circuitry](image)

**Fig. 1.** The basal ganglia circuitry. (A) The basal ganglia macro-circuit. Cortical input reaches both the GABAergic striatum and glutamatergic STN. The striatum is divided into two populations of projection neurons, respectively expressing the D1- or D2-type dopamine receptors. The D1 population send their principal projections to the substantia nigra pars reticulata (SNr) and GPI; the D2 population send their principal projections to the GPe. Both the SNr/GPI and GPe receive input from the STN; the GPe reciprocates that projection. Both send local projections that inhibit neighbouring neurons. Constant inhibitory output from the SNr/GPI reaches widespread targets in the thalamus and brainstem. (B) The main circuit can be decomposed into two copies of an off-centre, on-surround network. Cortical inputs are topographically organized into separate groups that project to corresponding populations in the striatum and on through the SNr/GPI. In the SNr/GPI pathway, there is a balance of focussed inhibition from the striatum and comparatively diffuse excitation from the STN. In the D2–GPe pathway, a similar overlap of projections to the GPe exists, forming a second copy of this circuit. Three parallel loops are shown in both pathways; for clarity, full connectivity is only shown for the second loop. (C) Modelling DBS as a spread of effect. Top: we considered our STN as a six-per-edge cube of neurons, with each channel arranged as a $6 \times 6 \times 2$ layer of neurons, and with the DBS electrode placed at the cube’s centre. Middle: the current injected into a model STN neuron with each DBS pulse was a Gaussian function of that neuron’s distance from the electrode. The distance axis is in arbitrary units (a.u.), with ±1 indicating the edge of the volume. Shown for $I_{max} = 1500$ nA. Bottom: the resulting distribution of current injected into the model STN neurons for $I_{max} = 1500$ nA.

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sources (in the present model only STN neurons received \( I_{\text{DBS}} \), detailed below). A neuron fired a spike when \( V \geq 0 \), and was reset to the resting potential \( V_r = 0 \) mV; an absolute refractory period was then forced by stopping the solution of Eqn 1 for 2 ms. All neurons also had Gaussian noise added at every time step as a voltage deflection of \( V \) sampled from a Gaussian distribution of 0 ± 0.3 mV; this modelled both the numerous sources of noise (such as synaptic transmission failure) and the effect of unmodelled inputs to each neuron.

Synaptic input was modelled using GABAergic synapses for all inhibitory connections and AMPA and N-methyl-d-aspartate (NMDA) synapses for all connections made by STN neurons and cortical inputs. Each synaptic event was modelled as a step-and-exponential-decay current. The current step was determined so that the average resulting post-synaptic potential peaked at ± 3 mV per input spike for GABAergic and AMPA synapses, and 0.1 mV per input spike for NMDA synapses. The decay constants were set to standard values: AMPA, 2 ms; GABA, 3 ms; and NMDA, 100 ms.

Although the model was based on point-neurons, we simulated a compartmental effect of GABAergic synapses as the dendritic location of GABAergic synapses plays a major role in synaptic integration, and they are differentially distributed on target dendrites in the basal ganglia depending on the type of projection. For each inhibitory projection type (e.g. GPe–STN), the GABAergic synapses on each target neuron were stochastically assigned to either a somatic, proximal, or distal pseudo-compartment, according to the synaptic distributions taken from data (Humphries et al., 2006). GABAergic input to the proximal pseudo-compartment shunted synaptic input to the distal compartment; similarly, GABAergic input to the somatic pseudo-compartment shunted synaptic input to both distal and proximal compartments; shunting was simulated as a division of the incoming synaptic current in proportion to the number and strength of GABAergic synapses in that pseudo-compartment. We had previously found (Humphries & Gurney, 2001) that this form of modelling GABAergic shunting was essential for replicating the dual modes of slow bursting in the STN–GPe loop recorded in vitro (Plenz & Kitai, 1999).

The tonic contributions took two forms. First, all neurons received a tonic injection current; a positive current in STN, GPe, and GPe neurons phenomenologically modelled the current cycle underlying their tonic, pacemaker firing (Surmeier et al., 2005). In Humphries et al. (2006), the positive currents were tuned to fit the tonic firing rates of these structures in awake rat; a negative current in striatal neurons phenomenologically modelled the strongly hyperpolarizing effect of their inward-rectifying potassium channel (Nisenbaum & Wilson, 1995). Second, STN neurons received an additional current source modelling the calcium-channel-dependent rebound bursting of these neurons (Beurrier et al., 1999; Bevan et al., 2002); the parameters were set mean values that allowed the model to replicate the duration and frequency of STN bursting in vitro (Beurrier et al., 1999; Plenz & Kitai, 1999; Humphries & Gurney, 2001).

Mean values for \( \tau_m \) and \( R \) were taken from published values for each neuron type (see Humphries et al., 2006). In each instantiation of the model, values of \( \tau_m \) and \( R \) for all neurons, and the burst-firing parameters for each STN neuron, were sampled from a Gaussian with an SD that was 10% of the mean value.

