Deep brain stimulation entrains local neuronal firing in human globus pallidus internus

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Deep brain stimulation (DBS) is a powerful therapeutic tool in the treatment of intractable neurological diseases and movement disorders (Aouizerate et al. 2004; Laxton et al. 2010; Mayberg et al. 2005). For patients suffering from Parkinson’s disease, DBS improves quality of life and motor function after medications lose efficacy or side-effects become intolerable. The most common stimulation targets for Parkinson’s disease are motor-related nuclei within the thalamus and basal ganglia, including the subthalamic nucleus (STN) and globus pallidus internus (GPI) (Ghika et al. 1998; Siegfried and Lippitz 1994). Although the locations of efficacious clinical targets are now well established, the therapeutic mechanisms of action are still not fully understood (Benazzouz and Hallett 2000; Hammond et al. 2008; McIntyre et al. 2004; Montgomery and Baker 2000). The expanding range of uses of DBS and increasing number of patients with implants emphasize the need to understand how stimulation produces its therapeutic effects to improve existing therapies and develop new treatments.

In the treatment of Parkinson’s disease, the symptomatic relief from stimulation of the GPI is similar to that of an ablative lesion, and so, inhibition of local neuronal activity was proposed as the mechanism of action for DBS (Bergman et al. 1990; Limousin et al. 1995; Siegfried and Lippitz 1994). This idea was supported by observations that firing rates for GPI neurons are pathologically increased in parkinsonian states and that high-frequency stimulation using microelectrodes suppresses somatic activation of local neurons (Boraud et al. 1996; Dostrovsky et al. 2000; Filali et al. 2004; Lafreniere-Roula et al. 2010). However, the idea of complete inhibition has been challenged by recent observations of sustained or even increased neuronal firing of local GPI neurons during therapeutic stimulation. When using DBS macroelectrodes, stimulation in the GPI of a parkinsonian nonhuman primate produces complex patterns of neuronal entrainment relative to the stimulus pulse (Bar-Gad et al. 2004; McCairn and Turner 2009). Additionally, therapeutically effective stimulation in the STN, an area that sends excitatory projections to the GPI, produces similar firing patterns of GPI neurons (Hashimoto et al. 2003; Moran et al. 2011). Thus rather than simply silencing GPI activity, the therapeutic action of DBS in basal ganglia targets may involve entrainment or regularization of neuronal firing (Garcia et al. 2005a; Guo et al. 2008; Hahn et al. 2008; Meissner et al. 2005; Montgomery and Baker 2000; Rubin and Terman 2004). The idea of blocking pathological patterns through increased regularity is supported by observations that irregular high-frequency stimulation is less therapeutically efficacious than temporally regular stimulation in reducing bradykinesia and tremor (Birdno et al. 2012; Dorval et al. 2010). These results from primate models suggest that therapeutic DBS in humans likely does not simply silence GPI neurons, although significant physiological differences often exist between animal models and true human disease states. To complement work in animal models, we evaluated how DBS in the human GPI changed firing of local neurons in unanesthetized patients with Parkinson’s disease. Stimulation with DBS macroelectrodes decreased somatic firing and entrained activity of local neurons, and these changes in firing were sufficient to reduce error in a model of thalamocortical (TC) firing.
METHODS

Patient consent. Eleven patients receiving a bilateral DBS implant in the GPi as treatment for Parkinson’s disease consented to participate in this study, which was approved by the local Institutional Review Board (Oregon Health & Science University Institutional Review Board #6169). The standard surgical procedure uses two neuronal recordings during implantation to verify correct stimulator placement within the boundaries of the GPi. Participation in the research study added ~15–30 min to the normal duration of the DBS implantation surgery.

