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Cortical Effects of Subthalamic Stimulation Correlate with Behavioral Recovery from Dopamine Antagonist Induced Akinesia

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High-frequency stimulation of around 130 Hz delivered to the subthalamic nucleus (STN-DBS [deep brain stimulation]) is an effective treatment of Parkinson's disease (PD), but the mechanisms of its therapeutic effect remain obscure. Recently, it has been shown in anaesthetized rats that STN-DBS antidromically activates cortical neurons with coincident reduction of the cortical slow wave oscillations that occur in this preparation. Here we extend this work; recording the effect of STN-DBS upon cortical EEG and akinesia, in unanesthetized rats rendered cataleptic by acute dopaminergic blockade. STN-DBS–like stimulation resulted in a short latency, presumed antidromic, evoked potential in the cortex. In cataleptic animals, there was a significant increase in the power of beta oscillations in the electroencephalography which was reversed by stimulation that evoked the cortical response. We also observed a significant rescue of motor function, with the level of akinesia (bar test score) being inversely correlated to the amplitude of the evoked potential ($R^2 = 0.84$). These data confirm that (probably antidromic) short latency cortical responses occur in the awake animal and that these are associated with reductions in abnormal cortical oscillations characteristic of PD and with improvements in akinesia. Our results raise the possibility that STN-DBS reduces PD oscillations and symptoms through antidromic cortical activation.

Keywords: antidromic cortical activation, basal ganglia, behavioral recovery, beta band frequencies, dopamine receptor blockers, EEG

Introduction

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is an effective treatment of Parkinson's disease (PD) in patients and animal models (Benazzouz et al. 1993; Benabid et al. 1994). However, the therapeutic action of STN-DBS remains poorly understood. Because lesions of the STN are also effective (Bergman et al. 1990), it has been postulated that STN-DBS reduces the firing of STN cells (Magarinos-Ascone et al. 2002; Garcia et al. 2003; Meissner et al. 2005) which in turn modulates the activity of the output nuclei of the basal ganglia (Hashimoto et al. 2003; Maurice et al. 2003; Taï et al. 2003; Shi et al. 2006; Meissner et al. 2007). However, STN-DBS induces an increase, and not the predicted decrease, of glutamate release in these structures (Windels et al. 2000). Gamma-aminobutyric acid (GABA) release also increases with DBS, but this GABA release does not depend on the STN, and may instead arise from direct activation of afferents from the globus pallidus pars externa (GPe) (Windels et al. 2005).

Indeed, biophysical and anatomical data suggests that STN-DBS may selectively activate fibers of passage (McIntyre et al. 2004). GPe efferent axons pass close to the STN (Kita and Kitai 1994), where the excitation of these fibers could trigger release of GABA in the basal ganglia output nuclei. In addition to these basal ganglia pathways, STN-DBS may be able to directly activate cerebral cortex via antidromic impulses in corticofugal axons. Corticofugal axons pass directly below STN en route for the brainstem and spinal cord, and fibers of the "hyperdirect" pathway from cortex enter STN (Kitai and Deniau 1981). These pathways may be affected by STN-DBS, and could cause cortical activity to change. In a study of PD patients, a short latency (3 ms) activation of the cortex was observed during STN-DBS (Ashby et al. 2001) and similar responses were observed in anaesthetized rats (Li et al. 2007). Antidromic activation of cortex is thus another candidate for mediating the therapeutic effects of STN-DBS.

The cortical electroencephalography (EEG) and basal ganglia local field potentials in parkinsonism show increased oscillatory activity in the beta band (12–30 Hz) (Hutchison et al. 2004; Boraud et al. 2005; Hammond et al. 2007). During STN-DBS, symptoms improve in association with decreased basal ganglia oscillations (Brown and Williams 2005; Kuhn et al. 2008). In anesthetized rats STN-DBS that antidromically activates cortical neurons is associated with reduction of anesthetic-induced cortical slow wave oscillations (Li et al. 2007). Such cortical activation may also disrupt abnormal oscillatory activity characteristic of PD. STN-DBS has already been shown to reverse akinesia in acute, drug-induced, catalepsy (Degos et al. 2005). However, correlation between behavioral improvement and cortical EEG has not been attempted. Although not sufficient proof, correlation is a necessary prediction of the antidromic hypothesis. Therefore, in the present study we set out to determine 1) whether the antidromic activation seen in anesthetized rats occurs in the awake animal; 2) if the stimulation modulates abnormal beta activity characteristic of PD; and 3) whether the stimulation effective for 1) and 2) is also capable of producing therapeutic effect.

Materials and Methods

Animals

Nine male Wistar rats (300–350 g) were kept under standard housing conditions at constant temperature (22 ± 1 °C), humidity (30%), and in reversed 12-h light/dark cycles (daylight period 8 PM–8 AM). Animal care and surgery were consistent with the National Institute of Health *Guide for the Care and Use of Laboratory Animals* as well as the NZ Animal Ethics Legislation and was approved by the Animal Ethics Committee of the University of Otago.