**The parkinsonian model**

Our basal ganglia model is able to simulate the effects of tonic dopamine on striatal projection neurons (separately for D1- and D2-receptor-expressing neurons), STN, and GPe, as detailed in Humphries et al. (2006). Here we examined DBS effects only under parkinsonian-like conditions, and so dopamine was absent from the model throughout. In terms of our model parameters from Humphries et al. (2006), we set \( k_1 = k_2 = 0 \). In Humphries et al. (2006), we showed how changing the model from its normal tonic dopamine state to this parkinsonian state captured a broad range of known effects of dopamine loss on basal ganglia dynamics. First, loss of dopamine increased the transmission of cortical oscillatory activity through the STN and GPe loop, thus increasing the correlation of neuron firing in these structures, as observed in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) primate model and patients with Parkinson’s disease (for review see Hammond et al., 2007). Second, a combined dopamine and cortical lesion uncovered the residual slow bursting in the STN–GPe loop, as observed in 6-hydroxydopamine (6-OHDA) lesioned rats (Magill et al., 2001). Third, loss of dopamine increased the proportion of substantia nigra pars reticulata/GPi neurons that increase their firing rate during putative motor commands, as observed in MPTP primates (Leblois et al., 2006b). Consequently, our simulations of STN DBS reported here were performed in a model consistent with a parkinsonian basal ganglia.

**Modelling deep brain stimulation**

We used a simple model of the effect of a DBS pulse on individual STN neurons, which attempted to qualitatively account for the spatial extent of tissue activated by DBS. Our starting assumption was that the change in extracellular voltage evoked by a DBS current pulse decays as a function of distance from the electrode (Rattay, 1999; Miocinovic et al., 2006; Zhang & Grill, 2010), and thus induced current flow into the neuron also decays as a function of distance. Here we qualitatively model this by distributing the magnitude of DBS-evoked current injection as a Gaussian function of distance \( d \) from the electrode

\[
I_{\text{DBS}} = I_{\text{max}} \exp[-(d/d_\text{g})^2].
\]

We considered the model STN as cube of six, equally-spaced neurons per edge of unit length, with each channel a 6 × 6 × 2 layer, and the DBS source as a point electrode placed in the centre (Fig. 1C). As not all of the STN is activated by DBS pulses (Miocinovic et al., 2006), we set the Gaussian width at \( d_\text{g} = 0.1812 \) to give a broad range of currents \( I_{\text{DBS}} \) across the model STN (an example distribution is plotted in Fig. 1C). As reported in the Results, we sought appropriate magnitudes for the maximum DBS-induced current flow \( I_{\text{max}} \) by fitting to DBS response data from MPTP primates (Hashimoto et al., 2003). Unless otherwise stated, trains of DBS current pulses \( I_{\text{DBS}} \) were delivered at 130 Hz, with a width of 100 μs.

This simple model omits many proposed effects of DBS, including suppression of synaptic input, somatic inhibition of STN neurons, and direct activation of STN axons (McIntyre et al., 2004). We noted, however, that the resulting mixture of firing rates in the STN (see, e.g. Fig. 2A) was consistent with the mixture of effects reported or predicted for STN high-frequency stimulation; some STN neurons showed stimulus-locked firing, replicating the DBS-locked somatic or axonal generation of STN spikes (Garcia et al., 2003, 2005; Miocinovic et al., 2006); some STN neurons were partially inhibited (Tai et al., 2003; Moran et al., 2011); some were completely inhibited (Miocinovic et al., 2006; Moran et al., 2011); and others showed synchronically-modulated firing patterns (Moran et al., 2011). In our model, this mixture arises entirely from the interaction between the DBS pulses into STN neurons and the effects of the STN–GPe loop in the network, but undoubtedly the actions of DBS include suppression of synaptic input and direct activation of axons (Ranck, 1975; Rattay, 1999; McIntyre et al., 2004; Miocinovic et al., 2006).
We also used a simple model of optogenetic DBS, in which each STN neuron received the same size current pulse \( I_{\text{DBS}} \) to simulate the driving of the STN neurons by light-activated opening of channelrhodopsin channels. Values for \( I_{\text{DBS}} \) were found by fitting to STN firing rate changes under optogenetic DBS (Gradinaru et al., 2009), reported in the Results.

Simulations and statistics

All simulations using STN DBS were run for a total of 30 s, divided into three epochs: pre-DBS (10 s), on-DBS (10 s) and post-DBS (10 s). Rate histograms for single neurons were computed using 1 s bins. Changes in firing rate caused by STN stimulation were detected by computing a two-tailed Mann–Whitney \( U \)-test between the pre-DBS and on-DBS epochs; we took \( P < 0.05 \) as indicating a significant change in rate due to STN stimulation. The fidelity of firing to stimulation frequency was computed as the proportion of DBS pulses after which the neuron fired at least one spike before the next DBS pulse. The regularity of firing for each neuron was measured by its inter-spike interval (ISI) coefficient of variation (CV): ISI CV = SD (ISI)/mean (ISI).