Intraoperative recordings. The standard stimulator implantation surgery is done with only local anesthesia and consists of placing the stimulating electrode (Activa Therapy model 3387 lead; Medtronic, Minneapolis, MN) into the GPi using predetermined stereotaxic coordinates, based on the Schaltenbrand and Wahren (1977) stereotactic atlas. Coordinates within the GPi were chosen using MRI with FrameLink Stereotaxic Linking System 4.1.9 (Medtronic), and patients were placed in a Leksell Frame G stereotaxic frame (Elekta AB, Stockholm, Sweden) for electrode guidance. Bilateral burr holes were drilled under local anesthesia; no study patients received intraoperative narcotics or sedation prior to the recordings. After the dura was opened, two microelectrodes (320–700 kΩ; 2 mm separation; FHC, Bowdoin, ME) were advanced through the introducer cannula until a clear transition from the external globus pallidus (GPs) to the GPi was identified. This transition generally occurs ≥5 mm from the ventral border of the GPi. The center (target) microelectrode was then replaced with the low-impedance DBS macroelectrode (~4 kΩ), with contact 0 at the same depth as the microelectrode (Fig. 1). Based on the DBS electrode radius of 0.635 mm, the surface of DBS electrode contact 0 was 1.365-mm away from the tip of the remaining recording microelectrode (Carlson et al. 2009).

Standard microelectrode recording/mapping of the GPi was carried out using a MicroGuide Pro microrecording system (Alpha Omega, Nazareth Illit, Israel). The DBS/microelectrode pair was advanced in micron increments, until the stable waveform of a single GPi neuron was distinguished. Baseline firing was recorded for at least 60 s, and then stimulation (88–180 Hz, 0.1-ms pulse width, 1–8 V) was applied through the DBS electrode using a handheld portable stimulator device (Medtronic Navigation, Louisville, CO). The majority of trials was centered on 100 Hz as the stimulation frequency, although the stimulation trials for one patient were conducted at 180 Hz (Table 1). Bipolar stimulation (5–25 s) was applied either locally, with the pair of contacts closest to the recording electrode (contact 0 as cathode, contact 1 as anode; referred to as “local stimulation”), or distally, with the pair farthest from the tip of the recording electrode (contact 2 as anode, contact 3 as cathode; referred to as “distal stimulation”; Fig. 1). For each cell, a number of trials at different voltages for either local or distal stimulation were performed, with at least 30 s between trials. Because of limitations and variability in human neuronal recordings and the artifact removal process, usable data were not available for all stimulation conditions for all neurons. In the occasional case where the same stimulation condition was applied more than once to the same neuron, the averaged response for the two trials was incorporated into the analysis. The electrode pair was advanced until encountering the ventral border of the GPi, which was identified from stereotaxic coordinates and characteristics of the microelectrode recording.

After neuronal recording and placement of the DBS electrode, the locations of the recording and DBS electrodes were verified as being on target using intraoperative fluoroscopy. For each cell, the relative distance of the DBS electrode from the ventral border of the GPi (the stereotaxic target) was recorded at the end of each procedure.

Spike sorting and artifact removal. Neuronal activity was displayed in real time and simultaneously recorded for offline analysis. Recordings were digitized at 15 kHz and stored as Alpha Omega systems files. Spike sorting and subsequent analyses were performed using Spike2 (CED, Cambridge, UK) and MATLAB (MathWorks, Natick, MA). Stimulation artifacts were apparent in most recordings, and these were detected and removed (Erez et al. 2010). Briefly, designated periods of the stimulation artifact were used to design an artifact template that was then subtracted from the original recording at the start of each stimulation impulse (Fig. 2A). The resulting signal often included a period at the beginning of the stimulation artifact, where complete amplifier saturation prevented recovery of the original signal; this unusable period was recognized and measured by the software. The mean duration of the unusable period was noted for each stimulation trial, and calculations were adjusted accordingly.

Following artifact removal, individual action potentials were sorted using waveform template-matching to confirm the continuity of a single cell recording before, during, and after stimulation (Fig. 2B). After satisfactory spike sorting, an autocorrelogram was generated for every neuronal recording using MATLAB to verify the presence of only a single neuron (Fig. 2C). The presence of the refractory period and the accompanying short-term peak indicates that only a single neuron was under consideration for a given period (Bar-Gad et al. 2001; Montgomery 2006). Forty-five neurons and 186 stimulation trials from 11 patients were of sufficiently high quality to ensure that a single neuron was recorded throughout. Only these data were used in subsequent analyses.

