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Axonal and synaptic failure suppress the transfer of firing rate oscillations, synchrony and information during high frequency deep brain stimulation

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Abstract

High frequency deep brain stimulation (DBS) of the subthalamic nucleus (STN) is a widely used treatment for Parkinson's disease, but its effects on neural activity in basal ganglia circuits are not fully understood. DBS increases the excitation of STN efferents yet decouples STN spiking patterns from the spiking patterns of STN synaptic targets. We propose that this apparent paradox is resolved by recent studies showing an increased rate of axonal and synaptic failures in STN projections during DBS. To investigate this hypothesis, we combine in vitro and in vivo recordings to derive a computational model of axonal and synaptic failure during DBS. Our model shows that these failures induce a short term depression that suppresses the synaptic transfer of firing rate oscillations, synchrony and rate-coded information from STN to its synaptic targets. In particular, our computational model reproduces the widely reported suppression of parkinsonian β oscillations and synchrony during DBS. Our results support the idea that short term depression is a therapeutic mechanism of STN DBS that works as a functional lesion by decoupling the somatic spiking patterns of STN neurons from spiking activity in basal ganglia output nuclei.

Keywords

Parkinson's disease; Deep brain stimulation; Axonal failure; Synaptic failure; Short term depression; Beta oscillations

1. Introduction

High frequency deep brain stimulation (DBS) of the subthalamic nucleus (STN) is a widely used treatment for Parkinson's disease (PD), but its therapeutic mechanisms are not fully understood. An early hypothesis posited that DBS acts as an effective lesion by suppressing

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STN firing and thereby blocking the transmission of pathological spiking activity from STN to basal ganglia output nuclei. This hypothesis was supported by clinical observations that DBS has similar therapeutic outcomes for PD patients as lesions and is also supported by evidence that DBS decouples neural activity in STN from activity in globus pallidus (GP) [54]. However, a growing wealth of evidence shows that DBS does not block STN synaptic output, but contrarily increases the synaptic excitation of STN efferents by eliciting action potentials along STN axons [34,47,41,52,74,11,55,59]. This raises the question of how, or whether, DBS in STN blocks the transmission of pathological spiking activity from STN to basal ganglia output nuclei. We propose that this question is answered by recent studies showing that increased activation of STN axons during DBS elicits a form of short term depression believed to arise from a combination of axonal and synaptic failures [65,78,55,2], consistent with similar findings during high frequency stimulation in other brain regions [4,35,3,46,19,51,10,37,21]. Theoretical studies and empirical studies in other brain systems show that short term depression can suppress the synaptic transfer of low frequency oscillations, information and synchrony during periods of increased presynaptic spiking [1,27,29,44,50,63,62], and experimental evidence suggests these effects can suppress the synaptic transfer of parkinsonian activity patterns during DBS [3,2]. In this article, we systematically explore the hypothesis that DBS-induced axonal and synaptic failure produce short term depression that can suppress the synaptic transfer of pathological spiking patterns from STN to basal ganglia output nuclei while still producing an increase of total STN synaptic output during DBS.

We begin by deriving a model of axonal and synaptic failure from in vitro recordings of rodent substantia nigra during DBS in STN. We use this model to demonstrate that DBS-induced short term depression can suppress the transfer of firing rate oscillations and information from STN to efferent brain regions even though the synaptic excitation of these regions by STN increases during DBS. Next, we present in vivo primate data that provides evidence of short term depression in the primate subthalamopallidal pathway during DBS in STN, consistent with previous findings [55]. We combine our model of axonal and synaptic failure with a model of the subthalamopallidal pathway and use the model to show that DBS-induced short term depression suppresses the transfer of pathological spiking patterns from STN to pallidus and can account for the widely reported suppression of parkinsonian β oscillations and synchrony in GP during DBS [49,76,54,75,8,39,20].

Our results support the previously posed hypothesis that DBS in STN modifies spiking patterns of basal ganglia output nuclei [53,72,30,64,25,49,31,17,2,59], but we argue that these patterns are modified by short term depression arising from axonal and synaptic failures. The therapeutic effects of lesions in STN and GP, studies from PD patients receiving pharmacological treatments, and studies from PD patients and 1-methyl-4-phenyl-1,2,3,6-tetra-hydropyridine (MPTP) treated primates receiving DBS together support the notion that suppressing the transfer of pathological activity from STN to basal ganglia output nuclei can alleviate motor symptoms of Parkinson's disease [32,40,39]. Thus, our results support the hypothesis that short term depression arising from axonal and synaptic failures is a major therapeutic mechanism of DBS for PD.

2. Materials and methods

2.1. Experimental methods - in vitro rodent data

Methods for collection of in vitro data reported in Fig. 1 have been described in detail in [78], and we give an overview of the methods here. Extracellular field potential recordings and whole-cell voltage-clamp recordings of dopaminergic neurons in SNc were performed in parasagittal brain slices (350 μ m thick) containing the basal ganglia circuits from juvenile Wistar rats. All procedures for slice preparation were carried out according to the guidelines

of and with the approval of the local government. Slices for recordings were submerged in warm ($3\pm1^{\circ}\text{C}$) artificial cerebrospinal fluid (aCSF) containing (in mM) 125 NaCl, 3 KCl, 2 CaCl_2 , 2 MgCl_2 , 1.25 NaH_2PO_4 , 25 NaHCO_3 and 10 D-glucose, gassed with 95% O_2 - 5% CO_2 (pH 7.4). Patch pipettes were filled with (in mM) 135 K-gluconate, 5 HEPES, 3 MgCl_2 , 5 EGTA, 2 Na_2ATP , 0.3 NaGTP , 4 NaCl (pH 7.3). Extracellular recording pipettes were filled with modified aCSF to avoid pH change. Constant current pulses (pulse width 60-90 μs) were delivered to a bipolar electrode positioned in STN to evoke postsynaptic currents (PSCs) in dopaminergic neurons or field potentials (both axonal and synaptic responses) in SNc. After establishing baseline recording at 0.1 Hz stimulation, high frequency DBS was simulated using 130 Hz stimulation. The portions of the field potential representing stimulation-induced axonal action potentials, termed fiber volleys (FVs), occurred within a few milliseconds of each stimulation pulse and were isolated by recording in the presence of the ionotropic glutamate receptor antagonist kynurenic acid (2 mM) and GABA_A receptor antagonist picrotoxin (100 μM) in low calcium aCSF (0.2 mM CaCl_2 / 3.8 mM MgCl_2) to abrogate synaptic responses. Signals were filtered at 1 kHz and sampled at 10 kHz using either an Axopatch 200 amplifier in conjunction with Digidata 1200 interface and pClamp 9.2 software or a Multiclamp 700B amplifier in conjunction with Digidata 1440A interface and pClamp 10 software (all from Molecular Devices).

2.2. Experimental methods - in vivo primate data

2.2.0.1. Animals—Two monkeys (*Macaca mulatta*; A, male 15 kg; B, male 8.2 kg) were used in this study. All aspects of animal care were in accord with the National Institutes of Health Guide for the Care and Use of Laboratory Animals, the PHS Policy on the Humane Care and Use of Laboratory Animals, and the American Physiological Society's Guiding Principles in the Care and Use of Animals. All procedures were approved by the University of Pittsburgh animal care and use committee.

2.2.0.2. Surgery—Many of the surgical methods employed here have been described previously [16]. Animals were anesthetized using Isoflurane. Recordings were performed unilaterally in both monkeys. All recordings from Monkey A were performed in the right hemisphere, while all recordings from Monkey B were performed in the left hemisphere. In Monkey B, two cylindrical titanium recording chambers (18 mm inside diameter) were affixed over craniotomies at stereotaxic coordinates to allow access to the left globus pallidus via a coronal approach and the left subthalamic nucleus via a parasagittal approach. In Monkey A, a single recording chamber was affixed over a craniotomy to allow access to the right subthalamic nucleus and pallidum via a parasagittal approach. The chambers and head fixation devices were fixed to the skull via bone screws and methyl methacrylate polymer. Prophylactic antibiotics and analgesics were administered post-surgically.