For a detailed comparison with the data from the primate STN high-frequency stimulation study of Hashimoto et al. (2003), we used a ‘models-as-animals’ protocol (Humphries et al., 2006; Humphries & Gurney, 2007b). Briefly, a typical electrophysiological study collects a total of \( T \) neurons across \( N \) animals and approximately \( C \) cells per animal; we matched this with \( T \) neurons from across \( N \) models and \( C \) neurons sampled per model. Each model has a different realization of the stochastic connectivity, and newly sampled distributions for \( R \), \( \tau_{\text{on}} \) and the free parameters for \( I_{\text{DBS}} \) thus each represents a different animal. This approach circumvents issues of the differing statistical power and differing sampling of response classes with different total numbers of neurons \( T \), and of the differing convergence of summary statistics depending on the combination of \( N \) and \( C \) (Humphries & Gurney, 2007b). In this way, we aimed to generate results, the statistical properties of which are similar to their experimental counterparts, thereby enabling statistically valid claims about the ‘fit’ between the model and the data.

Following our previous work (Humphries et al., 2006), cortical input was generated as 72 spike trains per channel, connected to each STN and striatum neuron in that channel with a probability of 0.25. Input from the cortex was modelled under a variety of recording conditions. For replications of the data from awake, resting, head-fixed primates (Hashimoto et al., 2003), we generated Poisson trains of 3 Hz (this input was used for all simulations unless otherwise specified). For optogenetic-like simulations in awake, freely-moving rats (Gradinaru et al., 2009), we generated Poisson trains of 15 Hz. For tuning of the optogenetic DBS model to changes in STN firing rate, recorded in rat under isoflurane anaesthesia (Gradinaru et al., 2009), we simulated the cortical slow wave at \( \sim 1 \) Hz induced by this anaesthetic (Ferron et al., 2009), following our similar simulations of urethane anaesthesia (Humphries et al., 2006). Every cortical train synchronously alternated between active up-states and silent down-states every 0.5 s; during each up-state, each train was assigned uniformly-spaced spikes at a rate \( f \), sampled from a Gaussian of 24 ± 1.15 Hz, and each spike was then jittered by \( \delta \), seconds, sampled from a Gaussian of 0 ± 0.25/f.

Results

Subthalamic nucleus high-frequency stimulation drives a mixture of responses in basal ganglia output

We begin by qualitatively illustrating the model’s two main predictions for the network effects of STN high-frequency stimulation. First, that regular, high-frequency, pulsed, positive current stimulation of the STN drives a mixture of changes in the basal ganglia output nuclei. Second, that this mixture of responses is a network effect, arising from variations in the balance of glutamatergic input (from the STN) and GABAergic input to each neuron in the basal ganglia output nuclei.
Figure 2A shows the spike output of all model neurons in the STN, GPe, and GPi immediately preceding and following the onset of 130 Hz stimulation of the STN. The onset of stimulation entrained some STN neurons, whereas others were silenced, and others continued to fire irregularly (Fig. 2C). All of these effects were due entirely to the network response to the stimulation, as we did not explicitly model synaptic suppression, somatic inhibition, or any other source of inhibition to the STN other than synaptic input (which is not to say that those factors do not contribute to the effect of STN DBS).

In the GPe and GPi, a subset of neurons also became entrained to their STN input, and increased their firing rate and regularity, but others showed reduced activity, and others did not change their firing rates. Figure 2B shows examples from the GPi of each firing rate response to STN stimulation.

Figure 2C shows that a subset of GPi neurons became tightly locked to the stimulation frequency and hence highly regularized in their output. Across the whole GPi, STN stimulation caused significant excitation and significant inhibition of responses in approximately equal proportions, with a small proportion of unresponsive neurons (Fig. 2D).

Although the excitatory responses were directly driven by STN firing, the equally prevalent inhibitory responses were a little counter-intuitive. By construction, we know that the model contains only three sources of GABAAergic input to GPi neurons: the striatum, GPe, and local collaterals in the GPi. The striatum was barely active under the background cortical firing input, and was unaffected by STN stimulation. Lesioning the GPe to GPi pathway in the model reduced the proportion of inhibitory responses in the GPi (Fig. 2D). An additional lesion of the GPi local collaterals further decreased the proportion of inhibitory responses in the GPi (Fig. 2D). With all GABAAergic sources accounted for, there remained only a small proportion of inhibitory responses in the GPi following STN high-frequency stimulation; thus, under this model of DBS, the silencing of some STN neurons makes a small contribution to the significant reduction of the firing rates of output neurons. The model thus shows that a mix of responses in basal ganglia output naturally arises from the network effects of STN high-frequency stimulation.

Using this model, we set out to answer the following. Is this the right mix of responses for therapeutically effective DBS in the STN? Does a “mixture of response” perspective offer an explanation for why STN DBS is therapeutically effective at greater than 100 Hz (Deep Brain Stimulation for Parkinson’s Disease Study Group, 2001)? Does it offer some clues to why an optogenetic model of STN DBS produced the right mix of responses for therapeutically effective DBS in the STN? To do so, we set out to replicate the data on STN stimulation-induced changes in both spike rate and regularity for different values of peak DBS current $I_{\text{max}}$. For replication of changes in firing rate, we measured: (i) the percentage change in mean rate from pre-DBS to on-DBS epochs from recorded neurons in the GPi and GPe; and (ii) the proportion of those recorded neurons that showed a significant increase, a significant decrease, and no change in firing rate. For the replication of changes in spike regularity, we measured the percentage changes in ISI CV from pre-DBS to on-DBS epochs from recorded neurons in the GPi.