Analysis of DBS-driven changes in firing rate. Analysis of firing focused on changes in firing rate and firing pattern in response to stimulation. Mean pre- and poststimulation firing rates were calculated using the number of action potentials in the 10 s before and after the stimulation epoch, respectively. The firing rate during stimulation was measured as the cumulative number of action potentials divided by the total stimulation time and corrected for the amount of unusable time resulting from stimulation artifact removal for that neuron, which was 3.2 ± 0.16 ms or roughly 32% of the duty cycle for 100 Hz stimulation. Comparisons of firing rates before, during, and after stimulation were made using a one-way, repeated-measures ANOVA, followed by a Newman-Keuls post hoc test, with \( P < 0.05 \) considered statistically significant. Voltage-dependent decreases in firing rate for local and distal stimulation were analyzed using linear regression. The confidence interval (CI) of the slope was analyzed using an F-test to determine if the slope was significantly different than zero.
The neuronal response to stimulation during each trial was classified as no change, increased firing, decreased firing, or complete silence. This classification was determined using a t-test to compare mean firing rates in 1-s bins for 10 s at baseline of the trial with mean corrected firing rates in 1-s bins during stimulation. A value of $P < 0.05$ was considered a significant change in firing rate.

The characterized neuronal responses to stimulation were then separated into trials with low (1–5 V) or high (6–8 V) stimulus voltages. This division was based on therapeutic voltages reported previously (Garcia et al. 2005a) and on the effective voltages selected postoperatively for this cohort of patients, in which 1–5 V was found to be clinically relevant (Table 1). When a single neuron had multiple stimulation trials in the low-voltage range, only the lowest-voltage trial was included in the distribution analysis to avoid repeated, nonindependent values. Similarly, only the highest-voltage trial was included in the distribution analysis when multiple trials were performed in the higher-voltage range. A $\chi^2$ test was used to check for a difference in the distribution of responses between high- and low-voltage cases.

**Table 1. Patient intra- and postoperative stimulation parameters**

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**Analysis of DBS-driven changes in firing pattern.** A peristimulus time histogram (PSTH) for each trial was made by aligning action potentials relative to stimulus pulses. Entrained firing was evident in the PSTH of a subset of trials for almost all neurons; therefore, we examined the distribution of these effects based on lower (1–5 V) and higher (6–8 V) voltages.

To quantify the effect of DBS on burst-firing, a Poisson distribution of interspike intervals classified activity as random or burst-firing for pre- and poststimulation periods (Carlson et al. 2009; Kaneoke and Vitek 1996). With the use of this method, most trials showed no gross change from “bursting” to “nonbursting,” and so a more specific quantification of the time in burst-firing was made using the Poisson surprise method (Legendy and Saleman 1985). With the use of this method, the period of time that the neuron spent in burst mode was measured for the pre- and poststimulation periods in each trial, for a minimum S-value of three ($S = -\log \text{probability of Poisson distribution}$, a measure of the likelihood of a given segment of firing being a burst). The total time in burst-firing was analyzed using a two-way, mixed-design ANOVA, with stimulus voltage (low vs. high) and time (pre- vs. poststimulation; repeated measure) as the factors. Separate analyses were undertaken for local and distal stimulation.

**Simulation of TC relay-cell responses to input from GPi.** To understand the underlying therapeutic mechanism of DBS in the GPi, we modeled the effects of the changes in GPi firing on TC relay cells. This model of a TC cell receiving synaptic input from GPi neurons has been validated and described in detail elsewhere (Guo et al. 2008; Rubin and Terman 2004). Briefly, the TC cell model consists of a system of differential equations that use membrane capacitance and ionic currents to determine changes in membrane voltage and action potential initiation. GPi neuronal activity is integrated into the model as an inhibitory synaptic input current to the TC cell. The model also includes a periodic train of excitatory synaptic inputs to the TC cell.