2.2.0.3. Implantation of indwelling DBS electrode and DBS parameters—The methods used to locate the STN and implant an indwelling macroelectrode have been described previously [70]. In short, the chamber coordinates of the STN were located using standard microelectrode mapping. STN neurons exhibit a characteristic high frequency firing pattern that contrasts sharply with the relative silence of the neurons and fibers of the zona incerta and internal capsule, which border the STN dorsally and ventrally. The boundaries of the STN were thus delineated.

Custom-built stimulating electrodes were implanted in the left STN of Monkey B and the right STN of Monkey A via the sagittal chamber using a protective guide cannula (28-gauge inside diameter) and stylus mounted in the microdrive. The proximal ends were led through a port in the side of the cranial chamber and soldered to a head-mounted connector. Stimulation was delivered using an isolated constant-current stimulator (Model 2100, A-M

Systems, Carlsborg, WA). The threshold stimulation current (1 second stimulation at 150 Hz, symmetric biphasic pulses, 60 μ s duration) for evoking movement or palpable muscle contraction was determined. Stimulation at currents up to 67% of this value, namely 200 μ A (still at 150 Hz with 60 μ s duration), were used in subsequent experiments in order to stimulate the largest volume of STN possible without directly activating the internal capsule.

Stimulating electrodes were custom built as described in detail previously [70,46,57]. The electrode consisted of three Teflon-insulated Pt-Ir micro-wires (50 μ m diameter) glued inside of a stainless steel cannula (0.5 mm separation between the distal ends of the microwires). The insulation was stripped from about 0.2 mm of the distal ends of the microwire such that the impedance of the wires was approximately 10-100 kOhm (exposed surface area 0.03 mm²).

2.2.0.4. Data acquisition and artifact subtraction—Much of the data acquisition and artifact subtraction process has been described previously [46]. In brief, the extracellular activity of isolated pallidal neurons was recorded using glass-insulated tungsten microelectrodes (0.5-1.5 M *Omega*, Alpha Omega Engineering) mounted in a hydraulic microdrive (Narishige International, Tokyo, Japan). Data were passed through a low-gain headstage (gain=4X, 2 Hz to 7.5 kHz band-pass), digitized at 24 kHz (16-bit resolution; Tucker Davis Technologies [TDT], Alachua, FL) and saved to disk as continuous data. During high frequency DBS, on-line signal processing (TDT) was used to adaptively subtract large stimulation-induced electrical artifacts from the digitized neuronal data [46].

2.2.0.5. Recording protocol—Pallidal neurons were identified by their characteristic high frequency mean firing rates and short duration action potentials [15,69]. Neurons of the globus pallidus internus (GPi) were distinguished from globus pallidus externus (GPe) neurons by a distinct lack of pauses, as well as their location along the recording track [15]. Once the discharge of a single pallidal unit was isolated stably, a short train (<5 s) of high-frequency DBS stimulation was delivered to train the artifact subtraction system.

Throughout the period of data collection the monkeys performed a choice reaction time reaching task that has been described in detail elsewhere [22]. Although the task is irrelevant to the specific questions addressed here, use of a task allowed us to collect data over long periods of time during a relatively consistent behavioral state. The task required the animal to move its hand from a start position at the animal's side to one of two possible target locations in response to visual instruction cues. Correct performance was rewarded by delivery of a small bolus of pureed food. During data collection, the animals spent the majority of time (89% of a data collection period) with the hand at rest either at the start position (59% of time, waiting for a visual go cue), or at the target position (30%, waiting for reward delivery). The remainder of time was spent moving the hand to a target (3%) or returning the hand to the start position (8%). Neuronal data and behavioral event codes were collected using a standard recording protocol in which 20 behavioral trials (mean 5.3 s per trial) were performed without STN stimulation, followed immediately by 20 behavioral trials performed during DBS stimulation. This set of 40 total trials (mean duration, 213.6 s) constituted one block. Ideally, data were collected over the course of 3 such blocks; however, data collection was halted if unit isolation deteriorated.

2.2.0.6. Offline analysis of neuronal activity—The initial step of offline processing removed any residual stimulation artifacts identified in the continuous neuronal data as intermittent, high-frequency (150 Hz) voltage transients that were not action potentials. This step was performed manually to ensure that neuronal data were not lost in the subtraction process. The neuronal data were then thresholded and candidate action potentials were sorted into clusters in principal components space (Off-line Sorter, Plexon, Plano, TX). A

neuronal recording was accepted for further analysis only if: (1) the unit's action potentials were of a consistent shape and could be separated reliably from background noise and the waveforms of other neurons; (2) $< 0.5\%$ of sorted spike waveforms violated a refractory period of 1.5 ms; and (3) the recording contained at least one block of data (20 trials off-stimulation, followed by 20 trials on-stimulation).

We tested for significant effects of DBS on a neuron's firing using a peristimulus time histogram (PSTH) constructed from the last 30 s of all completed stimulation blocks (bin size=0.2 ms, 35 bins; see Figure 5 of [46]). The PSTH was compared to control histograms (CtHs) constructed around a series of "sham stimulation" time points set at arbitrary 6.67 ms intervals during no-stimulation periods. A neuron's baseline control firing rate was defined as the grand mean across all CtHs. Areas of deviation from baseline firing were used as the fundamental statistic for tests of significance. Deviations from baseline firing rate (i.e., transient increases or decreases in firing rate) were detected in a PSTH and the areas of those deviations were converted to z-scores relative to the population of control deviation areas (i.e., the areas of all deviations in all CtHs for a neuron). The threshold for significance was adjusted to compensate for multiple comparisons [$\alpha=0.05/(\text{mean number of deviations detected per CtH})$]. Given our focus here on orthodromic activation of the STN-GP synaptic pathway and previous reports of the latency for monosynaptic excitation of GP neurons from the STN [38], we restricted further analysis to neurons with a PSTH containing a phasic increase in firing that peaked at 2.5 - 4.5 ms following stimulation (i.e., an increase $> 3.44\times$ the standard deviation of CtHs, yielding $\alpha=0.01$ after controlling for multiple comparisons). Neurons were excluded if they did not show a phasic increase in firing rate during the 2.5 - 4.5 ms peri-stimulus time interval or if they were driven antidromically.

2.3. Computational model

A brief description of the model is provided here and complete details are given in the Appendix. We model a population of $n = 500$ axons, each connected to a corresponding synapse and driven to spike by a combination of somatic spikes, which are generated stochastically, and DBS pulses, which occur periodically. Both somatic spikes and DBS pulses can induce axonal spiking [52], but not every somatic spike or DBS pulse induces a successful axonal action potential (axonal failure). We therefore use the term "nascent spike" to refer to any somatic spike or DBS pulse. Likewise, synaptic activations are driven by axonal spiking, but not every axonal action potential activates its corresponding synapse (synaptic failure). See Fig. 2 for a schematic of our model.

To capture the attenuation of FV amplitude during DBS (Fig. 1B) and its recovery after DBS (Fig. 1D), the probability that a nascent spike elicits an action potential in a given axon is decremented by each spike and recovers exponentially to a baseline value between spikes. Similarly, to capture the increase in FV latency during DBS (Fig. 1C), the latency of axonal action potentials is increased by each spike and recovers to a baseline value between spikes. Each axon terminates at a synapse with five vesicle docking sites. To capture the rapid decrease in synaptic efficacy during DBS (Fig. 1A), synaptic vesicle dynamics are modeled using a widely used stochastic model that exhibits short term synaptic depression arising from neurotransmitter depletion [71,23,26,61,63]. Each released vesicle adds a characteristic postsynaptic conductance waveform to the population synaptic conductance.