To compare with data, we first extracted individual neuron ISI CV responses from Fig. 2 of Hahn et al. (2008). In the experimental recordings, the mean ISI CV in the GPi did not significantly differ between pre-DBS and on-DBS epochs (Hahn et al., 2008); however, individual neurons had large changes in regularity, with a mean increase of $40.4 \pm 13.28\%$ ($n = 12$) and mean decrease of $-27 \pm 2.91\%$ ($n = 24$). Therefore, we assessed the replication of: (i) the proportion of neurons that showed an increase and decrease of ISI CV; (iv) the mean percentage change in ISI CV for increasing neurons; (v) the mean percentage change in ISI CV for decreasing neurons; and (vi) the ensemble mean ISI CV not significantly differing between pre-DBS and on-DBS epochs (two-tailed t-test, at $P = 0.05$). Thus, in total we assessed six measures of fit between GPi output in model and data.

For both rate and regularity, we assessed percentage changes because, as our model was explicitly of the rat basal ganglia, its tonic rates in the STN, GPe, and GPi were considerably less than those recorded in primates. Thus, we assessed magnitude changes, not exact values. To ensure similar statistics and sampling of distributions between models and data, we replicated the study design (see Materials and methods). The study of Hashimoto et al. (2003) used two monkeys, and Hahn et al. (2008) analysed a total of 20 GPe neurons and 36 GPi neurons recorded in both pre-DBS and on-DBS epochs. Thus, for each simulation of the model of Hashimoto et al. (2003), we used two instantiations of the model, sampling 10 GPe cells and 18 GPi cells from each.

Figure 3 shows that the model replicated all tested firing rate changes in the basal ganglia output during STN high-frequency stimulation: the percentage change in the mean rate of GPi neurons and the sampled mix of responses (increase, decrease, no change) in the GPi. These were simultaneously replicated across most tested values of $I_{\text{max}}$. The firing rate responses of the GPi in the MPTP primate were thus robustly well-fit. Figure 3 shows that, over a narrower range of $I_{\text{max}}$ ($\sim 1000–1500\, \text{nA}$), the model also simultaneously replicated the change in mean rate and sampled mix of responses in the GPi.

Figure 4 shows that the model replicated all tested GPi spike-train regularity changes during STN high-frequency stimulation: the mix of ISI CV responses (increase, decrease); the mean percentage change in ISI CV for neurons with increasing ISI CV; the mean percentage change for neurons with decreasing ISI CV; and the non-significant difference in mean ISI CV between pre-DBS and on-DBS epochs. Simultaneous replications of all regularity measures were robust across the lower range of $I_{\text{max}}$ ($\sim 500–1500\, \text{nA}$).

Across all fits to rate changes and mix of responses in the GPi and GPe, and to ISI CV changes and mix of responses in the GPi, the choice of $I_{\text{max}} = 1500\, \text{nA}$ was best able to simultaneously replicate all of these data properties (we quantify this statement in the next section). Thus, we used this value for further DBS simulations when assessing therapeutic effects.
Fig. 3. The model replicates the magnitude and mixture of rate changes in a primate DBS study. (A) Percentage change in mean rate caused by high-frequency STN stimulation. Increasing the DBS current magnitude ($I_{\text{max}}$) caused a larger increase in mean firing rates in both the GPe and GPi. For $I_{\text{max}} \geq 1000\text{ nA}$, the model was able to reproduce closely the magnitude rate changes observed in both the GPe and GPi of primate. Model plotted as mean ± SEM. Grey lines give the target data: mean (solid) ± SEM (dashed) percentage change in rates in response to STN DBS in the MPTP primate model (Hashimoto et al., 2003; Hahn et al., 2008). (B) Mixture of responses in sampled neurons. Increasing $I_{\text{max}}$ increased the number of excitatory responses (black) in the GPe, correspondingly decreasing the occurrence of both inhibitory responses (grey), and no change (white). By contrast, the mix of responses in the GPi was stable to the changes in $I_{\text{max}}$. The mix of responses observed under STN DBS in the MPTP primate model (Hashimoto et al., 2003; Hahn et al., 2008) was closely reproduced in the GPe over 500–1500 nA, and closely reproduced in the GPi for all tested currents. Data are given in the left-most bars.

The mixture of responses is robust to model variations

These results showed that the DBS-evoked mixture of rate and regularity responses, generated solely by the network of our model, was consistent with the mixture of rate and regularity responses seen under therapeutic STN DBS in primate. To further confirm the robustness of these results, we checked that plausible changes to the model still produced a mixture of responses in basal ganglia output, and replicated the primate data on STN DBS responses.