For each recording of a GPi neuron, the prestimulation, during, and poststimulation firing times of each trial were entered separately into the simulation. Trials with no GPi spikes were excluded, as these trivially give perfect relay, and thus the model is not informative for such cases. The output variable from this analysis was the error index, computed as the fraction of excitatory inputs to which the TC cell failed to generate an action potential or responded with excessive spiking. Lower error indices are associated with greater relay fidelity and have been shown to correspond to an enhanced therapeutic benefit (Guo et al. 2008; Rubin and Terman 2004). The mean effect of stimulation on the error index was compared for each set of stimulation voltages and contact pairs using repeated-measures ANOVA followed by a Dunnett’s post hoc test of the index during stimulation vs. its baseline value.
RESULTS

For each patient, correct stereotaxic placement of the DBS electrode was confirmed using microelectrode recordings and intraoperative X-ray. With final placement of the DBS electrode, the approximate position of each cell was recorded relative to the stereotaxic target, which was the ventral base of the GPi. The majority of cells was clustered along the ventral end of the GPi, with no cells likely recorded from the GPe (Fig. 1).

DBS depressed but did not uniformly silence GPi neuronal firing. Of the cumulative recordings, 45 neuronal recordings and 186 stimulus trials were of sufficient quality to ensure that a single neuron was monitored throughout an entire recording session. Of these trials, 137 were in the local configuration (contact 0 as cathode, contact 1 as anode) and 49 were in the distal configuration (contact 3 as cathode, contact 2 as anode).

The effects of DBS on firing rate in individual trials ranged from an increase in firing rate to complete silencing (Fig. 3, A–D). The effect on each trial was classified as increased firing, partially decreased firing, complete silence, or no change in firing rate, and the distribution of effects categorized for local and distal stimulation between high and low voltages (examples in Fig. 3E). For distal stimulation, no difference was found in the distribution of responses between low- and high-voltage stimulation ($X^2(3, df) = 2.7; P > 0.1$). Conversely, for local stimulation, a significant difference exists between the distribution of responses between high and low voltages ($X^2(3, df) = 20.5; P < 0.001$), with a greater number of cells silenced completely at high voltages.

Stimulation at all voltages, both locally and distally, significantly decreased the mean firing rate (Fig. 4), compared with pre- and poststimulation rates [repeated-measures ANOVA followed by a Newman-Keuls post hoc: local stimulation, 2 V $F(2,29) = 32.66, P < 0.001$; 4 V $F(2,30) = 87.95, P < 0.0001$; 6 V $F(2,17) = 36.75, P < 0.001$; 8 V $F(2,22) = 64.93, P < 0.001$; distal stimulation: 2 V $F(2,8) = 8.35, P < 0.01$; 4 V $F(2,15) = 15.93, P < 0.001$; 6 V $F(2,6) = 8.13, P < 0.01$; 8 V $F(2,8) = 14.58, P < 0.001$]. No significant differences existed between pre- and poststimulus mean firing rates, either for local or distal stimulation.

These changes in mean firing rates with local stimulation were voltage dependent, with greater decreases at higher voltages (slope of linear regression: $-9.4 \text{ Hz/V}; 95\% \text{ CI: } -16.2 \text{ to } -2.5 \text{ Hz/V}; P < 0.05$; Fig. 4). Distal stimulation did not show a similar voltage-dependent decrease in firing (slope of linear regression: $-5.5 \text{ Hz/V}; 95\% \text{ CI: } -10.5 \text{ to } 0.4 \text{ Hz/V}; P > 0.05$).

