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Modeling shifts in the rate and pattern of subthalamopallidal network activity during deep brain stimulation

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Abstract

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) represents an effective treatment for medically refractory Parkinson's disease; however, understanding of its effects on basal ganglia network activity remains limited. We constructed a computational model of the subthalamopallidal network, trained it to fit *in vivo* recordings from parkinsonian monkeys, and evaluated its response to STN DBS. The network model was created with synaptically connected single compartment biophysical models of STN and pallidal neurons, and stochastically defined inputs driven by cortical beta rhythms. A least mean square error training algorithm was developed to parameterize network connections and minimize error when compared to experimental spike and burst rates in the parkinsonian condition. The output of the trained network was then compared to experimental data not used in the training process. We found that reducing the influence of the cortical beta input on the model generated activity that agreed well with recordings from normal monkeys. Further, during STN DBS in the parkinsonian condition the simulations reproduced the reduction in GPi bursting found in existing experimental data. The model also provided the opportunity to greatly expand analysis of GPi bursting activity, generating three major predictions. First, its reduction was proportional to the volume of STN activated by DBS. Second, GPi bursting decreased in a stimulation frequency dependent manner, saturating at values consistent with clinically therapeutic DBS. And third, ablating STN neurons, reported to generate similar therapeutic outcomes as STN DBS, also reduced GPi bursting. Our theoretical analysis of stimulation induced network activity suggests that regularization of GPi firing is dependent on the volume of STN tissue activated and a threshold level of burst reduction may be necessary for therapeutic effect.

Keywords

Subthalamic nucleus; Globus pallidus; Basal ganglia; Oscillation; Burst

1 Introduction

Subthalamic nucleus (STN) deep brain stimulation (DBS) represents an established therapy for medically refractory Parkinson's disease (PD), but important gaps remain in the scientific characterization of its effects on the nervous system. Numerous experimental studies have analyzed the effects of DBS at the single cell level using *in vivo* microelectrode recordings (e.g. Hashimoto et al. 2003), and functional imaging studies have provided a global perspective on interactions between various nuclei (e.g. Phillips et al. 2006). However, a relative paucity of information exists on the neural network activity induced by therapeutic stimulation, even

while many of the prevailing hypotheses on the therapeutic mechanisms of DBS concentrate on network interactions (McIntyre and Hahn 2010).

One good way to address network interactions is with neural network models. Montgomery and Baker (2000) and Rubin and Terman (2004) laid much of the existing groundwork on the theoretical analysis of DBS induced network effects. Using simplified model systems they predicted that stimulation induced activation of STN output would regularize basal ganglia input to the thalamus and improve the ability of the thalamus to relay information. This general concept of DBS disrupting oscillatory activity has been further reinforced by others using a diverse range of basal ganglia network model implementations (Tass 2003; Shils et al. 2008; Modolo et al. 2008). However, much of this previous work suffered from a limited connection to experimental data. In turn, we attempted to directly parameterize a subthalamopallidal network model using *in vivo* microelectrode recordings from the basal ganglia (BG) of non-human primates. Our motivation for this approach was to enable more explicit comparisons between DBS network model predictions and the underlying neurophysiology.

The first goal of our network model development was to capture the characteristic shifts in rate and pattern of the subthalamopallidal network following the induction of parkinsonism. Experimental recordings made in the BG of non-human primates following treatment with the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) show increased firing rates, burst rates, and synchrony in the STN and globus pallidus internus (GPi), while globus pallidus externus (GPe) exhibits a decrease in rate (Wichmann et al. 1999; Bergman et al. 1994; Nini et al. 1995; Soares et al. 2004). Given these general experimental findings, there exist many different network model implementations that are capable of simulating parkinsonism. For example, Terman et al. (2002) focused on synaptic interactions between the STN and GPe to describe the shift from the “normal” to “parkinsonian” activity. However, growing experimental evidence implicate a cortical origin to beta rhythms associated with the parkinsonian state (Brown and Williams 2005; Brown et al. 2001; Courtemanche et al. 2003; Goldberg et al. 2004, 2003; Kuhn et al. 2005; Raz et al. 2000; Sharott et al. 2005a, b; Dejean et al. 2008). Therefore, we elected to develop a subthalamopallidal network model that relied on a stochastic description of cortical and striatal inputs to regulate its state. Even still, all network models consist of a large number of unconstrained parameters. One way to address this issue is to use available experimental data to parameterize the network model. In turn, we used conductance based single compartment neuron models that generated spiking outputs that could be directly compared to *in vivo* microelectrode recordings. These neuron models were connected together with a stereotyped synaptic architecture. An optimization algorithm was then used to define the specific parameters of connectivity such that the model activity mimicked experimental target data.

With a model in place we set out to evaluate the effects of STN DBS on network activity and identify a neural activity metric that closely correlated with therapeutic benefit. Hashimoto et al. (2003) provided *in vivo* single unit recordings of pallidal neurons during therapeutic STN DBS in the parkinsonian monkey. Therefore, we attempted to reproduce those experiments within our network model, exploiting the fact that the model allows for neural activity to be simulated across the entire network simultaneously. The model reproduced the experimental results well, and our network analysis suggested that controlling GPi bursting was an interesting metric linked to therapeutic benefit. However, it is well known that the therapeutic effects of STN DBS are frequency dependent (Rizzone et al. 2001), and lesioning the STN can generate analogous clinical outcomes to DBS (Alvarez et al. 2009). Unfortunately, the experimental data necessary to explicitly evaluate a connection between GPi bursting and DBS frequency dependence or STN lesioning does not currently exist. Fortunately, such analysis is easily performed in an appropriate model, and our simulations support the hypothesis that a reduction in GPi bursting is dependent upon both stimulation frequency and the volume of STN ablated.

Therefore, using a network model tightly bound by experimental electrophysiology we identified reduction in GPi bursting as a common theme between therapeutic STN DBS and STN lesion, where in both cases the degree of burst reduction was dependent on the volume of STN affected.

2 Methods

The major components of the network model include single compartment models of individual BG neurons (STN, GPe and GPi), input spike trains (cortico-subthalamic and cortico-striato-pallidal) and simulation of DBS induced currents. These individual components are described in greater detail below. The model was implemented using the NEURON v5.8 simulation package (Carnevale and Hines 2005) and run in parallel mode on a sixteen processor Saturn cluster (Rocketcalc, Kent, OH). NEURON default units are used for all parameters and variables unless otherwise specified. Population average rates were taken over 10 s simulation runs and are reported as mean±standard deviation. Burst detection was accomplished using a modified Poisson surprise method with a minimum surprise index of 3 and a minimum number of 3 spikes/burst (Hahn et al. 2008). The model was originally parameterized to simulate activity in the parkinsonian state (MPTP state). This base model was then modified to simulate activity in three additional states: Normal (non-parkinsonian), STN DBS, STN lesion. Parameter modifications used to transition between states consisted of changes in the input spike trains, dopamine sensitive parameter values, and configuration of the neural elements subjected to DBS/lesion.

2.1 Neuron models and network architecture

Single compartment pallidal and subthalamic neuron models were developed using biophysical properties of STN (Otsuka et al. 2004) and pallidal cells (Nambu and Llinas 1994; Cooper and Stanford 2000). The Hodgkin-Huxley type conductance-based models included basic currents with parameters chosen to implement appropriate functional characteristics (e.g. current response, rebound bursting, input resistance) recorded from rodent neurons in isolated *in vitro* preparations. Each cell followed the current balance equation:

$$C_m \frac{dV_m}{dt} = -I_{ion} - I_{leak} - \sum_k I_{syn}^k + I_{ext}$$

Ionic currents (I_{ion}) in each pallidal and STN cell included spike producing currents (I_{Na} and I_{Kdr}), a T-type low threshold calcium current (I_{CaT}), a calcium dependent potassium current (I_{AHP}), and a leak current (I_{leak}). STN cells also had an L-type, high threshold calcium current (I_{CaL}) and an A-type potassium current (I_{Ka}). Additional details on the neuron models can be found in the Appendix.