We checked three variants of the original model. The first variant omitted the discrete-channel architecture for the connections between basal ganglia structures. The presence of parallel loops running through the basal ganglia has strong support from anatomical studies (see, e.g. Alexander & Crutcher, 1990; Hoover & Strick, 1993; Romanelli et al., 2005). Nonetheless, imposing discrete channels in our relatively small and densely connected model creates some correlation between the inputs to neurons in the same channel, which could plausibly affect the results. For the no-channel model variant, every neuron connected with a probability of $P = 0.25/3$ to any neuron in each of its target structures. In this way, the expected number of connections between structures was exactly equivalent between the channel-based and no-channel models.

The second variant omitted the local axon collaterals in the GPe. As our model was originally of rat basal ganglia it explicitly modelled the substantia nigra pars reticulata as the main basal ganglia output nucleus, and consequently included the well-described local axon collaterals in that structure (Deniau et al., 1982; Mailly et al., 2003). However, beyond a brief note of their existence (Parent et al., 2001), there has been little work establishing an equivalent network of local axon collaterals in the primate GPe. We thus checked that their omission did not affect our results. Finally, the third variant shortened the NMDA synaptic current decay constant to 50 ms, the lowest plausible value in the basal ganglia (Gottz et al., 1997), to check that our results did not depend on prolonged excitation of GPe and GPi neurons by their STN inputs.

For each tested value of maximum DBS current $I_{\text{max}}$, we assessed each variant’s error in reproducing the mixture of responses in the GPe and GPe (as in Fig. 3B), and each variant’s ability to simultaneously fit all other measures of rate and regularity changes between pre-DBS...
and on-DBS epochs. We assessed fits to the same five measures as for the original model: the GPi and GPe mean rate (as in Fig. 3A), mean GPi ISI CV increase and decrease (as in Fig. 4B), and the non-significant difference between all GPi ISI CVs in the pre-DBS and on-DBS epochs. For rate and ISI CV changes, we used a conservative criterion for a fit to the data: that the mean values for model and data were within 1 SEM, as illustrated by the error bars for the model and data plotted in Figs 3A and 4B.

Figure 5 shows that each model variant was able to reproduce the mixture of responses in GPi output evoked by STN DBS, with similar error to the original model, while also still being able to replicate all other tested measures of rate and regularity changes. Thus, the mixture of STN DBS evoked responses in basal ganglia output resulting from the basal ganglia network is highly robust to plausible changes in the model. We noted that the original model was best able to reproduce the mixture of responses in GPe output while still fitting all other measures. Consequently, we used this model for subsequent simulations.

Changing deep brain stimulation frequency changes the mixture of rate and regularity responses

A key unknown in understanding how DBS works is why the therapeutic frequency for the treatment of Parkinson’s disease motor symptoms and tremor is normally above 100 Hz (Limousin et al., 1995; Deep Brain Stimulation for Parkinson’s Disease Study Group, 2001; Volkman et al., 2002). Here we show, using parameters for the DBS model established above, that our model predicts that basal ganglia output response patterns change dramatically with increasing DBS frequency, and a unique, stable balance of breadth of response and direction of response appears at therapeutic frequencies.

We assessed the firing rate and spike-train regularity changes of the model GPi neurons in response to a range of STN stimulation frequencies. We found that the mixture of firing rate responses (increase, decrease, no change) in the GPi became more stable above 100 Hz stimulation (Fig. 6A), with a marked step change in the proportion of inhibitory responses at 100 Hz stimulation (Fig. 6A, right). Figure 6B shows that the distribution of percentage firing rate changes across the GPi became strongly skewed above 100 Hz stimulation. Moreover, the distributions of changes were also stable for stimulation frequencies above 100 Hz (Fig. 6B, right). Thus, in addition to GPi neurons becoming strongly excited and entrained by STN stimulation, the larger proportion of significantly inhibitory responses included GPi neurons that became silenced only by stimulation above 100 Hz.

We found that the mixture of ISI CV direction changes in the GPi was not markedly altered by stimulation frequencies above 75 Hz (Fig. 6C). However, Fig. 6D shows that the distribution of ISI CV changes in the GPi became strongly asymmetric above 100 Hz. Moreover, the distributions of changes were also stable for stimulation frequencies above 100 Hz (Fig. 6D, right). Thus, although the proportion of GPi neurons showing increases and decreases in spike-train regularity did not markedly change at therapeutic stimulation frequencies, the magnitude of those changes did change.

Optogenetic model deep brain stimulation alters the response mix compared with the electrical deep brain stimulation model

Our results suggest that a specific mix of basal ganglia output rate and regularity changes is found under therapeutic STN DBS. We wondered if this observation could help to explain why using an optogenetic model of STN excitation by DBS failed to find any therapeutic effect in parkinsonian rats (Gradinaru et al., 2009).

In an innovative use of recent developments in optogenetic technology, Gradinaru et al. (2009) addressed the controversy over the effect of high-frequency stimulation on the STN by driving spiking activity in channel-rhodopsin-expressing STN neurons with 130 Hz light pulses. However, they found that such unambiguous direct 130 Hz stimulation of STN neurons did not alleviate behavioural deficits in parkinsonian rats. These results present a serious challenge to the idea that elevated, regularized STN spiking activity – whether axonally or somatically induced – is key to the effectiveness of standard, electrical DBS.