Loose entrainment to stimulation occurred in the majority of human GPi neurons. The effect of stimulation on firing pattern differed across voltages, stimulation parameters, and neurons. Changes in firing pattern were examined through PSTHs. Individual neurons and trials showed complex responses rela-

Fig. 2. Template subtraction, spike sorting, and waveform analyses allow individual action potentials to be discerned during stimulation with a high degree of confidence. A: in an example of artifact removal, at baseline, 2 distinct action potential waveforms are distinguishable (arrows and arrowheads indicate the 2 waveforms). During stimulation, a large artifact prevents distinguishing neuronal activity or matching action potentials to previously identified waveforms, but after subtraction, waveforms are again distinguishable. B: action potential waveforms are overlaid to show continuity of recording from a single neuron after artifact removal throughout the entire stimulation trial. Spikes recorded before and after stimulus train are shown in black; those during the stimulus train in gray. C: in this example autocorrelogram, the refractory period around time 0 and surrounding short-term peaks indicate that only a single neuron was under consideration during the recording (Bar-Gad et al. 2001; Montgomery 2006).
tive to the stimulus impulse, with alternating periods of increased and decreased likelihood of firing relative to each pulse (Fig. 5A). Cells often showed two distinct time periods of increased likelihood of firing separated by 1- to 2-ms periods when the cell was less likely to fire an action potential (Fig. 5A). Some cells showed other mixed responses, including fewer or more periods of increased likelihood of firing (Fig. 5, B and C), and a portion of cells did not change firing pattern (Fig. 5D). Figure 5E shows the distribution of response types with distal and local stimulation at low- and high-stimulus voltages. With distal stimulation, most cells were not entrained at lower voltages, but loose entrainment of firing was prevalent at higher voltages. With local stimulation, at lower voltages, the dominant change in pattern was entrainment, and at higher voltages, complete cessation of firing was most common.

Neurons with loose entrainment showed decreased firing at the onset of the stimulus train. In the seconds after the start of stimulation, some neurons showed a period of silence, followed by a slow increase in firing rate over the course of stimulation (example in Fig. 3C). This effect was observed predominantly in cells that also showed entrainment of firing. Without regard to voltage or contacts, cells that showed any form of entrained firing had a significantly lower average firing rate in the 1st s of stimulation compared with the last second of stimulation (respectively, 40.9 ± 5.4 Hz vs. 69.2 ± 5.4 Hz; P < 0.001, paired t-test). Cells with a flat PSTH (no entrained firing) did not have decreased firing at the start of stimulation and did not show a significant difference between rates at the start and end of stimulation (respectively, 75.7 ± 11.0 Hz vs. 82.3 ± 11.5 Hz; P = 0.62, paired t-test). Notably, by the end of the stimulus period, the firing rates of cells with entrainment were not significantly different from those of nonlocked cells (P = 0.24, unpaired t-test). Thus neurons exhibiting entrainment consistently fired fewer action potentials at the start of stimulation but resumed firing at a rate comparable with cells without entrainment by the end of the stimulus train. This effect was maintained even when the responses were subdivided into local and distal responses (data not shown).

Poststimulus-bursting was decreased. Neurons spent less time in burst-firing in the period immediately after the cessation of stimulation compared with the period of time just prior to stimulation (Fig. 6). Specific time in burst activity was quantified before and after stimulation, and these values were compared using a two-way ANOVA with time (pre- vs. post-stimulation) and voltage (low vs. high) as factors. Stimulation at both local and distal contacts significantly decreased the percent of time bursting after stimulation compared with immediately before, independent of voltage. Local stimulation significantly reduced burst activity from 41.2 ± 2.2% before the onset of stimulation to 33.7 ± 1.9% immediately after the end of stimulation [F(1,119) = 15.4; P = 0.0001]. In the distal configuration, stimulation also significantly reduced the time in

**Fig. 3.** Examples from separate neurons showing responses to local GPi stimulation. Responses ranged from (A) no change in firing rate during stimulation, (B) a significant increase in firing, (C) a significant decrease in firing, and (D) complete silence. E: the relative distributions of responses to distal and local stimulation are shown for low (1–5 V) and high (6–8 V) voltages. With distal stimulation, the most common neuronal response was decreased firing, although some cells showed no change in firing rate, and a small number of cells had a well-defined increase in firing. With low-voltage (1–5 V) local stimulation, most neurons had decreased firing but were not silenced completely. With local stimulation at higher voltages (6–8 V), most cells were silenced.