To contrast with the effects of short term depression, a static synapse model was used to produce Fig. 3D and parts of Fig. 4. In this model, every somatic spike and DBS pulse releases exactly one vesicle, but the amplitude of the postsynaptic conductance waveform was scaled so that the average synaptic conductance is the same for the static and depressing models in the absence of DBS.

Each STN somatic spike train is generated as an inhomogeneous Poisson process with firing rate $\nu_j(t) = \nu_0 + r_j(t)$ where $\nu_0 = 30$ Hz is a background firing rate and $r_j(t)$ is a rate fluctuation. For Fig. 1, $r_j(t) = 25 \sin(2\pi f_0 t)$ where $f_0 = 1$ Hz is the frequency of the rate fluctuation. For Fig. 4, the rate fluctuation is an unbiased Gaussian process with power at all frequencies below the cutoff of 50 Hz. For Figs. 5, 6, refF:Spectra and 8 the rate fluctuation is chosen so that the STN spike trains exhibit a power spectrum similar to that observed in recordings of MPTP-treated primates (see Fig. 6B,C).

DBS was simulated by adding periodic nascent spikes at the stimulation frequency. For Figs. 1, 3 and 4 DBS-induced spikes were added to all spike trains at 130 Hz to reflect the stimulation frequency of the in vitro data. For Figs. 5–8 spikes were added at 150 Hz to reflect the stimulation frequency of the in vivo data, but were only added to half (250) of the STN spike trains received by each GPi neuron, consistent with predictions that only a fraction of STN axons are activated by the application of standard DBS in STN [52].

Simulated GPi spike trains and synaptic currents were generated for Figs. 5–8 by incorporating the synaptic conductance produced by the model described above, in addition to a background inhibitory conductance, into a previously developed Hodgkin-Huxley style model GPi neuron [64].

3. Results

3.1. A computational model of axonal and synaptic failure reproduces experimentally observed DBS-induced short term depression

We first review previously reported evidence of axonal and synaptic failure during high frequency stimulation (HFS) of STN obtained from a combination of intracellular and extracellular recordings in rodent substantia nigra. We then use the data from this study to construct a computational model.

As described previously [78], STN stimulation evoked a mainly AMPA receptor-mediated postsynaptic current (PSC) in whole-cell recorded SNc dopaminergic neurons. During a train of STN stimulation (10 s) at DBS therapeutic frequency of 130 Hz, PSCs could only follow the first few stimuli before their amplitude declined (Fig. 1A; $n=9$). Such pronounced rundown of synaptic responses to HFS has also been observed in neurons recorded from SNr [65]. The PSC amplitudes recovered quickly to pre-train levels after cessation of HFS and no long-term synaptic plasticity to HFS was observed in extracellular field potential recordings that preserve the intracellular milieu [78]. Interestingly, the fiber volley (FV), the early component of extracellular field potentials that reflects axonal action potentials (see Methods and [78]), declined in amplitude during HFS. In experiments in which suppression of synaptic transmission isolated FV effects, HFS of STN rapidly reduced the amplitude (Fig. 1B; $n=8$) and increased the latency (Fig. 1C; $n=8$) of FV responses. The FV amplitudes recovered quickly to baseline after termination of HFS (Fig. 1D). A stimulation-induced accumulation of extracellular and/or submyelin potassium ions has been posed as a possible explanation for the attenuation of FV amplitudes during HFS [66,5,36,78].

We developed a phenomenological computational model of this stimulation-induced reduction in response amplitudes and fit the model parameters to accurately capture our experimental data. In our model, each stimulation pulse invokes an action potential in each of $n = 500$ model axons with a probability that is decreased by each pulse. This rule reproduces the experimentally observed reduction in FV amplitude after stimulation onset (Fig. 1B) by reducing the number of axons involved in each FV over time. Between pulses, the probability of successful action potential initiation recovers in time, reproducing the experimentally observed recovery of FV amplitudes after stimulation ceases (Fig. 1D). The

time at which an action potential reaches the axon terminal is also increased by each pulse and recovers exponentially in time, reproducing the dynamic shift in FV latency after stimulation onset (Fig. 1C). To reproduce the experimentally observed reduction in PSC amplitude after stimulation onset, we used a standard model of vesicle depletion and recovery in which each axon terminates at a synapse containing $N_0 = 5$ vesicle docking sites [71,73,23,26,61,63]. When an action potential successfully propagates to the axon terminal, a single vesicle is released with a probability that depends on the number of docked vesicles. After a vesicle is released, a new vesicle is docked at that site after a random waiting time. This model of vesicle depletion reproduces the experimentally observed reduction in PSC amplitude after stimulation onset (Fig. 1A).

3.2. DBS-induced short term depression suppresses the transfer of firing rate oscillations and information in a computational model

To explore the effects of DBS-induced short term depression on the transmission of presynaptic firing rate oscillations, we added background somatic spiking to the computational model described above. Somatic spikes represent ongoing activity in STN neurons and are treated identically to DBS pulses in our model: each is considered as a nascent axonal spike that may or may not result in successful axonal spike propagation and each decreases the probability of success for future nascent spikes. As above, even a successful axonal spike can fail to activate its corresponding synapse. Thus, only a fraction of DBS pulses and somatic spikes succeed in producing a synaptic response (Fig. 2).

Somatic spikes for each of 500 model axons and synapses were generated as an inhomogeneous Poisson process with a rate modulated periodically at 1 Hz around a baseline of 30 Hz (Fig. 3A,B). In the absence of DBS, oscillations in the somatic firing rates were transmitted reliably to the postsynaptic conductance (Fig. 3C, first 5 s). After the onset of 130 Hz DBS, the amplitude of low frequency oscillations in the postsynaptic conductance was substantially diminished (Fig. 3C, last 5 s). Note that the rate of nascent spikes at each axon increases from 30 Hz before stimulation to 180 Hz during stimulation. This large increase in nascent axonal spiking causes a large transient increase in synaptic conductance, but a comparatively small change in steady-state synaptic conductance ($g(t) = 0.021 C_m s^{-1}$ on average in the first 5 s and $0.037 C_m s^{-1}$ during the last 4 s in Fig. 3C; compare to Figure 3i of [3]) due to a substantial reduction in steady state synaptic efficacy during stimulation (5.8% of nascent spikes released a synaptic neurotransmitter vesicle during first 5 s in Fig. 3C and 1.9% during last 4 s).

To verify that short term depression is responsible for the suppression of slow oscillations during simulated DBS, we ran the same simulations with a static model that does not exhibit axonal or synaptic failures. The mean conductance increased substantially during DBS for the static model ($g(t) = 0.021 C_m s^{-1}$ on average in the first 5 s in Fig. 3D and $0.111 C_m s^{-1}$ in the last 4 s) and low frequency oscillations were transmitted reliably from the presynaptic spike trains to the postsynaptic conductance both in the presence and in the absence of DBS pulses (Fig. 3D). Hence, DBS-induced short term depression prevents the transmission of slow oscillations that are present in a population of presynaptic spike trains.

Although it is seldom considered in discussions of the mechanism of action of DBS, this suppression of low-frequency signal transfer by short term depression is a well-known phenomenon [1,29,44,50,63]. An intuition for this effect can be gained by considering the combined axon-synapse transfer function, which we define as the mapping from a steady state rate of presynaptic spiking to the steady state mean postsynaptic conductance it elicits. Short term depression causes this transfer function to saturate at high rates (Fig. 3E, black curve). Sufficiently slow oscillations in firing rates can be mapped to the oscillations in synaptic conductance they evoke by applying the transfer function to the time-dependent

presynaptic rate [63]. Oscillations around a high background firing rate are mapped through a region of the transfer function with a small derivative (low gain) and therefore evoke small-amplitude oscillations in synaptic conductance (Fig. 3E, red curves). Oscillations around a lower background firing rate are mapped through a steeper region (higher gain) and therefore evoke larger-amplitude conductance oscillations (Fig. 3E, blue curves). Since DBS effectively increases the presynaptic firing rate, it lowers the gain of the axonal and synaptic pathways, thereby suppressing the transfer of low-frequency oscillations. For a static (non-depressing) synapse model, the synaptic transfer function is linear so that the amplitude of conductance oscillations are independent of the baseline firing rate (Fig. 3F) and an increase in presynaptic spike generation rates does not suppress the transfer of low-frequency oscillations.