Surgery

Each animal was anesthetized with medetomidine (Domitor, Novartis NZ, Auckland, New Zealand, 0.5 mg/kg) and ketamine (Parnell Laboratories, Auckland, New Zealand, 75 mg/kg i.p.). The rat was

placed in a stereotaxic frame (Kopf Instruments, Tujunga, CA) then the skull was exposed by a midline sagittal incision and cleared of subcutaneous connective tissue. For each hemisphere, a hole (2 mm diameter) was drilled in the skull above the STN for bilateral implantation of stimulating electrodes. The STN coordinates were as follows: flat skull, bregma origin, anterior −3.8 mm, lateral ±2.5 mm, depth 8 mm from cortical surface (Paxinos and Watson 1986). For EEG recording 2 1-mm screws, each with a wire and socket attached, were screwed into holes drilled in the skull so that they were placed just above the dura mater in the region of the frontal cortex of each hemisphere (origin: bregma, anterior: +2.5 mm, lateral: ±2.5 mm). A third such screw was inserted above the cerebellum so that it did not pierce the bone and was used as a reference for the EEGs. Four additional anchoring screws were placed in the skull. All screws were embedded in dental cement (Vertex, Zeist, The Netherlands) with care taken to leave the holes above STN clear. The dura mater was then reflected above the STN and the bipolar concentric stainless steel electrodes (SNEX-100, Rhodes Medical Instruments, Summerland, CA) were slowly lowered to reach the depth defined for the target. Wires, from the EEG leads and the stimulating electrodes, were connected to a 9 pin circular socket (Ginder Scientific, Nepean, Ontario, Canada) through which they could be attached to recording and stimulation equipment via a commutator-swivel (Crist Instrument Co., Hagerstown, MD) during the experimental sessions. The exposed brain surface was sealed with petroleum jelly and the whole assembly was secured with dental cement. The wound area was disinfected and the animals were allowed to recover for at least 7 days before being handled to familiarize them with the experimenter and the headpiece attachment.

Electrophysiological Data Acquisition

During recording sessions, EEG signals were passed through unity gain impedance matching preamplifiers in the head-plug and amplified (100×) and filtered between 0.1 and 1 kHz using a CyberAmp signal conditioner (Molecular Devices, Union City, CA). The signals were then digitized (12 500 Hz) and recorded using a Power1401 A-D converter and Spike2 data acquisition program (version 6.04, Cambridge Electronic Design, Cambridge, UK).

Behavior

We assessed the degree of akinesia during catalepsy induced by the injection of the dopaminergic antagonists with the bar test (Hauber and Munkle 1995; Wadenberg and Seeman 1999). In this test the forepaws of the animal were placed on a horizontal bar 10 cm above the ground, and we recorded the latency for the animal to withdraw at least one forepaw from the bar and to touch the floor with it. A maximum latency cutoff time was set at 140 s.

Behavior during recording sessions was marked on the data file as either "moving" (including locomotion, rearing, grooming) or "still" by entering codes on a keyboard marker channel.

Protocol

We compared the behavior and frontal EEG before and after dopaminergic antagonists in 2 conditions: *nonstimulated* then *stimulated*. The experiment lasted for 3 days, as follows.

On day 1 (*nonstimulated* condition), the animal was placed in the recording chamber and EEG signals were recorded for 20 min. After the first 10 min the animal was given an injection of D1 and D2 antagonists Sch23390 (Sigma-Aldrich NZ, Auckland, New Zealand, 0.5 mg/kg, i.p.) and Raclopride (Sigma-Aldrich NZ, 2 mg/kg, i.p.) in 0.9% saline combined in a single syringe. The level of akinesia of the animal was assessed with 2 bar tests, performed immediately before beginning recordings (i.e., 10 min before injection) and at the end of the recording session (i.e., 10 min after the injection).

On day 2, experiments were performed without drug treatment to determine the threshold for direct motor activation by STN-DBS. The animal was placed in the recording chamber and a STN stimulation ramp was performed. Electrical stimulation consisted of square biphasic pulses of 60-μs length and 50 μA intensity delivered at a rate of 60 or 130 Hz, currents were increased in 20 μA steps until the threshold for motor activation was reached, or to a maximum of 300 μA. The relation between the intensity of the stimulation current and the amplitude of the evoked field potential response to stimulation was determined in the same session. The cortical effect of STN-DBS was tested on each side in different conditions: unilateral or bilateral and at 60 or 130 Hz. The trains of stimuli were delivered for 5 s in the 130 Hz condition and 11 s in the 60-Hz condition. The average response could thus be calculated from similar number of events; 650 and 660, respectively.

On day 3 at least 48 h after the previous drug dose, the first 20 min were the same as day 1 but STN-DBS was applied throughout the session as well as during the bar tests,(*stimulated* condition). The intensity of the current was set at 80% of the motor threshold and ranged from 80 to 225 μA in individual animals. At the end of the session, a bar test was performed in the absence of stimulation to verify the efficacy of the antagonist injection. Then the relation between the amplitude of the evoked potential and the improvement of the akinesia level was tested by conducting bar tests under several different stimulation intensities (3–8 tests). The number of tests was lowered in some animals in which the bar test elicited avoidance behavior. Finally, a bar test was performed upon ceasing stimulation in order to verify that the animal was still cataleptic in the absence of stimulation.