We considered this difficulty from the perspective that a specific mix of responses in basal ganglia output is the main cause of STN DBS effectiveness. We noted that, in the study of Gradinaru et al. (2009), the excitation of the STN was exceptionally uniform. They estimated that almost all neurons (95.73 ± 1.96%) were infected with the channel-rhodopsin promoter Ca2+/calmodulin-dependent protein kinases II (CaMKII), and thus likely to express the light-sensitive ion channels; further, they estimated that the wavelength of light used was able to penetrate the whole volume of the rodent STN (~0.7 mm2) at a sufficient intensity to activate the light-sensitive ion channels. We hypothesized that this uniform excitation was the key to the ineffectiveness of an optogenetic DBS model.

To test this, we compared the output of our basal ganglia model under an optogenetic DBS model with the electrical DBS model established in the preceding sections. To mimic the uniform take up and light penetration, we modelled optogenetic-like stimulation of the STN by applying the same magnitude current pulse I_{DBS} to every STN neuron. We first estimated an appropriate magnitude of current pulse to mimic the optogenetic stimulation by fitting the change in STN firing rate during the optogenetic stimulation (Gradinaru et al., 2009).

Gradinaru et al. (2009) reported an ~100% increase in STN firing rate in response to 130 Hz light stimulation, recorded in 6-OHDA-lesioned rats under isoflurane anaesthesia (whereas they tested the...
therapeutic effects of the optogenetic DBS model in awake, freely-moving rodents). Thus, we first found the appropriate magnitude of current pulse under isoflurane-like conditions, and then applied it to awake, freely-moving rat like conditions. Isoflurane systemically increases the efficacy of GABAa synapses (Krasowski & Harrison, 1999; Yamakura & Harris, 2000), and causes global slow-wave activity at 1 Hz in the cortex (e.g. Ferron et al., 2009). As these physiological effects of isoflurane are very similar to those of urethane (Rudolph & Antkowiak, 2004), we adopted a similar approach to our previous simulations of the effect of urethane on the basal ganglia (Humphries et al., 2006); cortical input oscillated at 1 Hz with an average firing rate of 24 spikes/s (see Materials and methods), and we increased the GABAa synaptic weights by a factor of 1.5. Under this isoflurane-condition model, we tried a range of $I_{DBS}$ uniformly applied at 130 Hz to every STN neuron during the on-DBS epoch. Following Gradinaru et al. (2009), for each tested $I_{DBS}$ we computing the mean firing rate over five sampled STN neurons for the pre-DBS and on-DBS epochs. Figure 7A shows that $I_{DBS} = 45$ nA was able to accurately reproduce the reported increase in STN firing rate during optogenetic DBS.

We then compared the basal ganglia output responses for the optogenetic DBS model (with $I_{DBS} = 45$ nA) with our electrical DBS model [Eqn 2, using the best-fit to the data of Hashimoto et al. (2003) of $I_{max} = 1500$ nA, resulting in the distribution of $I_{DBS}$ in Fig. 1C]. We ran 10 models of awake, freely-moving, 6-OHDA rodent basal ganglia (Gradinaru et al., 2009), with each model run twice, once with the optogenetic DBS model and once with the electrical DBS model applied during the on-DBS epoch.

Figure 7B shows that the two DBS protocols differed markedly in their distribution of STN neuron fidelity to the DBS frequency, skewed towards high fidelity for the optogenetic DBS stimulation model, and bimodal in the electrical DBS model. We noted that this distribution of fidelity in the optogenetic DBS model is in keeping with the known fidelity of channel-rhodopsin-expressing neurons to regular, high-frequency, pulsed-light stimulation (Arenkiel et al., 2007).

Our models showed that, with these differing STN response distributions, the optogenetic DBS and electrical DBS models had multiple differences in the mix of responses in the basal ganglia output. First, optogenetic DBS caused many more excitatory responses in the GPi than electrical DBS (Fig. 7C). Second, optogenetic DBS generally caused higher fidelity of GPi firing to the STN stimulation frequency, particularly in the regime of near 1 : 1 fidelity,
Discussion

We set out to begin to address the hypothesis that a mixture of responses in the basal ganglia output nuclei, combining regularized firing and inhibition, is a key contributor to the effectiveness of STN DBS. We had two goals: first, to use our computational model of the complete basal ganglia circuit (Humphries et al., 2006) to understand how such a mixture of responses in basal ganglia output may arise from the network effects of STN DBS; and second, we sought whether, from this ‘mixture of responses’ perspective, the model could suggest resolutions to two DBS puzzles: the therapeutically effective range of frequencies, and the ineffectiveness of direct-activation optogenetic models of STN DBS. We showed that the model predicts a mixture of responses in the basal ganglia output arising as a natural consequence of the network effects of STN DBS. We replicated the diversification of responses recorded in a primate STN DBS study (Hashimoto et al., 2003; Hahn et al., 2008) to show that the model’s predicted mixture of responses is consistent with therapeutic STN DBS. We then showed how, from this ‘mixture of response’ perspective, the model suggested the respective hypotheses for the two puzzles: that the mixture of responses in basal ganglia output undergoes a step change at therapeutic DBS frequencies; and that optogenetic DBS models failed because their uniform stimulation of the STN did not produce the putative therapeutically-effective mixture of responses evoked by standard, electrical DBS.