The example above considers a firing rate oscillation at a single frequency. To investigate how DBS-induced short term depression suppresses the transfer of oscillations at a variety of frequencies, we next ran a simulation where the presynaptic firing rate exhibits fluctuations at all frequencies under 50 Hz. This rate modulation can be thought of as a broadband presynaptic rate-coded signal [44,50,63]. DBS substantially reduces the coherence between this signal and the postsynaptic conductance produced by the depressing model (Fig. 4A, compare blue and red curves). For the static model, the coherence between the signal and conductance is unchanged by DBS (Fig. 4A, purple curves). Indeed, DBS at 130 Hz is provably incapable of altering coherence at lower frequencies because the mapping from input to conductance is a linear filter for the static model [68].

We next sought to quantify the DBS-induced change in mutual information between a rate-coded signal and the postsynaptic conductance it elicits. To do this, we used a measure of linear mutual information that represents the maximal amount of information per unit time available to an optimal linear decoder that estimates the rate-coded signal by observing the postsynaptic conductance (see [24,44,50,63] and Methods). We found that this linear information rate is reduced substantially by DBS for the depressing model (81.58 ± 0.16 bits/s before DBS and 28.29 ± 0.16 bits/s during DBS; Fig. 4B), but not for the static model (158.96 ± 0.12 bits/s before DBS and 158.28 ± 0.13 bits/s during DBS; Fig. 4C).

To test the dependence of our results on model parameters, we repeated the simulations from Fig. 4A for 1000 trials where each parameter varied randomly across trials over an interval from one fourth of its original value to four times its original value (see Appendix). Our findings indicate that the DBS-induced reduction in coherence reported in Fig. 4A is robust to parameter changes and is most pronounced at higher axonal and synaptic failure rates (Fig. 4D). This conclusion is consistent with mathematical analysis presented in [63] showing that short term depression and probabilistic vesicle release reduce the coherence between presynaptic spiking and postsynaptic conductance, especially when synaptic efficacy is low.

3.3. DBS-induced short term depression of the subthalamopallidal pathway in vivo

So far, we have presented in vitro evidence of DBS-induced short term depression of the rodent STN-SNc pathway caused by the combined effects of axonal and synaptic failures, and we have shown that a model that fits these data exhibits a diminished transfer of low-frequency oscillations and information. We next present evidence of DBS-induced short term depression in the primate subthalamopallidal pathway in vivo. To determine whether such depression occurs, we recorded during DBS from a total of 215 globus pallidus neurons in two monkeys ($n=107$ and 108 for Monkey A and Monkey B, respectively). Of these, 65 pallidal units met our criteria for analysis ($n=38$ and 27 for Monkey A and B, respectively; $n=32$ in GPi and 35 in GPe). This sub-population showed a phasic increase in firing rate that reached a maximum between 2.5 and 4.5 ms following stimulus delivery (consistent with

orthodromic synaptic activation) and was not activated antidromically by DBS. Fig. 5A shows a series of unprocessed spike train segments from one of these neurons (50 overlaid peri-stimulus segments from a recording in GPi of Monkey A). The action potential waveforms of this unit remained consistent before, during (0 ms and 6.67 ms, gray vertical line), and after stimulus delivery. The absence of stimulation-related electrical artifacts for all recordings included in the database allowed consistent single unit isolation throughout the peri-stimulus interval.

These stimulus-induced phasic activations generally declined in magnitude and shifted in latency across the course of stimulation (Fig. 5B-E), consistent with the trends observed in the FV and PSC responses in the in vitro data presented above (Fig. 1).

Mean population peri-stimulus histograms constructed from the first 10 seconds and last 10 seconds of DBS (blue and red traces, respectively, in Fig. 5B,C) illustrate the highly consistent depression in response magnitude and shift in timing that we observed in both monkeys. One-sided, paired student's t-tests confirm that the peak peri-stimulus firing rate (within the latency interval 2.5-5.5 ms) was significantly higher during the first 10 s of stimulation than the last 10 s ($p = 4.3 \times 10^{-10}$ for Monkey A and $p = 4.2 \times 10^{-4}$ for Monkey B) and also that the peak occurred at a longer latency during the last 10 s of stimulation when compared to the first 10 s ($p = 1.2 \times 10^{-5}$ for Monkey A and $p = 0.0011$ for Monkey B).

The latency of the peak pallidal firing rate following stimulation suggests that the pallidal neurons in question are entrained to the stimulation through a synaptic connection, presumably from STN afferents [34,55]. The attenuation and delay of the peak firing rate over time are consistent with the effects of axonal and synaptic failure observed in vitro and discussed above (compare Fig. 5B-E to Fig. 1A-C) and also consistent with previously reported data from MPTP-treated primates [55]. DBS only marginally altered steady state GP firing rates (77 ± 5 Hz before DBS and 90 ± 6 Hz during the last 10 s of stimulation for Monkey A; 69 ± 6 Hz before, 72 ± 6 Hz during last 10 s for Monkey B; Fig. 5D), consistent with previous studies [34,18,55].

We next sought to capture DBS induced depression of the primate subthalamopallidal pathway in a computational model. We used the same model of axonal and synaptic failure discussed above to generate a postsynaptic conductance that, in combination with a background inhibitory conductance, provided synaptic inputs to two instances of a previously developed model of a GPi neuron [64]. Presynaptic spiking consisted of 500 excitatory spike trains each firing at 30 Hz, intended to represent projections from STN, as well as a single train of background inhibitory spikes arriving at 1000 Hz intended to represent input from GPe and striatum (Fig. 6A). To simulate parkinsonian conditions, these STN spike trains were generated to exhibit power spectra consistent with those observed in recordings of MPTP treated primates ([54] and Fig. 6B,C), namely a peak at a low β frequency (13 Hz) and an exponential decay of power at higher frequencies. Presynaptic correlations were introduced by imposing that any two STN spike trains share a portion of their firing rate fluctuations. DBS was simulated by adding spikes at 150 Hz to half of the STN spike trains, consistent with evidence that only a portion of STN axons are excited by DBS [52].

We modified the parameters of our axonal and synaptic failure model to capture the longer timescale of firing rate dynamics after DBS onset in our in vivo data relative to our in vitro data (compare Figs. 1 and 5D,E). Our model reproduces the general trend of firing rate dynamics and latency shift of the spiking response observed in the data (Fig. 5D,E), suggesting that the primate subthalamopallidal pathway exhibits a short term depression arising from axonal and synaptic failures during DBS.

3.4. DBS-induced short term depression suppresses parkinsonian β oscillations and synchrony in a computational model

Parkinsonism is associated with an increase in low frequency (10-15 Hz) β oscillations and synchrony in STN, GPe and GPi [58,9,8,45], which are suppressed by DBS in non-human MPTP-treated primates [49,76,54] and in human PD patients [75,8,39,20]. We illustrated above that DBS-induced short term depression arising from axonal and synaptic failures can suppress the synaptic transfer of low-frequency firing rate oscillations (Fig. 3). We therefore reasoned that the suppression of parkinsonian β oscillations and synchrony during DBS is due, at least in part, to DBS-induced short term depression.

To test this hypothesis computationally, we computed the spectral properties of the synaptic currents and spike trains produced by our computational model GPi neurons and compared them to corresponding measurements from a recent study of MPTP-treated monkeys receiving DBS [54]. We found that DBS substantially reduced β oscillations in both the synaptic currents and spike trains in the model neurons, consistent with the experimental data (Fig. 7Ai-iii). DBS also reduced the coherence between STN spiking activity and GPi synaptic current as well as the coherence between STN spiking activity and GPi spiking activity, again consistent with the previously reported data (Fig. 7Bi-iii).