**Fig. 4.** Mean firing rate of GPi neurons at baseline and during stimulation with different voltages. Both local and distal stimulation produced significant decreases in mean firing rate compared with baseline, but only the effect of local stimulation was voltage dependent. sp/s, spikes/s. Values are means ± SE.
burst activity, from 42.6 ± 6.8% to 28.6 ± 3.7% [F(1,33) = 6.66; P = 0.015].

Low-voltage DBS in GPi reduced the TC cell error index. For each stimulation trial with GPi spiking, the prestimulation, during, and poststimulation spike times were used to generate an inhibitory synaptic input into a conductance-based model of a TC relay cell (Guo et al. 2008), which was also subject to a computationally generated excitatory synaptic signal. An error index was computed as a measure of the fidelity of the resulting signal transmission. When using the distal contacts, both low- and high-voltage stimulation produced a slight but not statistically significant decrease in the error index during stimulation compared with baseline values (Fig. 7). With local stimulation, lower voltages (1–5 V) produced a statistically significant decrease in the error index [F(2,48) = 3.71; P < 0.001]. Local stimulation with higher voltages (6–8 V) did not produce a
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Fig. 6. Raw recording showing an example of decreased burst-firing after stimulation. Prior to the onset of stimulation, this neuron showed a rapid burst of action potentials with decreasing amplitudes, followed by a short period of quiescence (arrowhead marks bursting, as detected by the Poisson surprise method). Immediately after a 14-s period of stimulation, the same cell displayed more regular firing without burst activity. These example segments were taken from 10-s epochs before and after stimulation, with mean firing rates of 67.1 Hz and 66.1 Hz, respectively.

significant change in the error index during stimulation but did mildly increase the error index after cessation of stimulation.

DISCUSSION

DBS in the GPi is thought to relieve movement-related symptoms of Parkinson’s disease through effects on the local neuronal somata, fibers of passage, and other nearby neuronal elements (Benazzouz and Hallett 2000; Garcia et al. 2005a; Hammond et al. 2008; Holsheimer et al. 2000; McIntyre and Hahn 2009; Montgomery and Baker 2000; Ranck 1975). The present experiments showed that DBS in the GPi of awake, unanesthetized patients with Parkinson’s disease induces changes in both firing rate and firing patterns of nearby neurons. Stimulation in the therapeutic voltage range reduced the mean neuronal firing rate, although not all neurons displayed decreased firing during stimulation. DBS also loosely entrained neuronal firing in complex patterns and reduced the time spent in burst firing immediately after the cessation of stimulation. To understand how these changes in firing could improve symptoms, the recorded spike times from human GPi were applied to a model TC cell with an excitatory input. The changes in firing associated with therapeutically relevant stimulation improved the reliability of TC relay, an effect likely related to changes in firing pattern and increased regularity.

DBS decreases the mean firing rate but does not uniformly silence GPi neurons. In Parkinson’s disease and animal models of Parkinson’s disease, GPi neurons have increased firing rates, and decreasing this pathologically increased firing has been proposed as a therapeutic mechanism of action of DBS (Bergman et al. 1994; Filion and Tremblay 1991; Starr et al. 2005). Indeed, decreasing the inhibitory output from GPi correlates with therapeutic effect (Boraud et al. 1996). However, in other settings, therapeutically effective DBS can paradoxically increase the firing of GPi neurons, so decreased GPi activity may not be the only, or even primary, therapeutic mechanism of DBS (Garcia et al. 2005a; Hahn et al. 2008; Hashimoto et al. 2003; Montgomery and Baker 2000; Obeso et al. 2000; Rubin and Terman 2004). In the present experiments, local stimulation decreased the mean neuronal firing rate in a voltage-dependent manner. Although some neurons exhibited no significant change in firing or even increased firing in response to stimulation, during local stimulation, the majority of neurons had moderately decreased firing at lower voltages and complete silencing at higher voltages. These decreases in firing are similar to predicted changes in firing rates from a computational model (Johnson and McIntyre 2008), although the interpretation of these decreases in firing should take into consideration the presence of an irremovable portion of the stimulation artifact. This remaining artifact after template subtraction could still obscure some tightly entrained action potentials occurring immediately after the pulse. Therefore, the changes reported here represent lower bounds on firing and may, in fact, underestimate the firing rate during stimulation.