Individual synaptic currents (I_{syn}) were triggered in target cells by detection of presynaptic action potentials. Synaptic currents (AMPA and GABA) were determined by the equation:

$$I_{syn}^k = R_k * (V_m - E_{rev})$$

where I_{syn}^k is the k^{th} synaptic current, R_k represents a first order process that captured the kinetics of the onset and decay of current following a presynaptic spike for synapse k and E_{rev} is the reversal potential for the appropriate type of synapse (Destexhe et al. 1994a, b). After a presynaptic spike and transmission delay (4 msec) the value of R_k increased exponentially for a set time (0.3 msec) toward the maximal conductance for the synapse and

then decayed toward zero. In turn, successive spikes summed if they occurred over a small space of time. Details of the voltage and calcium dependence for the ionic and synaptic currents and calcium dynamics are given in the Appendix.

Five hundred cells (100 STN, 300 GPe, 100 GPi) were organized in 100 functional channels by synaptic connections. The functional channel architecture was motivated by the concept of action selection, a putative function of the BG (Leblois et al. 2006; Humphries et al. 2006; Rubchinsky et al. 2003; Mink 1996; Mink and Thach 1993). However, all data (experimental and model) presented in this study were representative of the network in the rest state (i.e. no behavioral movement preparation or action). The relative nuclei population sizes were selected to preserve general histological ratios (Hardman et al. 2002). Figure 1 illustrates the connectivity template of the model, with excitatory and inhibitory connections shown in detail in two separate channels. Each STN cell sent excitatory connections to four GPi cells in neighboring channels and to the three GPe cells within its channel. Each GPe cell inhibited two STN cells in neighboring channels and the GPi cell within its channel. Each GPe cell also sent inhibition in a diffuse manner to ten other GPe cells, both within its own and in adjacent channels. This sparse, structured pattern of connection parameters allowed low frequency, clustered (checkerboard) bursting activity across the network in the absence of periodically modulated inputs (Terman et al. 2002). In addition, each STN cell received a set of cortical inputs and each pallidal cell received a set of striatal inputs.

2.2 Cortical input structure

External inputs to the network model consisted of individual, stochastic spike trains that activated excitatory synapses in STN cells (CtxSTN) and inhibitory synapses in pallidal cells (StrGPe, StrGPi). Seven independent (driven by separate stochastic processes) input synapses were included in each cell (Fig. 2(a)). Input synapses were driven by virtual spike trains that switched between two modes of firing, a low mean rate background activity and a high mean rate active phase. Switching to the active mode was determined by a timing signal corresponding to a global cortical rhythm that was maintained at 16 Hz. Every 1,000/16 ms each input synapse determined, based on a set probability (p_{syn}), whether it switched to the active phase or not. Input synapses that became active did so following a brief, random delay ($\text{mean} \pm \text{std}$ of current active phase interspike interval) and returned to the background rate at the end of a randomly determined duration (normally distributed 25 ± 5 ms). The probability of a weak response (few synapses responding) decreased as p_{syn} increased (Fig. 2(a)). Thus, the total input current to a cell with higher p_{syn} had both more frequent high amplitude episodes and a greater mean value (Fig. 2(c)). In the MPTP state, p_{syn} was set to 0.25 for all input synapses. When we later attempted to simulate a Normal state, p_{syn} was set to 0.05 for all input synapses. Values of p_{syn} were chosen to provide a contrast between Normal and MPTP input while maintaining a random quality in the input of any given cell. Background and active phase spike intervals were normally distributed depending on the state of the model being run and the particular input (StrGPe, StrGPi, CtxSTN). Parameters describing the effects of dopamine and the input spike train rates were also modified to reflect differences between the MPTP and Normal states, as further described in the Appendix.

2.3 Training algorithm

Neural network models suffer from a large number of unknown and/or unconstrained parameter values. In an attempt to develop a subthalamopallidal network model that adhered as closely as possible to *in vivo* experimentally recorded firing properties, we identified a set of parameters to be adjusted (Table 1) to provide the best possible fit to experimental outcome measures. As the training algorithm explored this parameter space, many network model instances were generated. An instance consisted of specific values for I_{ext} for each cell type along with synaptic strengths (maximal conductances) for each of the five inter- and intranuclear pathways and the

three input pathways. A final network instance was the result of running a training algorithm from randomized starting parameter values and evaluating its ability to match target values constrained by data from MPTP treated monkeys (Hashimoto et al. 2003; Wichmann and Soares 2006; Hahn et al. 2008) (Table 2). Initial parameters were obtained by randomizing an empirically defined default set. The six target data values were the population mean spike rates and bursting rates for each of the three nuclei in the model (STN, GPe and GPi).

The training algorithm (Fig. 3) was a least mean square error optimization (Press et al. 1992). Given a parameter set, the model simulation was run and the target measures were calculated and compared to the target values (Table 2). The differences were scaled, squared and summed. The square root of that sum was a score for that particular network model instance. The Jacobian matrix J of partial derivatives was numerically determined at each step and the update vector for the parameters calculated by solving the resulting linear system

$$J^T J d = -J^T F$$

where F is the vector of differences and d is the step in parameter space. Backtracking was used to insure that the new parameter step remained within limits and reduced the score. If at any time a reduction in error score was determined for a given step, the current parameter set was incremented by that amount. If no improvement in score was found for a calculated step d after backtracking, J was recalculated for the current parameter set and backtracking for the new step d was tried. After a predetermined number of calculations of J without progress (5 iterations) the parameter values were randomly shifted by a small amount, keeping track of the overall lowest score obtained from a particular starting parameter set. The process was iterated until a threshold minimum score value (scaled MSE <10) was achieved or the maximum number of iterations (75 per phase) was exceeded. Training took place in two phases; the first phase matched only population spike rates and the second phase matched the full target set. Figure 4(a, b) shows the error score for two typical, successful training trials. Each trial began with a large error in population spike rates using a randomized parameter set. During the first phase of training (spike rate match only) error decreased in a non-smooth manner. Error often increased at points where parameters were randomly bumped and at the start of the second phase (both spike and burst rate matches) and then decreased as the algorithm converged toward a solution ($\mathbf{x}_\infty$). The parameter set did not move directly toward the final minimum score set over the course of the trial (Fig. 4(c, d)). The training algorithm was applied to fifty sets of randomized starting parameters. Twenty-five sets having the lowest error scores were kept for this study (final score 150 ± 61).

2.4 DBS simulation

Electric fields resulting from current passed through STN DBS electrodes may have a variety of effects on surrounding neural tissue (Butson et al. 2007; Miocinovic et al. 2006). To simplify the network model implementation of STN DBS we focused only on the direct activation of STN efferent activity. A 136 Hz DBS timing signal was maintained in the model. During each stimulus pulse, neural elements preconfigured for activation were activated with a probability of 0.8 by sending a presynaptic event signal to their downstream target synapses.

Configuration of the stimulated STN efferent output was based on the modeling results of Miocinovic et al. (2006). For therapeutic DBS, referred to as the STN DBS state in this paper, 40% of the STN efferent output was activated. This resulted in synaptic events at each appropriate synapse (STN-GPe and STN-GPi) when the STN axon was activated. However, to be consistent with previous experimental recordings and theoretical models, these axonally generated action potentials did not antidromically invade the STN soma during STN DBS, but

instead only provided a sub-threshold current injection to the soma. In addition, somatically generated spikes (spontaneous and/or network driven) were monitored for collision block with stimulation generated spikes. Activated STN cells were chosen as a contiguous central block of the appropriate number of cells (40%=40 cells). Additional simulations were also run using a higher or lower percentage of STN efferent activation, as well as simulations where a specified percentage of STN neurons were ablated from the model as a contiguous central block.

3 Results

We constructed a subthalamopallidal network model that faithfully reproduced spike and burst activity under parkinsonian conditions. The model was connected to independent inputs with activity patterns that depended on cortical rhythms prominent in PD. Experimental data from MPTP treated monkeys was used as target values for training the synaptic weights of the network. Twenty five individual instances of the network were created and analyzed to account for variability in equally plausible networks with different connection weights. After training the model to mimic the MPTP state, we investigated the impact of altering the network input to be more representative of a Normal state. These simulations suggest that many of the subthalamopallidal firing patterns associated with parkinsonism can be attributed to inputs to the basal ganglia. Next we evaluated the effects of STN DBS and STN lesions on the network activity in the MPTP model. Consistent with previous experimental results, we found that stimulation induced a regularization of GPi activity. The model allowed us to explore this general finding further, showing that increasing the percentage of STN activated or lesioned, or increasing the frequency of stimulation, all lead to a decrease in GPi bursting.