To study the effects of DBS-induced synaptic depression on correlations between the activity of GPi neurons, we performed the same simulations with a second population of simulated STN spike trains – which were correlated to the population used in the first simulation through shared rate fluctuation – and a corresponding second target GPi neuron. DBS reduced the coherence between the synaptic currents across the two GPi neurons' membranes and also reduced the coherence between the two GPi spike trains, consistent with previously reported data (Fig. 7Ci-iii).

The striking similarity between the effects of DBS on power spectra and coherence in our model and the effects observed experimentally suggests that short term depression arising from axonal and synaptic failures is at least partially responsible for the widely reported suppression of parkinsonian β oscillations and synchrony during DBS.

3.5. DBS effects depend on stimulation frequency, stimulation pattern and extent of STN activation

The therapeutic effects of DBS depend on stimulation frequency: stimulation is typically most therapeutic at frequencies over 100 Hz and low frequency stimulation can actually worsen symptoms or have no effect [60,56,7]. We used our model to test the dependence of GPi β oscillations and synchrony on stimulus frequency and found that the power of GPi β oscillations as well as the β coherence between GPi spike trains decrease at sufficiently high stimulation frequencies, but STN-GPi β coherence attains a minimum near 150 Hz stimulation (Fig. 8A-C, black curves). Unsurprisingly, stimulating at 12 Hz increased the power of GPi spike train oscillations in the 10-15 Hz range as well as the GPi-GPi coherence in the 10-15 Hz range, consistent with some experimental observations (compare Fig. 8A to Figure 5 of [8]; although see [6] and [56] where high stimulation frequencies reduce therapeutic effects).

Recent studies explore the dependence of clinical improvement in motor symptoms on the pattern of DBS stimulation, finding that stimulation protocols with irregular inter-pulse intervals and protocols that contain long pauses were generally less therapeutic than periodic stimulation [17,7]. We used our model to test the dependence of GPi β oscillations and synchrony on stimulation pattern by introducing two additional stimulation protocols: one in which pulses occur as a Poisson process and another in which 3 s trains of periodic pulses

are interrupted by 3 s without pulses (see Methods and Fig. 8 inset). At stimulation frequencies faster than 50 Hz, both of these protocols were less effective at suppressing β oscillations and β synchrony within GPi than the periodic stimulation protocol (Fig. 8 A-C), given the same average number of DBS pulses delivered per unit time. Poisson stimulation introduces coherence at all frequencies since Poisson processes have equal power at all frequencies. Thus, Poisson stimulation is not as effective at reducing low frequency coherence as periodic stimulation (Fig. 8C, greenline). Long pauses between stimulation pulses allow synaptic efficacy to recover, which temporarily eliminates the ability of synapses to suppress the transfer of low frequency coherence, leading to a larger coherence than obtained for periodic stimulation (Fig. 8C, purple line). Thus, periodic stimulation is superior to these other stimulation protocols at suppressing low frequency coherence through short term depression. The precise placement and orientation of stimulating electrodes as well as the amplitude of stimulation pulses can affect the number of STN axons activated by each DBS pulse and the number of STN axons activated is correlated with clinical improvement of motor symptoms [52]. We used our model to test the dependence of GPi β oscillations and synchrony on the number of presynaptic STN axons activated by stimulation and found that the prominence of GPi β oscillations and peak GPi coherence decrease as the number of stimulus-entrained STN axons increases (Fig. 8D-F). Thus, our model predicts that electrode placement and stimulation amplitudes that maximize the number of STN axons activated will most effectively suppress the transfer of β oscillations and synchrony from STN to GPi.

Discussion

DBS evokes action potentials in axons located near the stimulation site, thereby activating synapses on efferent fibers [34,47,41,52,74,55,59], but short term depression can limit the rate at which synaptic release results. Our model of DBS-induced short term depression was derived from recordings in rodent SNc and primate GPi during stimulation in STN, but similar evidence of DBS-induced short term depression has been found in several pathways during thalamic epAnderson:2004cg,Iremonger06,Anderson06,Middleton10, subthalamic [65,78,55,2], pallidal [46,19,10], cortical [77] and hippocampal [37,21] stimulation and is believed to arise from a combination of axonal and synaptic failures [33,78,37,21]. We combined in vitro data, in vivo data and computational modeling to show that this DBS-induced short term depression suppresses the synaptic transfer of firing rate oscillations, synchrony and rate-coded information.

Although our results have implications for DBS in any brain region in which stimulation-induced short term depression occurs, we focused on STN projections to SNc and GPi during DBS in STN. We found that synaptic excitation from STN is moderately increased during DBS, but the transfer of firing rate oscillations, information and synchrony from STN is suppressed substantially. We showed that this suppression of firing rate oscillations and synchrony by DBS-induced short term depression can explain the widely reported reduction in parkinsonian β oscillations during therapeutic DBS. Since motor symptoms of Parkinson's disease are believed to arise, at least partly, from pathological neural activity passing from STN to basal ganglia output nuclei, our results suggest that short term depression is a therapeutic mechanism of DBS.

Relationship to existing models of DBS function

Part of the efficacy of DBS may stem from antidromic mechanisms [43,28,14]. We expect antidromic activation to elicit the same increased rate of axonal failures discussed here. Indeed axonal failures were shown to depress the antidromic activation of STN neurons during STN stimulation in [78]. Another recent study found that antidromically elicited

action potentials in motor cortex exhibited spontaneous failures with a failure rate that increased with stimulation frequency [42], consistent with our model of axonal failure. This increased rate of failures occurred in unison with a suppression of β oscillations in motor cortex, consistent with the failure-induced suppression of pallidal β oscillations discussed here. We therefore conjecture that DBS-induced axonal failure can regularize neural activity through antidromic pathways via mechanisms similar to those discussed here.

It has also been proposed that high-frequency entrainment of GPi by DBS may reduce motor signs by regularizing the inhibitory signal from GPi to its thalamic targets, restoring thalamic relay that had been compromised by parkinsonian oscillations and bursting [64,31]. We have shown that DBS-induced short term depression can regularize synaptic input received from STN by basal ganglia output nuclei (Figs. 3C and 7), which would be well suited to restoring thalamic relay. Importantly, we have also found a loss of GPi spike synchrony (Fig. 7Cii) that, when integrated across many individual GPi neurons, would contribute to regularization of the total synaptic signal to a thalamic neuron. Thus, the mechanisms that we have proposed are consistent with earlier proposals relating to the alteration of GPi firing patterns by DBS [53,64,25,49,31,2,59,12], and our results also predict a modest increase in steady state GPi firing rates, consistent with experimental observations [34,18,55].

We based our model of combined axonal and synaptic failure on recordings from rodent SNc during stimulation in STN, but several studies of DBS-induced short term depression report dynamic changes in stimulation-induced postsynaptic responses in other brain regions that bear striking resemblance to the effects of combined axonal and synaptic failure discussed here. Consistent with data shown in Figs. 1A,C and 5D,E, a simultaneous decrease in response amplitude and increase in response latency after stimulation onset has been found during subthalamic [55,65], pallidal [19,46] and hippocampal [37,21] stimulation. Additionally, depression of the early and late components of the postsynaptic response to subthalamic [65] and thalamic [35] stimulation has previously been shown to exhibit two distinct onset timescales, consistent with the distinct onset timescales of axonal and synaptic depression considered here (Fig. 1A,B). Finally, the STN-GP pathway has been shown to exhibit synaptic depression [33]. Together, these findings suggest that DBS-induced short term depression arises from similar mechanisms – namely, a combination of axonal and synaptic failure – in various brain regions.