These observations of voltage-dependent decreases in firing compare well with previous recordings from human GPi, where increasing stimulation intensity produced greater decreases in firing of local neurons (Dostrovsky et al. 2000; Lafreniere-Roula et al. 2010). However, in prior observations, the decreased activity was in the period immediately after each stimulation pulse, and increasing the stimulation frequency completely silenced neuronal activity by connecting these short periods of inhibition. In the present work, we observed cessation of neuronal activity primarily at higher voltages, and during therapeutically relevant voltages we found modest decreases in firing in conjunction with loose entrainment. These differences may be explained by the use of recording microelectrodes for stimulation, which have a higher impedance and lower surface area (500 kΩ impedance, approximate point stimulation) than DBS macroelectrodes (1 kΩ impedance, 6 mm² of stimulation surface area). Electrode choice could thus result in a difference in current density by as much as two orders of magnitude (Carlson et al. 2009; Garcia et al. 2005b). Also, the greater distance from the recording electrode to the stimulating electrode in the present work could contribute to the differences in observed effects (Holsheimer et al. 2000).

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Fig. 7. Low-voltage local stimulation significantly improves model thalamocortical (TC) cell relay. Spiking data from human recordings prior to, during, and after DBS were used as input for a model TC relay-cell subject to a periodic excitatory signal, and an error index was computed based on TC relay performance. Only local stimulation at therapeutic voltages produced a statistically significant decrease in the error index during stimulation relative to nonstimulation periods (***P < 0.001, repeated-measures ANOVA, Dunnett’s post hoc test). Values are means ± SE.
That is, cathodic stimulation can produce a core of complete neuronal inhibition near the electrode and then progressively decrease neuronal inhibition farther from the source (Kiss et al. 2002; Perlmutter and Mink 2006; Ranck 1975). Here, complete silencing of neuronal activity occurred primarily during local stimulation with higher voltages when the stronger stimulation source was closer to the neuron. During distal stimulation, the neurons did not show the same voltage-response relationship, although they still frequently showed entrainment.

**Entrained firing and increased neuronal regularity occur during DBS.** Reduction of burst activity and alteration of pathological firing patterns have also been proposed as therapeutic mechanisms in the treatment of Parkinson’s disease (Benabid et al. 1991; Fogelson et al. 2005; Grill et al. 2004; Rubin and Terman 2004). Neurons recorded here had both decreased burst-firing after stimulation and increased regularity during stimulation. This regularity manifests as a loose entrainment of firing relative to each stimulation impulse. The entrainment included complex patterns of alternating increases and decreases in firing probability, although the activity was not sufficiently time locked to be antidromic. These complex patterns were observed more frequently in stimulation with therapeutically relevant parameters than with higher voltages or distal stimulation. Such loose entrainment is not unique to GPI stimulation, as similar patterns of entrainment have been observed in other therapeutic contexts. GPI neurons in the nonhuman primate show entrainment with either local GPI stimulation or stimulation in the STN (Bar-Gad et al. 2004; Hashimoto et al. 2003; McCaig and Turner 2009). Stimulation in either the STN or GPI likewise entrains firing of thalamic neurons (Anderson et al. 2003; Montgomery 2006; Xu et al. 2008), and DBS in the STN produces similar complex firing patterns in local neurons and in neurons of the contralateral STN (Carlson et al. 2009; Walker et al. 2011). Since DBS in either GPI or STN is sufficient to entrain firing in both GPI and thalamic neurons, high-frequency stimulation in different sites could engage a common therapeutic mechanism. Loose entrainment has been proposed to replace pathological rhythms with more ordered, regular firing, and indeed, regular stimulation is more therapeutically efficacious than irregular stimulation (Anderson et al. 2003; Dorval et al. 2010; Garcia et al. 2005a; Montgomery 2005).