3.1 Impact of cortical rhythms on synaptic input

The activity of each cell in the network was determined by its intrinsic characteristics as well as by internuclear connections, intranuclear connections and external inputs (cortical or striatal). The effect of inhibition by striatal inputs was examined in an isolated GPi cell disconnected from the network (Fig. 5). The full model in the MPTP or Normal state (see below) was run for one second and the total striatal synaptic input to one cell was recorded. The GPi cell was then isolated from the network by setting its STN, GPe and striatal afferent connection weights to zero. An external current was applied to restore a firing rate of approximately 70 Hz and the previously recorded striatal synaptic current was re-injected into the GPi cell. Figure 5 shows the total inhibitory synaptic current applied and its affect on the membrane voltage for the MPTP state (Fig. 5 (a)) and the Normal state (Fig. 5(b)). This process was repeated and successive one second trials were aligned to the cortical rhythm and averaged. The averaged total inhibitory synaptic current and corresponding instantaneous spiking rate were determined for the MPTP state (Fig. 5(c)) and the Normal state (Fig. 5(d)). In the MPTP state the mean inhibitory current level was greater (0.11 versus 0.06 nA), with a more pronounced modulation depth in the synaptic current (0.17 versus 0.06 nA), modulation in the mean spike rate (48 versus 66 Hz), and modulation depth of the spike rate (48 versus 24 Hz).

3.2 Population activity in the MPTP state

Experimental recordings from the GPe and GPi of MPTP treated monkeys were acquired from Hashimoto et al. (2003). Figure 6(a) shows a pseudo population spike raster consisting of one second segments taken from those experimental recordings. Each row in the experimental raster plot corresponds to a unique cell and unique trial. Contiguity of row indices (cell/trial) in the experimental raster plot is not an indication of contiguity of recordings in time or space, so correlated activity between cells cannot be addressed with the experimental data. STN rasters are not present as experimental recordings were not made in STN. The traces reveal bursts and

pauses occurring at irregular intervals in both GPe and GPi (Fig. 6(a)). Statistically identified bursts are demarcated with horizontal lines through the rasters.

Population rasters for one instance of the 500 cell network model in the MPTP state are shown for comparison with the available experimental recordings (Fig. 6(b)). High frequency spiking with bursts and pauses are evident in GPe and GPi. Transmembrane voltage traces from four GPi model cells illustrate the typical activity underlying single cells within the network model (Fig. 6(B₂)). Modulation of activity in phase with the imposed cortical rhythm is evident in STN; however, these periods of increased firing were not directly identified as bursts. In both the experimental and model data, bursting was irregular. Interestingly, the model does not show spatial synchronization of bursts between nearby channels (Fig. 6(b)) (synchronized bursts in GPe are within the same functional channel of the model). Unfortunately, such an analysis could not be performed on the experimental data because the recordings were not performed simultaneously.

Burst and spike rates in the model compared favorably with experimental data. In GPi, the mean burst and spike rates in the MPTP state of the model were 119 bursts/min and 63 Hz. Results from parkinsonian non-human primates at rest, using the same burst detection algorithm, noted 104 bursts/min and 59 Hz for GPi (Hahn et al. 2008). The good agreement between the model and experiment are not surprising given that the model was trained to reproduce these experimental values. However, the model also reproduced burst features it wasn't trained to reproduce. For example, the average GPi spike rate within detected bursts was 135 Hz in the model and 164 Hz in experiments. Between detected bursts the average GPi spike rates were 42 Hz in the model and 47 Hz in experiments. One discrepancy was that GPi bursts accounted for 61% of spikes and 28% of the total time in the model compared to 32% and 10% respectively in the experiments (Hashimoto et al. 2003; Hahn et al. 2008).

Sensitivity to perturbation in the MPTP network model was evaluated by increasing or decreasing individual connectivity parameter values by 25% (Table 3). Each of the 25 instances of the model trained to match the MPTP state was tested. The resulting rates were averaged across all instances. The first column in each row of Table 3 lists the average rate for the unperturbed case (Control value). The entries given for each condition are ratios of the rate of the perturbed model and the control value. These results illustrate the stability of the model in response to moderate perturbations of its parameters.

3.3 Effects of simulated normal inputs

A long standing debate in the PD literature has focused on whether parkinsonian firing properties recorded in the basal ganglia are the result of changes within the basal ganglia itself, or alterations to its inputs (Bevan et al. 2002). In turn, we attempted to simulate a transition in the network model from the MPTP state to a more "Normal" state by only shifting input parameters (Fig. 7). These parameters consisted of p_{syn} the probability that a given input responds to the high state of the cortical beta rhythm, the statistical properties of the external inputs themselves (mean/std), and the efficacy of BG synapses in each DA state (see Appendix for additional details). Figure 7 shows the mean spike (Fig. 7(a)) and burst (Fig. 7(b)) rates for each trained instance of the model in the MPTP ($p_{syn}=0.25$) and Normal states ($p_{syn}=0.05$). For comparison, mean and standard deviations from available experimental recordings are indicated in each panel. Averages across all instances of the model are consistent with the experimentally observed rate trends in pallidal spiking activity (Fig. 7(c), Table 4). These results show that inputs to the subthalamopallidal network can play a major role in dictating both normal and parkinsonian activity patterns.

3.4 Effects of simulated STN DBS

The MPTP state of the model was also run with the inclusion of simulated STN DBS and compared to corresponding experimental recordings from the pallidum. Figure 8(a) shows experimental recordings from GPe and GPi neurons during STN DBS (Hashimoto et al. 2003). Each row of the experimental spike rasters show data from the same cell in the corresponding row of Fig. 6(a), with the difference being that the data in Fig. 8(a) was acquired during STN DBS applied later in the same recording session. Cells that achieved a higher spike firing rate during stimulation were sorted toward the middle of the raster plot to facilitate comparison with the model results. The STN DBS state in the model was achieved by initiating spikes in the efferent output of 40% of the STN cells in a centrally positioned block (Miocinovic et al. 2006). Figure 8(b) shows one second of one instance of the entire network model while 40% of the STN was stimulated. Network channels associated with direct stimulation experienced a substantial change in both firing rate and pattern. Model cells fell into three categories, cells in channels directly stimulated, cells in channels topologically distant from the stimulated block, and cells in the border region between the other two groups where some synaptic interaction occurred. Horizontal lines through the rasters in Fig. 8 demarcate bursts and show that directly stimulated channels exhibited a strong reduction in burst firing.

Each of the 25 network model instances were run in the STN DBS state for 10 s and spike rates and burst rates were determined for each nucleus (Fig. 9(a, b)). Averages across all model instances show increases in both GPi and GPe spike firing rates and decreases in both GPi and GPe burst rates (Fig. 9(c), Table 4). Most notably the population burst rate in GPi was reduced from 119 ± 9 bursts/min in the MPTP state to 78 ± 18 bursts/min in the STN DBS state (Fig. 9(c), Table 4). For comparison, the mean and standard deviations for experimental recordings during therapeutic STN DBS are indicated for GPe and GPi in Fig. 9 (Hashimoto et al. 2003; Hahn et al. 2008). While the model did an admirable job of reproducing experimentally documented effects of STN DBS that it was not trained against, it should be noted that it failed to simulate the increase in GPe bursting observed experimentally.

In addition to burst rate, other dynamic properties of bursting spike trains were modified by DBS. The percentage of GPi spikes occurring in bursts (38%) and the percentage of time in bursts (20%) were both reduced during STN DBS relative to the MPTP state (61% spikes in bursts and 28% time in bursts). Similarly, the number of GPi spikes between bursts and the time between bursts both increased. The average burst duration decreased from 140 ms to 86 ms, and the average number of spikes per burst decreased from 20 to 12. The average GPi spike rate during bursts decreased (135 Hz to 96 Hz) and the average spike rate between bursts increased (42 Hz to 53 Hz). These results suggest that therapeutic STN DBS decreases not only the number of bursts in GPi, but also their intensity when they do occur.