Predictions

Our model makes several predictions that can be used to test the hypothesis that short term depression arising from axonal and synaptic failure suppresses signal transfer during DBS. First, we predict that DBS causes a simultaneous decrease in synaptic efficacy and increase in synaptic output from STN. Authors have argued against the idea that short term depression is responsible for the effects of DBS because STN synaptic output is increased, instead of silenced, during DBS [48], but our model demonstrates that DBS can simultaneously induce both increased STN synaptic output and short term depression of STN signaling. Our model also predicts that DBS-induced suppression of STN signal transfer is positively correlated with an increased rate of axonal and synaptic failures (Fig. 4D). Finally, we predict several dependencies of the reduction in GPi oscillations on stimulation parameters (Fig. 8).

Future directions

We used a phenomenological model of action potential generation in STN axons that captures the salient features of FV amplitude dynamics observed in the data but lacks biophysical detail. DBS-induced axonal failure is conjectured to arise from a buildup of

extracellular potassium ions [66,36,78,37,21], but a biophysically precise characterization of this effect is lacking. A computational model of submyelin potassium accumulation during DBS has been developed tepBellinger08, but only at the level of a single axon. It is not immediately clear how the predictions made using that model scale to the population level. For example, the model in [5] predicts an all-or-none cessation of synaptic activation at sufficiently high stimulation frequencies due to a reduction in axonal action potential amplitude, but the data presented here and in [78] show only a reduction in FV and PSC amplitude at the population level, without complete cessation. Is this reduction in response amplitude due to a reduced probability of each synapse being activated by each DBS pulse or is it due to the complete silencing of a portion of the synapses? More detailed experimental measurements and computational modeling are necessary to understand the precise biophysical mechanisms responsible for axonal and synaptic failure observed in our data.

Our results support the idea that DBS acts, at least in part, by decoupling the temporal structure of STN somatic spiking activity from the temporal structure of STN synaptic output without reducing the total amount of STN synaptic output. This findingsuggests that less invasive pharmacological methods of decoupling STN spiking activity from STN synaptic output, whether by increasing the occurrence of axonal or synaptic failures or through other mechanisms, could be developed to treat Parkinson's disease.

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Appendix: Description of computational model

3.5.0.7. Computational model of axonal and synaptic failure

We model a population of $n = 500$ axons, each connected to a corresponding synapse and driven to spike by a combination of somatic spikes, which are generated stochastically (see below), and DBS pulses, which occur periodically. Both somatic spikes and DBS pulses can induce axonal spiking [52], but not every somatic spike or DBS pulse induces a successful axonal action potential (axonal failure). We therefore use the term “nascent spike” to refer to any somatic spike or DBS pulse. Likewise, synaptic activations are driven by axonal spiking, but not every axonal action potential activates its synapse (synaptic failure). See Fig. 2 for a schematic of our model.

A nascent spike for axon $j = 1, \dots, n$ that occurs at time t_0 elicits an action potential in axon j at time $t_{\text{spike}} = t_0 + L_j(t_0)$ with probability $x_j(t_0)$ where $x_j(t)$ represents the efficacy of axon j at time t . Fast axonal spiking induced by high frequency stimulation can decrease axonal efficacy and increase the latency of axonal spikes [78,21], perhaps due to the buildup of extracellular potassium ions [66,5,36]. To capture these effects in our model, we stipulate that $x_j(t)$ is decremented and $L_j(t)$ is incremented by each successful spike, according to the rules

$$x_j(t_0) \leftarrow x_j(t_0) - U_x x_j(t_0) \quad (1)$$

and

$$L_j(t_0) \leftarrow L_j(t_0) + U_L [L_{\text{max}} - L_j(t_0)] \quad (2)$$

where $0 < U_x < 1$ and $0 < U_L < 1$ control the amount by which each spike affects the probability and latency of future axonal spikes; and $L_{\max}$ is the maximum latency of axonal spikes. Since this axonal failure is thought to result from a buildup of extracellular potassium ions that can diffuse to neighboring axons, we expect that the efficacy of axon j is affected by the activity of neighboring axons. To account for this, we additionally decrement $x_j(t)$ for each spike that occurs in *any* axon $i \neq j$ in the population, according to the rule,

$$x_j(t_i) \leftarrow x_j(t_i) - \frac{U_{x,\text{pop}}}{n} x_j(t_i) \quad (3)$$

where t_i is the time at which the spike occurs, $U_{x,\text{pop}}$ controls the degree to which spikes of other axons depress their neighbors. We scale $U_{x,\text{pop}}$ by the population size, n to assure that the total amount of depression an axon experiences does not depend on the number of axons being modeled. We were best able to fit recorded data by applying rule 3 at each nascent spike in the population, but applying rules 1-2 only when a nascent spike successfully elicited an action potential in axon j . Recordings in [78] show that axonal efficacy recovers after DBS is stopped. To capture this recovery, we impose that, between spikes, each axon recovers according to the differential equations

$$\begin{aligned} \tau_x x_j(t) &= -x_j(t) + 1 \\ \tau_L L_j(t) &= -L_j(t) + L_{\min}. \end{aligned}$$

Here, τ_x and τ_L represent the recovery timescales of the axon and $L_{\min}$ is the minimum latency of axonal spikes.

In addition to axonal failure, STN projections are subject to short term depression caused by an increased probability of synaptic failures at high stimulation frequencies [33,78]. We represented synaptic depression with a widely used computational model of neurotransmitter vesicle dynamics [71,73,23,26,61,63]. Each axon terminates at a synapse with $N_0 = 5$ vesicle docking sites. Define $n_j(t) \leq N_0$ to be the number of docked vesicles at time t for synapse j (at which axon j terminates). Each time there is a successful action potential in axon j (see above), a vesicle is released with probability $p_j(t) = 1 - (1 - U_w)^{n_j(t)}$ where $U_w < 1$ is a parameter that controls the probability of release for docked vesicles. When a vesicle is released, $n_j(t)$ is decremented by one and a characteristic post-synaptic conductance waveform, $\alpha(t)$, is added to the total postsynaptic conductance, $g_j(t)$, generated by the synapse. Once a vesicle is released, the waiting time until it is re-docked is an exponentially distributed random variable with mean τ_w . This model of synaptic depletion takes into account the stochastic nature of vesicle release and recovery, which play an important role in determining the synaptic transfer of oscillations and information [63]. The model allows at most one vesicle to be released by each action potential, but the dependence of $p_j(t)$ on $n_j(t)$ assures that the probability of release increases with the number of docked vesicles [79]. When synapse j releases a vesicle, the resulting postsynaptic conductance is given by

$$g_j(t) = \sum_k \alpha(t - t_k)$$

where t_k is the time of the k th vesicle released by synapse j . The postsynaptic conductance waveform was modeled as a difference of exponentials [13],

$$\alpha(t) = \frac{J}{\tau_2 - \tau_1} \Theta(t) \left(e^{-t/\tau_2} - e^{-t/\tau_1} \right),$$

where $T(t)$ is the Heaviside step function, $\tau_1 = 4$ mns, $\tau_2 = 1$ ms, $J = 10^{-4} C_m$ is a synaptic weight chosen to obtain firing rates within the range observed in recordings of GPi neurons, and C_m is membrane capacitance of the postsynaptic neuron (see below). The population synaptic conductance is defined as the sum of synaptic conductances from all synapses,

$$G_{\text{AMPA}}(t) = \sum_{j=1}^{500} g_j(t).$$

We used this model to capture the short term depression observed in two data sets: one data set from in vitro recordings of rodent SNc during 130 Hz DBS in STN, and one data set from in vivo recordings of primate GP neurons during 150 Hz DBS in STN. We used a different version of our model with different parameters to capture each data set.

The first version of our model was fit by hand to the in vitro data reported in Fig. 1. Parameters chosen were $U_x = 2.5 \times 10^{-3}$, $U_{x,\text{pop}} = 2 \times 10^{-3}$, $U_L = 1.5 \times 10^{-2}$, $\tau_x = \tau_L = 27$ s, $L_{\min} = 2.8$ ms, $L_{\max} = 3.5$ ms, $N_0 = 5$, $U_w = 0.06$, and $\tau_w = 850$ ms. This version of our model was used to produce the model data reported in Figs. 1, 3 and 4A-C.