Subthalamic nucleus deep brain stimulation drives a mixture of responses in basal ganglia output

We have shown that STN DBS can induce a mix of excitatory and inhibitory responses in the basal ganglia output nuclei, with some neurons entrained to stimulation frequency and others strongly inhibited. This mix of responses arose purely from the basal ganglia network; simulated STN DBS only affected STN neurons, and we did not simulate other hypotheses for the distal action of DBS, including recruitment of passing axon fibres or antidromic activation of STN afferents (McIntyre et al., 2004; McIntyre & Hahn, 2010; Bosch et al., 2011). Nonetheless, this mix of responses in both spike rate and regularity accurately reflected those observed following therapeutic STN DBS in parkinsonian primates (Hashimoto et al., 2003; Hahn et al., 2008). Our model replicated the mixture of firing frequency responses of GPe and GPi neurons, and the mean percentage changes in GPe and GPi firing rate following STN high-frequency stimulation. It also replicated the mixture of the changes in spike-train regularity of GPi neurons, the respective mean percentage increase and decrease, and the non-significant change in overall mean regularity following STN high-frequency stimulation. The model thus showed how the DBS results in this study were consistent with a purely network effect of STN DBS. We also showed that replication of these results was not dependent on a number of modelling assumptions (the imposition of a discrete-channel architecture, the presence of collaterals in the GPi, or the precise time-course of NMDA synaptic currents). Our results thus support the idea that a main contributor to the therapeutic effectiveness of STN DBS is its network effect, which creates a mixture of responses in the basal ganglia output through the balance of STN-originating excitation and GPe-originating inhibition arriving at the GPi (Kita et al., 2005; McIntyre & Hahn, 2010; Bosch et al., 2011; Reese et al., 2011).

Subthalamic nucleus deep brain stimulation frequency determines the mixture of responses

The therapeutically-effective frequency of STN DBS is typically above 100 Hz in human patients (Deep Brain Stimulation for...
Parkinson’s Disease Study Group, 2001). Although stimulation frequencies in this range may enable STN neuron firing to track the DBS pulses (Garcia et al., 2005), our model suggests a network-based explanation for this range. We found that increasing stimulation frequency to the effective range for DBS caused a step change in the basal ganglia output’s response characteristics. The distributions of both spike-rate and spike regularity changes became strongly skewed above 100 Hz, reflecting the appearance of GPI neurons that were strongly entrained or silenced by STN DBS. Moreover, the proportion of inhibitory responses in the GPI non-linearly increased at 100 Hz. The model’s results are thus consistent with a transition from symmetric to asymmetric effects of STN DBS on basal ganglia output at therapeutic frequencies.

Optogenetic deep brain stimulation may alter the mixture of responses
Gradinaru et al. (2009) recently used optogenetics to address the controversy over the effect of DBS on the STN. They tested the hypothesis that DBS directly activates STN neurons, by driving spiking activity in channel-rhodopsin-expressing STN neurons with 130 Hz light pulses. However, they found that such direct 130 Hz stimulation of STN neurons did not alleviate behavioural deficits in parkinsonian rat models, strongly challenging the idea that elevated and regularized STN spiking activity alone underpins the effectiveness of standard, electrical DBS. To address this, we simulated optogenetic DBS as a uniform stimulation of STN neurons, with a stimulating current pulse tuned to fit the reported change in STN firing rate following the onset of optogenetic DBS (Gradinaru et al., 2009). The model showed that optogenetic DBS stimulation was unable to provide the same diversity of responses in basal ganglia output as the electrical DBS stimulation. Optogenetic DBS predominantly caused an increased firing rate in GPI output, and a corresponding increase in regular, stimulation-tracking, firing and in the correlation of GPI neuron output. If the effectiveness of STN DBS indeed rests on a particular mixture of responses, then this may explain why a direct-excitation optogenetic model of STN DBS, causing uniform stimulation of STN neurons, did not result in the effective alleviation of motor symptoms in the parkinsonian rat (Gradinaru et al., 2009). Thus, in addition to other possible contributors to the therapeutic failure of the optogenetic model of STN DBS (such as milliseconds different time-scales of STN neuron synchronization by electrical and light stimulation), our model offers a novel network-based hypothesis.

Why then, from this perspective, did Gradinaru et al. (2009) find that optogenetic high-frequency stimulation of either all layer 5 cortical terminals in the STN or layer 5 neurons in the motor cortex could alleviate the parkinsonian motor symptoms? As they noted, these results are consistent with the therapeutic effect of electrical STN DBS arising from antidromic activation of these cortical neurons. However, we note that both stimulations could cause a non-uniform excitation of STN neurons. In both cases, whether stimulating all cortical afferents from layer 5 or just those with somas in the motor cortex layer 5, these make up only a subset of glutamatergic projections to STN neurons. A major glutamatergic input arises from the parafascicular thalamus (Bevan et al., 1995), and others from across the upper brainstem (Bevan & Bolam, 1995). Thus, the stimulated terminals or neurons will be differentially distributed across the STN, with some STN neurons strongly innervated by layer 5 cortical neurons and others more weakly innervated. Moreover, as the optogenetic stimulation in both cases was driving synaptic input to the STN and not direct spiking, it is probably more susceptible to modulation by GABAergic input from the GPe. Thus, we speculate that optogenetic high-frequency stimulation of layer 5 terminals or somas has a similar effect on STN neurons to the spreading current model of electrical DBS used here, thus resulting in the mixture of basal ganglia output responses corresponding to therapeutic DBS.