Stimulation parameters and electrode position determine the activation of STN efferents during STN DBS (Miocinovic et al. 2006). Further, the frequency of stimulation is known to be an important parameter in STN DBS clinical outcomes, with the best outcomes achieved with frequencies greater than 100 Hz (Rizzzone et al. 2001). Low frequency stimulation (25–50 Hz) in the network model resulted in a smaller reduction in GPi burst rate (Fig. 10(a)). As the stimulation frequency increased the GPi burst rate fell, saturating at its lowest levels when greater than 100 Hz. Variability in these results (Fig 10(a) error bars) was due to the presence of some MPTP trained networks that did not respond to STN DBS with lower GPi burst rates (Fig. 10(b)). We also examined the affect of the size of the stimulated STN block by varying the percentage of STN efferent activation from 0 to 100% using 136 Hz pulse trains (Fig. 10(c)). The mean burst rate in GPi decreased linearly as the percentage of STN stimulated increased (Fig. 10(c)—grey bars). Similar to the stimulation frequency simulations, variability in these results was affected by data from the same network model instances that were outliers above (Fig. 10(d)).

Lesions in the subthalamic region are known to generate therapeutic benefits analogous to those achieved with STN DBS. A simple test of the effect of a lesion is to remove the output of 'lesioned' cells from the network. Eliminating increasing numbers of STN neurons from the network (Fig. 10(c)—hatched bars) reduced GPi bursting in a manner analogous to simulating increasing numbers of STN neurons with DBS. However, lesioning and DBS had opposite effects of GPi firing rate. Lesioning 40% of the STN decreased the average GPi firing rate to 53 ± 15 Hz, while stimulating 40% of the STN increased the average GPi firing rate to 84 ± 26 Hz.

4 Discussion

The primary goals of this study were: 1) present a new training algorithm for the parameterization of large-scale neural network models, 2) evaluate the effects of STN DBS on subthalamopallidal network activity, and 3) identify a basal ganglia neural activity metric that robustly correlated with therapeutic benefit from DBS. Multiple instances of the network model were obtained via a least mean square error training algorithm that parameterized the model to match firing properties of MPTP treated non-human primates. We then used the model to recreate the original experiments of Hashimoto et al. (2003) *in silico* such that all aspects of the network could be monitored simultaneously during STN DBS. Analysis of both the experimental data and our simulations suggested that reducing GPi bursting is linked to the therapeutic benefits of STN DBS (Figs. 8, 9). Therefore, we used the model to further explore GPi burst activity during alterations in STN DBS parameters, as well as STN lesions (Fig. 10). The results of these simulations further support the hypothesis that therapeutic outcomes from STN interventions are related to reducing GPi bursting.

4.1 Network model training

Neural network models suffer from a large number of unknown and/or unconstrained parameter values, and our subthalamopallidal network model is no exception. However, decades of experimental recordings in MPTP treated non-human primates have provided a gold standard for basal ganglia models to reproduce. Therefore, we set out to match the *in vivo* firing rate and burst rate characteristics of the STN, GPe, and GPi principally via adjustments in the synaptic connection weights of our network. Even though our model was constructed with a relatively simplistic and stereotyped functional channel architecture, there still existed an extremely large parameter space to search. Previous strategies to address this issue have focused on parameter sensitivity analyses to identify unique parameter sets that provide the desired network firing properties (e.g. Terman et al. 2002). However, as network models become increasingly detailed such an approach becomes intractable. Therefore, we employed a least mean square error optimization algorithm to search through the complex parameter space. Under this approach a given set of parameter values represent a model instance, the model is run and the target output measures are calculated and compared to the target experimental values. The differences are weighted, squared and summed yielding a score for that network model instance. At each step an update vector for the parameters is calculated, and the process is iterated until a threshold minimum score is achieved.

A byproduct of using a training algorithm to define network model parameters is the opportunity to create a population of equally qualified network models, where each model employs a somewhat different parameter set. This presents an opportunity to capture a fundamental feature of biological networks, intrinsic variability. For example, individual experimental subjects differ in the details of their anatomy and physiology; but on average they display common functions and/or pathologies. Likewise, our models also have multiple commonalities that underlie the general network activity. In turn, this type of numerical optimization procedure and analysis, similar in some ways to genetic algorithms, could be

useful in future studies to help identify network parameters that are of fundamental importance in creating the neural activity seen experimentally.

Our general method of training the network to match experimental data is independent of the network architecture used or the brain region under investigation. It could also be extended to match synchronization measures or other dynamic features of network output. For example, synchronization of GPi bursting has been suggested as an important feature in the pathology of parkinsonian symptoms that may be disrupted during STN DBS (Hammond et al. 2007). Acquisition of simultaneous multi-channel microelectrode recordings in behaving parkinsonian animals implanted with DBS systems will provide data necessary to address this hypothesis and further evolve the network model.

4.2 Cortical beta input

Recently, the PD research community has focused on the relationship between cortical and BG neural activity in the various frequency bands, particularly in the context of voluntary movements (Brown 2000; Kuhn et al. 2005). Within the basal ganglia, beta activity during rest increases and gamma activity decreases following administration of MPTP in non-human primates (Courtemanche et al. 2003; Raz et al. 2000). Beta activity is considered antikinetic and gamma activity prokinetic, though a detailed mechanism for this affect is lacking (Brown and Williams 2005). Our results suggest that parkinsonian activity patterns can be generated in the subthalamopallidal network by modulating its input to be coherent with beta activity. This model prediction represents an alternative viewpoint to the hypothesis that interactions between STN and GPe instigate pathological activity patterns in a dopamine depleted state (Plenz and Kital 1999; Terman et al. 2002). Interestingly, intrinsic burst patterns are possible in our general network architecture, but the parameter values reached through our training algorithm relied primarily on the descending cortico-subthalamic and striato-pallidal inputs to generate the burst statistics observed in our simulations (Fig. 7).

The cortico-basal-ganglia-thalamo-cortical network is a closed loop system with multiple sub-loops. Over the course of development of parkinsonian symptoms, dopamine loss in the striatum, pallidum and STN lead to changes in activity within these loops. It has been well documented with functional imaging (Nandhagopal et al. 2008) and electrophysiological (Galvan and Wichmann 2008) studies that cortical changes are a fundamental component of transition to the parkinsonian state. This study presents an open loop model where the dynamic relationship between BG activity and descending cortical signals is considered an input parameter to the subthalamopallidal microcircuit. We simplified the higher level influences on the subthalamopallidal microcircuit by representing its inputs as generic spike trains with oscillatory patterns based on local field potential recordings (Goldberg et al. 2004; Courtemanche et al. 2003). This approach provided a tractable method to parameterize the network model and analyze its results. However, it did not account for the subsequent return effect of the microcircuit on the cortical activity. It was therefore not possible to address the affects of thalamocortical interactions (Xu et al. 2008) or antidromic cortical activation (Li et al. 2007; Gradinaru et al. 2009) during STN DBS. Thus, an important future step in our network model development will be incorporation of cortical feedback, either through a closed-loop version of the network or by imposing a functional relationship between the output of GPi and the inputs to the model.

4.3 Deep brain stimulation

STN DBS influences numerous neural elements in the vicinity of the electrode depending on the electrode location relative to the anatomy, stimulation parameter settings, and the nature of the neural tissue surrounding the electrode (Miocinovic et al. 2006; Moks et al. 2009). In the subthalamic region this includes STN soma, STN efferents, GPe afferents, cortical

afferents, and GPi fibers of passage, just to name a few. Our simulations focused on direct stimulation of selected STN efferents that trigger synaptic events in their GPe and GPi targets. This simplifying assumption was derived from the theoretical analysis of Miocinovic et al. (2006) which identified STN efferent activation as the therapeutic stimulation target in the Hashimoto et al. (2003) experiments we attempted to simulate. Our STN DBS network model implementation reproduced many of the experimental findings of Hashimoto et al. (2003) (Figs. 6, 8, 9); however, one limitation was its failure to capture the increase in GPe bursting observed during therapeutic STN DBS (Hahn et al. 2008). The origin of this deficiency in the model remains unclear, but could be related to the open-loop structure and/or the lack of GPe antidromic activation. Another issue could have been our assumption of 80% transmission probability for stimulated STN efferents, which could be lower given the possibility of synaptic fatigue under high frequency inputs. It should also be noted that definition of the actual neural elements directly responsible for stimulation induced therapeutic benefit remain unclear, and may even be glial in origin (Bekar et al. 2008). Such questions reinforce the need to better understand the effects of DBS on network activity (McIntyre and Hahn 2010). Large-scale network models represent excellent tools to analyze the impact of directly stimulating each neural population individually to decipher their particular impact on the overall network activity. We propose that such analysis could be an important aspect of future studies, especially relative to recent results highlighting the role of cortical afferent activation in STN DBS (Li et al. 2007; Gradinaru et al. 2009).