For Fig. 4D, we repeated the simulation in Fig. 4A with one thousand randomly chosen parameter values. For each simulation, the parameters U_x , $U_{w,\text{pop}}$, U_L , τ_x , U_w and τ_w were chosen independently from uniform distributions with a minimum at one fourth of the values given above and a maximum at four times the values given above (for example, U_x was drawn from a uniform distribution on the interval $[6.25 \times 10^{-4}, 10^{-2}]$). To assure that $L_{\min} < L_{\max}$ for each simulation, we fixed $L_{\min} = 2.8$ ms and chose $L_{\max} - L_{\min}$ from a uniform distribution with a minima and maxima at one fourth and four times the baseline value of 0.7 ms. Since N_0 must be an integer, we drew values randomly from a discrete uniform distribution ranging from $N_0 = 1$ to $N_0 = 20$.

The second version of our model was used to capture the in vivo data reported in Fig. 5. To capture the spiking response of GP cells, we combined the model of axonal and synaptic failure with a previously developed model of a GPi neuron [64]. See Fig. 6 for a schematic of this model and see below for a more detailed description. We modified our axonal failure parameters to fit the in vivo data as follows: $U_x = U_{x,\text{pop}} = 5.5 \times 10^{-4}$, $U_L = 1.8 \times 10^{-4}$, $\tau_x = 100$ s, $L_{\min} = 1.3$ ms, $L_{\max} = 3.25$ ms. This version of our model was used to produce the model data reported in Figs. 5, 7, and 8.

3.5.0.8. Static synapse model

To determine the importance of short term depression in our simulations, we also ran simulations with a static synapse model for Figs. 3 and 4. In this model, there is no axonal or synaptic failure, so each presynaptic spike has the same synaptic efficacy and the synaptic conductance produced by synapse j is given by

$$g_j(t) = \bar{w} \sum_k \alpha(t - t_k),$$

for $j = 1, \dots, 500$ where $w = 0.058$ was chosen so that the static model yields the same mean synaptic conductance as the depressing model in the absence of DBS (i.e., with somatic spikes only).

3.5.0.9. STN spike train generation

Each STN spike train was modeled as an inhomogeneous Poisson process with rate given by $\nu_0(t) = \nu_0 + r_j(t)$ where $\nu_0 = 30$ Hz is a constant background firing rate and $r_j(t)$ is the rate fluctuation.

For Fig. 3, the firing rate of each of 500 spike trains was given by $\nu_j(t) = \nu_0 + 25 \sin(2\pi f_0 t)$ Hz where $f_0 = 1$ Hz is the frequency of the firing rate modulation. For Fig. 4 the firing rate of each spike train was given by where each $s_j(t)$ is an independent, unbiased stationary Gaussian noise process with a broadband power spectrum given by

$$S_s(f) = \nu_0 \frac{0.1}{1 + e^{(f-f_0)/\alpha}}$$

with $\alpha = 1$ Hz and cutoff frequency $f_0 = 50$ Hz. The power spectrum of each spike train is then given by the identity [63] $S_{STN}(f) = \nu_0 + S_s(f)$.

For Fig. 7, each of two model GPi neurons received input from 500 STN spike trains. The firing rate of the j th STN input to the k th GPi neuron was given by

$$\nu_j^k(t) = \nu_0 + \sqrt{c_b} s_b(t) + \sqrt{c_w - c_b} s_w^k(t) + \sqrt{1 - c_w} s_j^k(t)$$

for $k = 1, 2$ and $j = 1, \dots, 500$. Here, $s_b(t)$ is a rate modulation shared by all inputs, $s_w^k(t)$ is a rate modulation shared by all inputs to GPi neuron k , and $s_j^k(t)$ is a rate modulation observed only by the j th input to GPi neuron k . The parameter $c_b = 0.1$ determines the correlation between the inputs to the two GPi neurons and the parameter $c_w = 0.2$ determines the correlation between inputs to the same GPi neuron. All of the rate modulations were unbiased, independent and had the same power spectrum, $S_s(f)$. We chose $S_s(f)$ so that the power spectrum of each STN spike train was given by

$$S_{STN}(f) = \nu_0 \left(1 + 2e^{-(f-f_0)^2/(2\sigma^2)} + 3e^{-f/\alpha} \right)$$

where $f_0 = 13$ Hz, $\sigma = 1.25$ Hz, and $\alpha = 8$ Hz. This spectrum was chosen to match the power spectrum of STN activity reported in [54] (Fig. 6B,C).

3.5.0.10. Simulating DBS in STN

To simulate DBS in our computational model, spikes were inserted into STN spike trains periodically at the stimulation frequency. For Figs. 1, 3 and 4 DBS-induced spikes were added to all spike trains at 130 Hz to reflect the stimulation frequency of the in vitro data. For Figs. 5, 7 and 8 spikes were added at 150 Hz to reflect the stimulation frequency of the in vivo data, but were only added to half (250) of the STN spike trains received by each GPi neuron, consistent with predictions that only a fraction of STN axons are activated by the application of standard DBS in STN [52].

For Fig. 8, stimulation frequency and the fraction of the STN axons entrained to DBS stimulation were varied from their 150 Hz and 0.5 respective baseline values. Also for Fig. 8, two additional stimulation protocols were introduced. In one protocol, which we refer to as “Poisson stimulation”, DBS pulses occur as a Poisson process with the rate parameter given by the stimulation frequency. For another stimulation protocol, which we refer to as

“periodic stimulation with pauses”, pulses occur periodically for 3 seconds, followed by a silent period with no pulses that lasts 3 seconds, and this pattern is repeated for the duration of stimulation. The frequency of stimulation outside of the silent periods is chosen to be twice the desired mean stimulation frequency. This choice assures that the average number of pulses per unit time is the same for all three stimulation protocols whenever the stimulation frequency is chosen to be identical for the three models (i.e., at corresponding points along the horizontal axis in Fig. 8).

3.5.0.11. GPi neuron model

We used a single-compartment GPi neuron model from [64]. The membrane potential equation in this model takes the form

$$C_m V' = -I_L - I_K - I_{Na} - I_T - I_{Ca} - I_{syn}$$

where I_L is a leak current, I_{Na} is a sodium current, I_K is a potassium current, I_T is a low-threshold calcium current, and I_{Ca} is a high-threshold Ca^{2+} current. A complete description of the parameters and kinetics for each of these currents can be found in previous work [67,64]. The synaptic current, $I_{syn}(t)$, for the model GPi neuron is given by

$$I_{syn}(t) = I_{AMPA}(t) + I_{GABA}(t).$$

The excitatory synaptic current from STN is defined by

$$I_{AMPA}(t) = G_{AMPA}(t)(V - V_{AMPA})$$

where $V_{AMPA} = 0$ mV is the reversal potential of the excitatory synapses and $G_{AMPA}(t)$ is the population conductance defined above. The inhibitory synaptic current is given by

$$I_{GABA}(t) = g_{GABA}(t)(V - V_{GABA})$$

where $V_{GABA} = -80$ mV,

$$g_{GABA}(t) = \sum_{inh} \alpha(t - t_{inh}),$$

and t_{inh} arrive as a Poisson process with constant rate $\nu_{inh} = 1$ kHz.

3.5.0.12. Computer simulations and analysis of simulated data

All computer simulations were performed using a combination of custom-written C code and Matlab code (The MathWorks, Natick, MA). Power spectra and coherence functions were computed using the `pwelch` and `mscohere` functions respectively in Matlab. The linear information rate, $I_L(G;s)$, between the rate fluctuation and conductance for Fig. 4 was computed using the equation [44,50,63]

$$I_L(G;s) = - \int_0^\infty \log_2(1 - C_{sG}(f)) df$$

where $C_{sG}(f)$ is the coherence between the rate-coded signal $s(t)$ and the population postsynaptic conductance, $G(t)$ (see above). This measure of information represents the maximal amount of information about $s(t)$ that can be obtained by a linear decoder that reads $G(t)$ [24].