How might a mixture of responses to deep brain stimulation restore function?
We have used computational models here to generate mechanistic hypotheses for the action of STN high-frequency stimulation on basal ganglia output nuclei, and for the effectiveness of DBS. The next, crucial step will be to address if and why such a mix of responses is key to the restorative effect of DBS. We comment on three perspectives here. First, from the perspective that DBS restores function to the targets of the basal ganglia by output regularization. Elegant studies by Rubin and colleagues (Rubin & Terman, 2004; Guo et al., 2008) and Dorval et al. (2010) have provided compelling demonstrations of how, by regularizing basal ganglia output to the thalamus, STN DBS may improve the transmission of the excitatory inputs of thalamo-cortical neurons. Our results are consistent with STN DBS regularizing the output of a subset of GPI neurons, and hence the reinstatement of thalamic information transfer, but our results also point to the silencing of a substantial number, and a mixture of responses in the rest of the basal ganglia output. The studies of thalamo-cortical relay fidelity have typically considered the effect of one or a few GPi inputs, on an isolated thalamo-cortical cell, relaying one type of input (a pulsed current), and using one model of error in thalamic information transfer (a 1 : 1 spike-locking regime). Consequently, in the context of a full basal ganglia-thalamo-cortical circuit or of other models of thalamic information transfer to the cortex (such as the necessary synchronization of thalamo-cortical neurons) (Bruno & Sakmann, 2006; Bruno, 2011), it may turn out that regularizing all basal ganglia output simply overwrites one form of pathological activity with another, artificially generated form. Indeed, a prediction of our model is that the optogenetic DBS model failed to alleviate parkinsonian motor symptoms (Gradinaru et al., 2009) because it over-regularized the basal ganglia output. Thus, one possibility is that a balance of regularization and inhibition amongst the basal ganglia output neurons is necessary for the restoration of thalamic relay fidelity.

Second, we consider how DBS might restore function to targets of the basal ganglia output through the seemingly paradoxical removal of inhibition. The dominant theory of basal ganglia function is that they operate by disinhibition — signalling the selection of motor programmes by selectively reducing their tonic inhibitory output to their target structures (Mink, 1996; Redgrave et al., 1999; Hikosaka et al., 2000). The therapeutic success of STN DBS, and its activation of basal ganglia output nuclei (Hashimoto et al., 2003; Shi et al., 2006; Bosch et al., 2011; Moran et al., 2011; Reese et al., 2011), is a considerable challenge to this theory (Nambu, 2008), as how can stimulating the STN alleviate motor symptoms, when it increases the activity of basal ganglia output, and consequently decreases, not reduces, their tonic inhibition of target structures? Our results suggest a resolution, i.e. that, through its network effect, STN DBS actually generates widespread, permanent inhibition of much basal ganglia output, including the silencing of a number of neurons (see Fig. 6A, right). Consequently, STN DBS would permanently reduce the tonic inhibition of a subset of neurons in the basal ganglia target structures, allowing them to respond to their other inputs. Moreover, we showed that this inhibition of basal ganglia output was consistent with the effects of therapeutically-effective STN DBS on the primate GPI (Hashimoto et al., 2003; Hahn et al., 2008). Thus, our model shows...
how both information transfer through and disinhibition of basal ganglia target nuclei could be reinstated by STN DBS.

Finally, a view-point strangely lacking from theoretical STN DBS studies to date is how it might re-enable information flow through the basal ganglia from the striatum to its outputs (Hammond et al., 2007). That is, in both the above perspectives, STN DBS restores function to target structures through permanently altering basal ganglia output, but they do not address if or how STN DBS restores function to the basal ganglia through reinstating control over that output. Our results suggest a preliminary observation. In our model, the mixture of responses to STN DBS amongst the basal ganglia output neurons is underpinned by each neuron’s balance of excitatory input from the STN and GABAergic input from the GPe and local collaterals. By reinstating the dominance of inhibition over some basal ganglia output neurons and the dominance of excitation over others, STN DBS may thus allow phasic inhibitory input from the striatum to again modulate basal ganglia outflow, and reestablish basal ganglia computation (Mink, 1996; Redgrave et al., 1999; Gurney et al., 2001; Humphries et al., 2006; Leblois et al., 2006a). Understanding if such a mixture of responses is indeed key to the restoration of function in the basal ganglia is our next challenge.

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Abbreviations
6-ODHA, 6-hydroxydopamine; CV, coefficient of variation; DBS, deep brain stimulation; GPe, globus pallidus pars externus; GPi, globus pallidus pars internus; ISL, inter-spike interval; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; NMDA, N-methyl-D-aspartate; STN, subthalamic nucleus.

References


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