Given the simplifying assumptions of the model, it was able to make the interesting and robust prediction that therapeutic interventions in the STN result in a common reduction in GPi burst activity (Fig. 10). This finding was consistent with the available experimental data (Fig. 9). In addition, statistical significance did not depend on the parameters of the burst detection algorithm (data not shown). Previous studies have documented that GPi burst firing increases following treatment with MPTP (Wichmann et al. 1999), and intraoperative recordings from PD patients also exhibit strong GPi burst activity (Magnin et al. 2000). Hahn et al. (2008) found that bursting in individual GPi neurons was reduced from 104 ± 8.3 bursts/min to 76 ± 10.8 bursts/min in the Hashimoto et al. (2003) monkeys during therapeutic STN DBS, while non-therapeutic stimulation did not affect GPi bursting. We used the network model to extend upon the experimental analyses and show that the decrease in GPi bursting was directly proportional to the percentage of STN stimulated or ablated (Fig. 10). This theoretical prediction highlights a common physiological effect between these two interventions known to generate similar behavioral outcomes with dramatically different effects on STN neurons. In either case the physiological significance of GPi burst firing on its thalamic targets remains unclear, but theoretical work suggests that it directly affects the ability of the thalamus to relay spikes (Rubin and Terman 2004). Interestingly, when GPi spike trains from the Hashimoto et al. (2003) monkeys, acquired during therapeutic STN DBS, were feed into thalamic relay models they overcame the deficits incurred in the parkinsonian state (Guo et al. 2008).

Defining relationships between stimulation parameter settings, the relative proportion of neurons directly stimulated, the stimulation-induced network activity, and the resulting behavioral outcomes, has potential to enhance understanding of the therapeutic mechanisms of DBS. This study represents a step in that general direction with the development of a subthalamopallidal network model useful for the evaluation of neural activity in response to clinically relevant stimulation conditions. Our results point toward controlling GPi burst activity as an important effect of DBS. We propose that this and future model predictions on DBS induced network activity patterns will enable the design of more efficacious stimulation paradigms (Feng et al. 2007; Tass 2003) that someday may be worthy of testing in human subjects (Birdno et al. 2008). As new experimental data becomes available, and modeling technology evolves, we believe it will be possible to synergistically integrate the results of systems neurophysiology with large-scale neural network models to create a realistic

representation of the cortico-basal-ganglia-thalamo-cortical circuit. The model presented in this study provides a building block and methodological path toward achieving that goal.

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References

- Alvarez L, Macias R, Pavon N, Lopez G, Rodriguez-Oroz MC, Rodriguez R, et al. Therapeutic efficacy of unilateral subthalamotomy in Parkinson's disease: results in 89 patients followed for up to 36 months. *Journal of Neurology, Neurosurgery and Psychiatry* 2009;80:979–985.
- Bekar L, Libionka W, Tian GF, Xu Q, Torres A, Wang X, et al. Adenosine is crucial for deep brain stimulation-mediated attenuation of tremor. *Nature Medicine* 2008;14:75–80.
- Bergman H, Wichmann T, Karmon B, DeLong MR. The primate subthalamic nucleus. II. Neuronal activity in the MPTP model of parkinsonism. *Journal of Neurophysiology* 1994;72:507–520. [PubMed: 7983515]
- Bevan MD, Magill PJ, Terman D, Bolam JP, Wilson CJ. Move to the rhythm: oscillations in the subthalamic nucleus-external globus pallidus network. *Trends in Neurosciences* 2002;25(10):525–31. [PubMed: 12220881]
- Birdno MJ, Kuncel AM, Dorval AD, Turner DA, Grill WM. Tremor varies as a function of the temporal regularity of deep brain stimulation. *NeuroReport* 2008;19:599–602. [PubMed: 18388746]
- Brown P. Cortical drives to human muscle: the Piper and related rhythms. *Progress in Neurobiology* 2000;60:97–108. [PubMed: 10622378]
- Brown P, Williams D. Basal ganglia local field potential activity: character and functional significance in the human. *Clinical Neurophysiology* 2005;116:2510–2519. [PubMed: 16029963]
- Brown P, Oliviero A, Mazzone P, Insola A, Tonali P, Di Lazzaro V. Dopamine dependency of oscillations between subthalamic nucleus and pallidum in Parkinson's disease. *Journal of Neuroscience* 2001;21:1033–1038. [PubMed: 11157088]
- Butson CR, Cooper SE, Henderson JM, McIntyre CC. Patient-specific analysis of the volume of tissue activated during deep brain stimulation. *Neuroimage* 2007;34:661–670. [PubMed: 17113789]
- Carnevale, NT.; Hines, ML. *The Neuron book*. Cambridge University Press; 2005.
- Cooper AJ, Stanford IM. Electrophysiological and morphological characteristics of three subtypes of rat globus pallidus neurone *in vitro*. *Journal of Physiology* 2000;527(Pt 2):291–304. [PubMed: 10970430]
- Courtemanche R, Fujii N, Graybiel AM. Synchronous, focally modulated beta-band oscillations characterize local field potential activity in the striatum of awake behaving monkeys. *Journal of Neuroscience* 2003;23:11741–11752. [PubMed: 14684876]
- Dejean C, Gross CE, Bioulac B, Boraud T. Dynamic changes in the cortex-basal ganglia network after dopamine depletion in the rat. *Journal of Neurophysiology* 2008;100:385–396. [PubMed: 18497362]
- Destexhe A, Mainen ZF, Sejnowski TJ. An efficient method for computing synaptic conductances based on a kinetic model of receptor binding. *Neural Computation* 1994a;6:10–14.
- Destexhe A, Mainen ZF, Sejnowski TJ. Synthesis of models for excitable membranes, synaptic transmission and neuromodulation using a common kinetic formalism. *Journal of Computational Neuroscience* 1994b;1:195–230. [PubMed: 8792231]
- Feng XJ, Greenwald B, Rabitz H, Shea-Brown E, Kosut R. Toward closed-loop optimization of deep brain stimulation for Parkinson's disease: concepts and lessons from a computational model. *Journal of Neural Engineering* 2007;4:L14–L21. [PubMed: 17409470]
- Galvan A, Wichmann T. Pathophysiology of parkinsonism. *Clinical Neurophysiology* 2008;119:1459–1474. [PubMed: 18467168]