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Highlights

1. DBS increases synaptic output, but decouples pre- and post-synaptic spiking patterns.
2. This decoupling explains the suppression of pallidal _ oscillations in PD patients.
3. DBS-induced short term depression is a major therapeutic mechanism of DBS for PD.

Figure 1.

Synaptic and axonal failure during high frequency stimulation of STN. A-B) Amplitude of the mean post-synaptic currents (PSCs) and fiber volleys (FVs) in SNc elicited by 130 Hz high frequency stimulation (HFS) in STN, plotted as a function of the time evolved since stimulation onset and normalized by the amplitude of the first event. C) Latency of the FV peak after each HFS pulse. D) FV amplitude after HFS is replaced by slow 0.1 Hz stimulation, normalized by the final (recovered) amplitude. Blue error bars are from in vitro recordings in rodent SNc (intracellular whole-cell recordings for A and extracellular field potential recordings for B-D, see Methods). Red curves are from simulations of the computational model. Error bars here and in all subsequent figures have a radius of one standard error.

Figure 2.

Schematic illustration of axonal and synaptic failure. Each somatic spike in the presynaptic neuron and each DBS pulse is treated as a nascent axonal spike. A portion of the nascent spikes fail to elicit an action potential at the axon terminal (axon failure). Out of the successful axonal spikes, a portion fail to elicit a synaptic response (synaptic failure).

Figure 3.

DBS-induced short term depression suppresses the transfer of firing rate oscillations in a computational model. A population of 500 presynaptic spike trains were generated, each with a firing rate that fluctuated periodically at 1 Hz around a baseline rate of 30 Hz. After 5 sec, additional nascent spikes were added periodically at 130 Hz to model DBS-evoked axonal activation. A computational model of axonal and synaptic short term depression was used to generate a population postsynaptic conductance from the presynaptic spike trains. A) Oscillating firing rate of the presynaptic spike trains. B) Spike raster for 100 of the 500 generated spike trains. Each blue dot represents a spike. C) Population synaptic conductance produced using computational model of short term depression. Blue curve shows raw conductance (units $C_m s^{-1}$ where C_m is cell membrane capacitance) and black curve shows low pass filtered conductance (2nd order Butterworth with 50 Hz cutoff). D) Same as (C) but derived from a static synapse model without short term depression. E) A schematic illustration of how short term depression suppresses the transmission of low frequency oscillations at high firing rates. The mapping from presynaptic rate to mean synaptic conductance (black curve) saturates at high rates for depressing synapses. As a result, rate fluctuations superimposed on a high baseline rate (lower red curve) are mapped to small amplitude fluctuations in the conductance (upper red curve), but rate fluctuations around a lower baseline are mapped to larger fluctuations in conductance (blue curves). F) Same as (E) but derived from a static synapse model, which maps presynaptic spiking to conductance linearly, such that the amplitude of conductance fluctuations is independent of baseline rate.

Figure 4.

DBS-induced axonal and synaptic failure suppress the transfer of rate-coded information over a wide frequency band in a computational model. A) Coherence between a broadband presynaptic rate fluctuation and the postsynaptic conductance it induces before (blue) and during (red) DBS using the depressing model from Figs. 1 and 3C. For the static, non-depressing model from Fig. 3D, the coherence is larger and is unaffected by DBS (overlapping purple curves show coherence before and during DBS). B,C) The linear mutual information rate between the rate-fluctuation and conductance (see Methods) is reduced by more than 3-fold during DBS for the depressing model (compare blue and red bars in B), but is unchanged by DBS for the static model (blue and red bars in C)). D) The simulation from (A) was performed one thousand times with model parameters chosen randomly from one fourth to four times the values used in (A) (see Methods). Percent reduction in coherence averaged over the frequency band 0-50 Hz plotted against percent increase in axon/synapse failure rate (proportion of nascent spikes that fail to release a vesicle) during DBS. Blue dots are from randomly chosen parameters and red dot is from data in (A).

Figure 5.

DBS-induced depression of the primate subthalamopallidal pathway. A) Fifty overlaid peri-stimulus segments from a recording in GPi of Monkey A. In each case, stimulation of STN was applied both at 0 ms and at 6.67 ms (marked by a vertical gray line). B-C) Peri-stimulus histograms (PSTHs; computed as the average number of spikes per unit time after a DBS pulse) averaged over $n=38$ GP neurons for Monkey A (panel B) and $n=27$ GP neurons for Monkey B (panel C) and averaged over the first 10 s (blue curve) and last 10 s (red curve) of stimulation. Black dashed lines represent the baseline firing rate before stimulation. D) Evolution of the average GP firing rate after stimulation onset for Monkey A (green curve), for Monkey B (purple curve) and for the computational model (black curve). Rates were averaged over 5 s blocks. The data points at time zero represent the baseline firing rate before stimulation. E) The PSTH latency, defined as the latency at which the PSTH reached its maximal value, increases after stimulation onset. PSTHs for (E) computed over 5 s blocks.

Figure 6.

Computational model of subthalamopallidal pathway. A) Each of two model GPi neurons receives input from $n = 500$ correlated STN spike trains that exhibit β oscillations in their firing rates. To simulate DBS in STN, periodic 150 Hz spikes are added to one half of the STN spike trains. Each spike train drives a depressing synapse model and the resulting conductances are summed to determine the total synaptic conductance across each GPi neuron's membrane. Each GPi neuron additionally receives background inhibitory input. The spike trains produced by these two GPi neurons are extracted. B) The power spectrum of STN spike trains has a peak at 13 Hz and decays at higher frequencies. C) Power spectrum of STN spiking recorded in vivo before (blue) and during (red) 150 Hz DBS, from recordings in STN of Macaca fascicularis monkeys and reproduced with permission from Moran, et al., 2011a.

Figure 7.

DBS-induced short term depression suppresses β oscillations in a computational model, consistent with previously reported in vivo data. A) Normalized power spectra of i) the excitatory synaptic conductance across the membrane of one model GPi neuron, ii) one model GPi neuron's spike train and iii) single unit spiking activity in primate GPi. B) STN-GPi coherence calculated between i) one model STN spike train and the synaptic conductance across the membrane of one model GPi neuron, ii) one model STN spike train and one GPi model spike train and iii) background unit activity (BUA) in STN and BUA in GPi. BUA, which is believed to reflect the summed spiking activity of neurons in the near vicinity of the electrode, is the residual high-frequency signal present following deletion of discriminable action potential waveforms (Moran et al., 2011a). C) GPI-GPi coherence calculated between i) the synaptic conductance across the membranes of two model GPi neurons, ii) the spiking activity of two model GPi neurons and iii) the BUA from two

electrodes in primate GPi. In all panels, blue traces correspond to the absence of DBS, red to the presence of DBS. All model data were generated using the model illustrated in Fig. 6. Power spectra were normalized by the average power in the 5-30 Hz range. All panels in this figure containing primate data (column iii) are from recordings in STN and GPi of *Macaca fascicularis* monkeys and are reproduced with permission from Moran, et al., 2011a.

Figure 8.

β oscillations and synchrony are suppressed at higher DBS frequencies and with more STN axons activated in a computational model. A) Peak β power in GPi spike trains, B) peak β coherence between STN and GPi spike trains, and C) peak β coherence between two GPi spike trains as a function of the frequency of DBS pulses. Peaks are defined as maximum of the power spectrum or coherence over the frequency domain 10-15 Hz. Three different stimulation protocols were tested: periodic, periodic with pauses, and Poisson (see inset and Methods). D,E,F) Same as (A-C), but plotted as a function of the proportion of STN axons entrained to the DBS pulses. In all plots, the left-most point (zero stimulus frequency and zero axons stimulated) is calculated from simulations with no DBS. Simulations were performed identically to those in Fig. 7 other than the indicated parameter changes.