A computational model of the basal ganglia-thalamic pathway predicts that regular, high-frequency stimulation produces therapeutic effects by entraining or otherwise regularizing activity downstream from the stimulation site (Rubin and Terman 2004). In this model, tonic or highly regular firing produces the lowest error index in simulated TC neurons, whereas irregular firing and bursting produce the highest error indices (Guo et al. 2008). A decrease in the thalamic relay error index has previously been observed when driving model neurons using spike times from GPI neurons recorded during application of STN–DBS at therapeutic voltages (Guo et al. 2008). Here, we used activity recorded from human GPI during stimulation, and we tested whether the observed stimulation effects on activity recorded from the somata of local neurons were sufficient to improve thalamic relay fidelity. A significant decrease in error index was only seen during local stimulation in the therapeutic voltage range, and these stimulation parameters also most consistently produced loose entrainment of neuronal activity. From these observations, we conclude that the increased regularity of somatic activity in human GPI neurons is sufficient to improve TC cell relay fidelity and that this mechanism could contribute to the therapeutic action of DBS.

The observed changes in somatic activity of GPI neurons are sufficient to improve TC relay fidelity, but the definitive neuronal mechanism underlying symptomatic relief remains unclear. The changes in somatic activity seen here, including variable latency responses with stereotyped patterns of activation, are consistent with presynaptic axonal stimulation with subsequent synaptic effects—a mechanism that has been implicated previously in the therapeutic effects of DBS (Birdno et al. 2012; Gradinaru et al. 2009). However, DBS can also drive axonal firing, independent of somatic activity (McIntyre and Grill 1999; Miocinovic et al. 2006), and fibers of passage and axons are now accepted as important therapeutic targets for DBS (Gradinaru et al. 2009; Johnson and McIntyre 2008; Maks et al. 2009). Axonal activation, independent of somatic activity, would explain how increased neuronal output could occur during stimulation of either STN or GPI (Anderson et al. 2003; Hashimoto et al. 2003; Xu et al. 2008), despite decreased or unchanged somatic firing rates (Benazzouz et al. 1995; Beurrier et al. 2001; Carlson et al. 2009; Dostrovsky et al. 2000; Lafreniere-Roula et al. 2010). Regardless, a significant physiological effect from axonal activation does not rule out a separate contribution from alterations in somatic activity, as pharmacological inhibition of GPI neuronal activity is alone sufficient to relieve parkinsonian motor symptoms in primate models (Baron et al. 2002). The symptomatic benefits of DBS in GPI, therefore, may arise from combined effects on multiple neuronal elements, as suggested by Johnson et al. (2012). They proposed that DBS decreases rigidity through the activation of fibers of passage in the adjacent section of the internal capsule, and the improvements in bradykinesia come from activation of neurons in GPI and GPe (Johnson et al. 2012). Just as Parkinson’s disease manifests with complex symptoms involving multiple brain sites, symptomatic relief with DBS may involve multiple neuronal mechanisms.

**Conclusion.** These results show that DBS, using implanted macroelectrodes in the GPI of the unanesthetized human, does not uniformly silence GPI activity but instead modestly decreases population activity while entraining somatic firing. Modeling of TC relay-cell activity shows that these changes in GPI firing patterns, if synaptically transmitted to downstream targets, would have the capacity to restore relay fidelity. These results illustrate one possible therapeutic mechanism of DBS, although other effects of DBS likely contribute in parallel, including axonal activation and entrainment of neurons in other regions.

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DISCLOSURES

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AUTHOR CONTRIBUTIONS

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