- Goldberg JA, Kats SS, Jaeger D. Globus pallidus discharge is coincident with striatal activity during global slow wave activity in the rat. *Journal of Neuroscience* 2003;23:10058–10063. [PubMed: 14602820]
- Goldberg JA, Rokni U, Boraud T, Vaadia E, Bergman H. Spike synchronization in the cortex/basal-ganglia networks of Parkinsonian primates reflects global dynamics of the local field potentials. *Journal of Neuroscience* 2004;24:6003–6010. [PubMed: 15229247]
- Gradinaru V, Mogri M, Thompson KR, Henderson JM, Deisseroth K. Optical deconstruction of parkinsonian neural circuitry. *Science* 2009;324:354–359. [PubMed: 19299587]
- Guo Y, Rubin JE, McIntyre CC, Vitek JL, Terman D. Thalamocortical relay fidelity varies across subthalamic nucleus deep brain stimulation protocols in a data-driven computational model. *Journal of Neurophysiology* 2008;99:1477–1492. [PubMed: 18171706]
- Hahn PJ, Russo GS, Hashimoto T, Miocinovic S, Xu W, McIntyre CC, et al. Pallidal burst activity during therapeutic deep brain stimulation. *Experimental Neurology* 2008;211:243–251. [PubMed: 18355810]
- Hammond C, Bergman H, Brown P. Pathological synchronization in Parkinson's disease: networks, models and treatments. *Trends in Neurosciences* 2007;30:357–364. [PubMed: 17532060]
- Hardman CD, Henderson JM, Finkelstein DI, Horne MK, Paxinos G, Halliday GM. Comparison of the basal ganglia in rats, marmosets, macaques, baboons, and humans: volume and neuronal number for the output, internal relay, and striatal modulating nuclei. *Journal of Comparative Neurology* 2002;445:238–255. [PubMed: 11920704]
- Hashimoto T, Elder CM, Okun MS, Patrick SK, Vitek JL. Stimulation of the subthalamic nucleus changes the firing pattern of pallidal neurons. *Journal of Neuroscience* 2003;23:1916–1923. [PubMed: 12629196]
- Humphries MD, Stewart RD, Gurney KN. A physiologically plausible model of action selection and oscillatory activity in the basal ganglia. *Journal of Neuroscience* 2006;26:12921–12942. [PubMed: 17167083]
- Kuhn AA, Trottenberg T, Kivi A, Kupsch A, Schneider GH, Brown P. The relationship between local field potential and neuronal discharge in the subthalamic nucleus of patients with Parkinson's disease. *Experimental Neurology* 2005;194:212–220. [PubMed: 15899258]
- Leblois A, Boraud T, Meissner W, Bergman H, Hansel D. Competition between feedback loops underlies normal and pathological dynamics in the basal ganglia. *Journal of Neuroscience* 2006;26:3567–3583. [PubMed: 16571765]
- Li S, Arbuthnott GW, Jutras MJ, Goldberg JA, Jaeger D. Resonant antidromic cortical circuit activation as a consequence of high-frequency subthalamic deep-brain stimulation. *Journal of Neurophysiology* 2007;98:3525–3537. [PubMed: 17928554]
- Magnin M, Morel A, Jeanmonod D. Single-unit analysis of the pallidum, thalamus and subthalamic nucleus in parkinsonian patients. *Neuroscience* 2000;96:549–564. [PubMed: 10717435]
- Maks CB, Butson CR, Walter BL, Vitek JL, McIntyre CC. Deep brain stimulation activation volumes and their association with neurophysiological mapping and therapeutic outcomes. *Journal of Neurology, Neurosurgery and Psychiatry* 2009;80:659–666.
- McIntyre CC, Hahn PJ. Network perspectives on the mechanisms of deep brain stimulation. *Neurobiology of Disease*. 2010.1016/j.nbd.2009.09.022
- Mink JW. The basal ganglia: focused selection and inhibition of competing motor programs. *Progress in Neurobiology* 1996;50:381–425. [PubMed: 9004351]
- Mink JW, Thach WT. Basal ganglia intrinsic circuits and their role in behavior. *Current Opinion in Neurobiology* 1993;3:950–957. [PubMed: 8124079]
- Miocinovic S, Parent M, Butson CR, Hahn PJ, Russo GS, Vitek JL, et al. Computational analysis of subthalamic nucleus and lenticular fasciculus activation during therapeutic deep brain stimulation. *Journal of Neurophysiology* 2006;96:1569–1580. [PubMed: 16738214]
- Modolo J, Henry J, Beuter A. Dynamics of the Subthalamopallidal Complex in Parkinson's Disease During Deep Brain Stimulation. *Journal of biological physics* 2008;34:251–266. [PubMed: 19669474]
- Montgomery EB Jr, Baker KB. Mechanisms of deep brain stimulation and future technical developments. *Neurological Research* 2000;22:259–266. [PubMed: 10769818]

- Nambu A, Llinas R. Electrophysiology of globus pallidus neurons *in vitro*. *Journal of Neurophysiology* 1994;72:1127–1139. [PubMed: 7807199]
- Nandhagopal R, McKeown MJ, Stoessl AJ. Functional imaging in Parkinson disease. *Neurology* 2008;70:1478–1488. [PubMed: 18413571]
- Nini A, Feingold A, Slovin H, Bergman H. Neurons in the globus pallidus do not show correlated activity in the normal monkey, but phase-locked oscillations appear in the MPTP model of parkinsonism. *Journal of Neurophysiology* 1995;74:1800–1805. [PubMed: 8989416]
- Otsuka T, Abe T, Tsukagawa T, Song WJ. Conductance-based model of the voltage-dependent generation of a plateau potential in subthalamic neurons. *Journal of Neurophysiology* 2004;92:255–264. [PubMed: 15212440]
- Phillips MD, Baker KB, Lowe MJ, Tkach JA, Cooper SE, Kopell BH, et al. Parkinson disease: pattern of functional MR imaging activation during deep brain stimulation of sub-thalamic nucleus—initial experience. *Radiology* 2006;239:209–216. [PubMed: 16567487]
- Plenz D, Kital ST. A basal ganglia pacemaker formed by the subthalamic nucleus and external globus pallidus. *Nature* 1999;400:677–682. [PubMed: 10458164]
- Press, WH.; Teukolsky, SA.; Vetterling, WT.; Flannery, BP. Numerical recipes in C, The art of scientific computing. 2. Cambridge University Press; 1992.
- Raz A, Vaadia E, Bergman H. Firing patterns and correlations of spontaneous discharge of pallidal neurons in the normal and the tremulous 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine vervet model of parkinsonism. *Journal of Neuroscience* 2000;20:8559–8571. [PubMed: 11069964]
- Rizzone M, Lanotte M, Bergamasco B, Tavella A, Torre E, Faccani G, et al. Deep brain stimulation of the subthalamic nucleus in Parkinson's disease: effects of variation in stimulation parameters. *Journal of Neurology, Neurosurgery and Psychiatry* 2001;71:215–219.
- Rubchinsky LL, Kopell N, Sigvardt KA. Modeling facilitation and inhibition of competing motor programs in basal ganglia subthalamic nucleus-pallidal circuits. *Proc Natl Acad Sci USA* 2003;100:14427–14432. [PubMed: 14612573]
- Rubin JE, Terman D. High frequency stimulation of the subthalamic nucleus eliminates pathological thalamic rhythmicity in a computational model. *Journal of Computational Neuroscience* 2004;16:211–235. [PubMed: 15114047]
- Sharott A, Magill PJ, Bolam JP, Brown P. Directional analysis of coherent oscillatory field potentials in the cerebral cortex and basal ganglia of the rat. *Journal of Physiology* 2005a;562:951–963. [PubMed: 15550466]
- Sharott A, Magill PJ, Harnack D, Kupsch A, Meissner W, Brown P. Dopamine depletion increases the power and coherence of beta-oscillations in the cerebral cortex and subthalamic nucleus of the awake rat. *European Journal of Neuroscience* 2005b;21:1413–1422. [PubMed: 15813951]
- Shils JL, Mei LZ, Arle JE. Modeling parkinsonian circuitry and the DBS electrode. II. Evaluation of a computer simulation model of the basal ganglia with and without subthalamic nucleus stimulation. *Stereotactic and Functional Neurosurgery* 2008;86:16–29. [PubMed: 17881885]
- Soares J, Kliem MA, Betarbet R, Greenamyre JT, Yamamoto B, Wichmann T. Role of external pallidal segment in primate parkinsonism: comparison of the effects of 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine-induced parkinsonism and lesions of the external pallidal segment. *Journal of Neuroscience* 2004;24:6417–6426. [PubMed: 15269251]
- Tass PA. A model of desynchronizing deep brain stimulation with a demand-controlled coordinated reset of neural subpopulations. *Biological Cybernetics* 2003;89:81–88. [PubMed: 12905037]
- Terman D, Rubin JE, Yew AC, Wilson CJ. Activity patterns in a model for the subthalamopallidal network of the basal ganglia. *Journal of Neuroscience* 2002;22:2963–2976. [PubMed: 11923461]
- Wichmann T, Soares J. Neuronal firing before and after burst discharges in the monkey basal ganglia is predictably patterned in the normal state and altered in parkinsonism. *Journal of Neurophysiology* 2006;95:2120–2133. [PubMed: 16371459]
- Wichmann T, Bergman H, Starr PA, Subramanian T, Watts RL, DeLong MR. Comparison of MPTP-induced changes in spontaneous neuronal discharge in the internal pallidal segment and in the substantia nigra pars reticulata in primates. *Experimental Brain Research* 1999;125:397–409.
- Xu W, Russo GS, Hashimoto T, Zhang J, Vitek JL. Subthalamic nucleus stimulation modulates thalamic neuronal activity. *J Neurosci* 2008;28:11916–11924. [PubMed: 19005057]

Appendix

The network model was composed of single compartment, conductance based neuron models. The membrane voltage of each single cell was evaluated in the NEURON simulation environment (v5.8). Action potentials were detected and postsynaptic cells were notified following a set delay that a presynaptic event occurred. Source code for the published network model is available on the NeuronDB database.

Membrane currents

The active currents included in the single cell models followed a basic Hodgkin-Huxley paradigm. The individual channel kinetics were based on the formulation described in Otsuka et al. (2004), and parameters were defined to reproduce the *in vitro* firing properties of isolated rodent neurons (Otsuka et al. 2004; Nambu and Llinas 1994; Cooper and Stanford 2000). Corresponding intracellular current-clamp and voltage-clamp recordings from primates do not exist, so we used the next most appropriate animal model. However, we believe this is a relatively minor issue, as isolated neurons of the basal ganglia are typically tonic firers with highly consistent pacemaker activity. We propose that the vast majority of the modulation seen *in vivo* is the result of network interactions, and as such we elected to concentrate on the network influence of neural activity rather than the possible nuances of interspecies channel kinetic differences. The maximum conductances for the STN and pallidal models are given in Table 5.

$$\begin{aligned}
 I_{Na} &= g_{Na} m^3 h (V_m - E_{Na}) \\
 I_{Kdr} &= g_{Kdr} n^4 (V_m - E_K) \\
 I_{AHP} &= g_{AHP} r^2 (V_m - E_K) \\
 I_A &= g_A a^2 b (V_m - E_K) \text{ (STN only)} \\
 I_T &= g_T p^2 q (V_m - E_{Ca}) \\
 I_L &= g_L c^2 d_1 d_2 (V_m - E_{Ca}) \text{ (STN only)} \\
 I_{leak} &= g_{leak} (V_m - E_{leak})
 \end{aligned}$$

The gating variables follow first order dynamics of the form

$$\frac{dx}{dt} = \frac{x_{\infty}(V_m) - x}{\tau_x(V_m)}$$

where $x_{\infty}(V_m) = \left[1 + \exp\left(\frac{V_m - \theta_{\infty,x}}{\sigma_{\infty,x}}\right) \right]^{-1}$ and

$$\tau_{\infty}(V_m) = \tau_{0,x} + \tau_{1,x} \left[1 + \exp\left(-\frac{V_m - \theta_{1,x}}{\sigma_{1,x}}\right) \right]^{-1} + \tau_{2,x} \left[\exp\left(-\frac{V_m - \theta_{2,x}}{\sigma_{2,x}}\right) \right]$$

Tables 6 and 7 list the values of the parameters for the STN and pallidal model kinetics. The steady state activation value for the calcium dependent potassium current (r_{∞}) and the inactivation value for L-type calcium current ($d_{2,\infty}$) were functions of calcium level (Ca_i), rather than membrane voltage.

Calcium dynamics

Calcium level (Cai) follows the equation

$$\frac{dCai}{dt} = \varepsilon_{Ca} \left(-\frac{I_T + I_L}{2F} - k_{Ca} Cai \right)$$

The variable Cai was not meant to be a uniform intracellular calcium concentration. Rather, it was the calcium available at or near membrane bound potassium channels. Cai was increased by calcium currents (negative inward by convention) and decreased by calcium pumps. The constant ε_{Ca} represents the combined effects of intracellular calcium buffering mechanisms and cellular geometry and F is Faraday's constant. The constant k_{Ca} is the calcium pump rate. For all simulations $\varepsilon_{Ca}=337.1$ and $k_{Ca}=.2/\varepsilon_{Ca}$.

Synaptic currents

Synaptic currents were modeled by the equation $I_{syn} = R(V_m - E_{rev})$ where R is an activation level and E_{rev} is the reversal potential (0 for AMPA and -80 for GABA synapses) (Destexhe et al. 1994a,b). Each synapse received events from its presynaptic cells. The conductance of the synapse increased exponentially toward the maximum conductance (g_{SrcTar} set for each pathway) following a presynaptic event, and decreased exponentially following a set time (t_{rise}) during which no presynaptic events occurred. If multiple events occurred within a short period of time, R did not decay back to 0 and therefore reached levels closer to g_{SrcTar} . The synapse could be thought of as having two states, "ON", where $\frac{dR}{dt} = \alpha(R_{max} - R)$ and "OFF", where $\frac{dR}{dt} = -\beta R$ and the initial condition was taken as R at the time of the last spike. This scheme was implemented as a continuous function dependent on the time of the last spike and the count of spikes occurring within a recent interval corresponding to the rise time of the synaptic current ($t_{rise}=3$).

Affects of DA level

Changing DA level from the MPTP state to the Normal state effected three parameters for each pathway in the network model, namely p_{syn} and mean background interspike interval for input pathways, as well as scaling of maximal conductance for most BG pathways. The value of p_{syn} was 0.25 in the MPTP state and 0.05 in the Normal state, as described in Methods. The mean interspike interval increased from 75 in the MPTP state to 100 in the Normal state in the CtxSTN and StrGPe pathways. The mean interspike interval decreased from 150 in the MPTP state to 100 in the Normal state in the StrGPi pathway. DA level has also been modeled as a scaling factor multiplying maximal synaptic conductances in BG (Humphries et al. 2006). Accordingly, a multiplicative factor for maximal synaptic conductances decreased from 1.25 in the MPTP state to 1.0 in the Normal state for the CtxSTN, StrGPe, GPeSTN and GPeGPi pathways and increased from 1.25 to 2.0 in the STNGPe pathway. These changes enabled the model to more closely follow the cortical beta rhythm in the low DA state.

Fig. 1. Subthalamopallidal network architecture. The excitatory connections are shown on the left (functional column 2), and inhibitory connections are shown on the right. Inputs to the model are shown as excitatory cortical inputs to STN and inhibitory striatal inputs to GPe and GPI

Fig. 2.

Network input properties. **(a)** Each cell receives seven external synaptic inputs that are stochastically determined by a common excitatory cortical rhythm. $p(i,j)$ is the probability that input j to cell i responds on any given cycle of the cortical rhythm with an strong increase in activity level. **(b)** Cumulative probability of response magnitude. The probability of a weak response during an excitatory cortical phase decreases as p increases. Each curve corresponds to a value of p (the probability of a single synapse responding strongly) ranging from 0.05 to 0.55 in steps of 0.1. **(c)** Examples of total excitatory cortical synaptic input over time in an individual STN cell for three levels of p

Fig. 3. Training algorithm. The training algorithm takes an initial randomized parameter vector ($\mathbf{x} \in \mathbf{R}^m$) through a series of steps to minimize the error between the model output values ($\mathbf{y} \in \mathbf{R}^n$) and target values ($\mathbf{y}_T \in \mathbf{R}^n$). Each step in parameter space is determined by the numerical approximation of partial derivatives of the system

Fig. 4.

Network training examples. Columns represent the training of two of the 25 model instances used in the Results. **(a, c)** Error ($\|\mathbf{y} - \mathbf{y}_T\|$) is reduced in a non-smooth manner through the two phases of training in each trial (open circle—step taken, filled circle—no improvement, star—random bump). The first phase of training considered only spike rates, the second phase of training (*identified by black overline*) considered both spike rates and burst rates. **(b, d)** As the algorithm takes steps through parameter space, the distance between the current parameter vector and the final parameter vector for that instance of the model ($\|\mathbf{x} - \mathbf{x}_\infty\|$) increases and decreases, eventually reaching zero

Fig. 5.

Single GPi neuron model. Neural response to varying levels of cortico-striatal input. **(a, c)** Inputs derived from the MPTP ($p=.25$) state of the network. **(b, d)** Inputs derived from the Normal ($p=.05$) state of the network. **(a, b)** Upper trace shows the transmembrane voltage and lower trace shows total synaptic current to the GPi neuron from a single trial. **(c, d)** One second traces were aligned on the phase of the cortical rhythm and averaged over many trials (smoothed with 20 ms sliding window). The upper trace shows the instantaneous spiking rate and the lower trace shows total synaptic current to the GPi neuron

Fig. 6. Modeling the MPTP state. Raster diagrams show spike times as small vertical hashes. In each row, detected bursts are indicated by horizontal lines through the corresponding burst spikes for that cell. **(a)** Population raster approximations for experimental data. Each row (1 s duration) corresponds to spike times taken from segments of separate experimental recordings (GPe or GPi) from MPTP treated monkeys (Hashimoto et al. 2003). A₂ expands 500 ms of the four cells indicated. **(b)** Population spike time rasters for one second of activity from the network model in the MPTP state. B₂ illustrates the transmembrane voltage for 500 ms of the four cells indicated

Fig. 7.

Comparison of MPTP and Normal states. **(a)** Spike rate and **(b)** burst rate shifts in response to changes in input parameters from the MPTP to Normal state. Each point represents population means for an individual instance of the network model. The target value used for training the network to the MPTP state is indicated by a triangle on each left axis. The mean and standard deviation of the spike and burst rates from normal and MPTP monkeys are displayed (*gray markers and error bars*—Wichmann and Soares (2006); *black markers and error bars*—Hahn et al. (2008)). **(c)** The mean and standard deviation for spike (C_1) and burst (C_2) rates across all instances of the BG network in MPTP (*open box*) and Normal (*grey box*) states

Fig. 8.

Modeling the STN DBS state. Raster diagrams show spike times as small vertical hashes. In each row, detected bursts are indicated by horizontal lines through the corresponding burst spikes for that cell. **(a)** Population raster approximations from experimental data. Each row (1 s duration) corresponds to spike times taken from a separate experimental recording (GPe or GPi) from MPTP treated monkeys during STN DBS (Hashimoto et al. 2003). **(b)** Population rasters for one second of network model activity during STN DBS condition. STN cells with directly stimulated efferent output are indicated by a vertical bar

Fig. 9.

Comparison of MPTP and STN DBS states. **(a)** Spike rate and **(b)** burst rate shifts for the model in MPTP state with simulated STN DBS. Each point represents population means for an individual instance of the network model. The target value used for training the network to the MPTP state is indicated by a triangle on each left axis. The mean and standard deviation of the spike and burst rates from MPTP monkeys are displayed (*gray markers and error bars*—Wichmann and Soares (2006); *black markers and error bars*—Hahn et al. (2008)). **(c)** The mean and standard deviation for spike (C_1) and burst (C_2) rates across all instances of the network model before (*open box*) and during (*grey box*) simulated STN DBS

Fig. 10.

GPI burst rate changes. **(a)** Population mean burst rate (averaged from all 25 model instances) in GPI as a function of STN DBS frequency. **(b)** Average GPI burst rate from each model instance during STN DBS. **(c)** Population mean burst rate (averaged from all 25 model instances) in GPI as a function of the percentage of the STN neuron population directly stimulated (*grey bars*) or lesioned (*hatched bars*). **(d)** Average GPI burst rate from each model instance during STN DBS. Color coding for the model instances is consistent for **(b)** and **(d)**

Table 1Trained values (MPTP state, $n=25$)

iExtSTN	0.0252 ± 0.0042
iExtGPe	0.0425 ± 0.0071
iExtGPi	0.0937 ± 0.0185
gSTNGPi	0.0226 ± 0.0031
gGPeGPi	0.0131 ± 0.001
gSTNGPe	0.0601 ± 0.003
gGPeGPe	0.0017 ± 0.0002
gGPeSTN	0.0125 ± 0.0012
gCtxSTN	0.0116 ± 0.0004
gStrGPe	0.0024 ± 0.0005
gStrGPi	0.0028 ± 0.0005

Table 2

Training target values

Spike rate (Hz)	STN	30
	GPe	50
	GPI	70
Burst rate (bursts/min)	STN	60
	GPe	120
	GPI	120

Table 3

Sensitivity analysis ($n=25$)

	Control	1	2	3	4	5	6	7	8	
+25% →										
Spike rate (Hz)	STN	28.3±1.6	0.99	1.00	1.01	1.02	1.00	1.09	1.01	1.000
	GPe	50.4±3.4	1.15	1.00	1.03	0.95	1.00	1.06	0.96	1.00
	GPI	63.1±2.8	0.98	1.17	1.02	1.03	0.95	1.02	1.02	0.96
Burst rate (Hz)	STN	49.9±8.6	1.08	1.03	1.21	0.96	1.02	1.01	0.99	1.02
	GPe	94.7±9.3	1.14	1.01	1.01	0.98	1.01	1.06	1.00	1.01
	GPI	118.9±9.0	1.03	1.02	0.98	0.98	1.08	1.06	1.00	1.02
-25% →										
Spike rate (Hz)	STN	29.0±1.7	1.02	1.00	1.02	0.98	1.00	0.91	0.99	1.00
	GPe	40.8±3.3	0.81	1.00	0.99	1.04	1.00	0.94	1.04	1.00
	GPI	67.1±2.8	1.06	0.83	0.98	0.97	1.10	0.98	0.98	1.04
Burst rate (Hz)	STN	43.4±12.9	0.87	1.03	0.72	1.05	1.02	1.06	1.05	1.02
	GPe	80.4±14.6	0.85	1.02	0.95	1.05	1.01	0.96	1.02	1.01
	GPI	111.6±14.7	0.94	0.98	0.99	1.04	0.88	0.96	1.02	1.00
gSTNGPe, 2 gSTNGPi, 3 gGPeSTN, 4 gGPeGPe, 5 gGPeGPI, 6 gCuxSTN, 7 gStrGPe, 8 gStrGPI										

1 gSTNGPe, 2 gSTNGPi, 3 gGPeSTN, 4 gGPeGPe, 5 gGPeGPe, 6 gCuxSTN, 7 gStrGPe, 8 gStrGPI

Table 4Population rates ($n=25$)

		MPTP state	Normal state	STN DBS state
Spike rate (Hz)	STN	28±1.6	21±1.4	20±1.8
	GPe	50±3.4	61±7.1	82±6.7
	GPI	63±2.8	61±8.4	90±25.8
Burst rate (bursts/min)	STN	50±8.7	67±12.1	30±5.5
	GPe	95±9.3	123 ±24.9	53±6.8
	GPI	119±9.0	108±17.5	78±18.6

Table 5

Maximal conductances

	STN	GPx
g_{Na}	49e-3	40e-3
g_{Kdr}	57e-3	4.2e-3
g_{AHP}	0.7e-3	0.1e-3
g_a	5e-3	
g_T	5e-3	6.7e-5
g_L	15e-3	
g_{leak}	.29e-3	4e-5

Table 6

STN kinetic parameters

	θ_{∞}	σ_{∞}	τ_0	τ_1	τ_2	θ_1	θ_2	σ_1	σ_2
m	-40	-8	0.2	3	0	-53		-0.7	
h	-45.5	6.4	0	24.5	1	-50	-50	-15	16
n	-41	-14	0	11	1	-40	-40	-40	50
r	1.7e-4	-8e-5	2	0	0				
a	-45	-14.7	1	1	0	-40		-0.5	
b	-90	7.5	0	200	1	-60	-40	-30	10
p	-56	-6.7	5	0.33	1	-27	-102	-10	15
q	-85	5.8	0	400	1	-50	-50	-15	16
c	-30.6	-5	45	10	1	-27	-50	-20	15
d1	-60	7.5	400	500	1	-40	-20	-15	20
d2	1e-4	2e-5	130	0	0				

Table 7

GPx kinetic parameters

	θ_{∞}	σ_{∞}	τ_0	τ_1	τ_2	θ_1	θ_2	σ_1	σ_2
m	-38	-7	0.001	0.1	0	-53		-0.7	
h	-45.5	6.4	0	4.5	1	-50	-50	-15	16
n	-42	-14	0	2.4	1	-40	-40	-40	50
r	1.7e-4	-8e-5	2	0	0				
p	-56	-6.7	5	0.33	1	-27	-102	-10	15
q	-85	5.8	0	400	1	-50	-50	-15	16