Following completion of the recordings, the chronaxie of the stimulated neural elements was determined from 4 out of the 9 rats. The thresholds for the evoked potentials at pulse widths of 20, 50, 100, and 200 μs were used to plot a strength–duration curve. The chronaxie was defined as the pulse width corresponding to a stimulus intensity twice that of the rheobase (the threshold current at the longest pulse width). The type of neural elements that are activated is related to the "chronaxie" length of the stimulation pulse. For example, measures of less than 100 μs are unlikely to result from the stimulation of unmyelinated structures like cell bodies, whereas shorter values are consistent with stimulation of more excitable myelinated axons (Ranck 1975; Ashby et al. 1998, 2001).

Analysis of Cortical Evoked Potentials

Poststimulus time histograms (PSTHs) of the EEG voltage were used to assess the response of the frontal cortex to STN-DBS. PSTHs were computed by averaging the voltage of the EEG signal in a fixed time window triggered by each stimulus marker. For the purpose of this analysis EEG signal was high-pass filtered above 100 Hz to remove slower oscillations not related to DBS stimulation so the averaging focused on the frequency range of typical antidromically evoked potentials reported by Li et al. (2007).

Spectral Characterization of EEG

For sessions in which animals were undergoing STN-DBS, stimulation artifacts were removed using a *median filter* (Spike2) with a time constant p of 0.8 ms (Supplementary Fig. S1). This filter computes a moving median so that the output at time t is the median value of the input data points from time $t - p$ to $t + p$ seconds. The time constant has been set empirically so that this filter has a maximum effect on the short artifacts (period = 0.06 ms) but a very small influence on events with slower periodicity such as EEG oscillatory components (period generally >10 ms). The signal was down sampled to 250 Hz and high-pass filtered above 1 Hz to exclude very low frequencies and reduce the influence of mechanical artifacts, as well as to remove DC drift from the signal.

The power spectral density (PSD) of the EEG signal was computed using fast Fourier transform (FFT) analysis, and sliding windows of 250 samples (1 s), over the frequency range from 0 to 125 Hz (1 Hz resolution).

The qualitative effect of the antagonists on specific frequency bands was investigated by computing the percentage of change of PSD after the injection. For each frequency, the displayed power value is the percentage of the baseline power averaged over the entire predrug period (from 0 to 10 min). For the purpose of display (Supplementary Fig. S2) percentage of change was computed every minute for the whole test period (20 min) and averaged across all recordings (9 animals, 18 hemispheres). As shown in Figure S2, the antagonists produce an increase in power that is particularly marked in the beta band. As a consequence further analysis were conducted with a focus on the 12–30 Hz range.

The quantitative spectral analyses were conducted with PSD histograms that were normalized across animals by expressing PSD as a percentage of the spectrum below 100 Hz. This threshold was chosen to reduce the influence of the rhythmic evoked potentials (130 Hz) in the frequency domain when comparing stimulated to nonstimulated condition. Power spectra as a function of time were constructed every second from nonoverlapping windows of data using the same parameters as above (Matlab 7.4, The Mathworks, Natick). Power in specific bands was averaged over every minute for the purpose of statistical testing of the detailed comparison of the influence of stimulation and drugs across time.

Statistical Analysis

Statistical analyses were performed using GraphPad Prism (version 4.00, GraphPad Software, San Diego, CA). A probability level of 5% ($P < 0.05$) was considered significant. Variables are presented as mean ± SEM.

All analyses were performed among the 9 animals that entered the study except the chronaxie analysis performed on a subset of 4 rats of the original batch. In each animal we collected EEG data from both hemispheres bringing the number of observations to 18 (or 8 in the case of the chronaxie experiment).

Normality of all data sets was tested with a Kolmogorov–Smirnov test. When the data fulfilled the assumption of a Gaussian distribution, we used a parametric test, otherwise nonparametric tests were used.

The threshold for eliciting cortical response and motor artifacts was compared with the nonparametric Wilcoxon test for paired samples. The locomotor activity of the animal was defined as the time spent moving within 10 min. The oscillatory activity in the beta band was defined as the average percentage of spectral power between 12 and 30 Hz either computed over 10 min or for each minute during this 10-min interval. We compared the effect of 4 experimental conditions (Pre-Drug + STN-DBS OFF; Post-Drug + STN-DBS OFF; Pre-Drug + STN-DBS ON; Post-Drug + STN-DBS ON) on locomotion and beta oscillatory activity over 10 min using a one-way analysis of variance for repeated measures (one-way RM ANOVA). We compared the effect of 2 experimental conditions (STN-DBS OFF; STN-DBS ON) on the evolution of beta oscillatory activity for every 1-min time steps using a one-way RM ANOVA. For both analysis in the cases where the one-way RM ANOVA revealed a significant difference between the sampled populations (F values are reported in the Results section) we performed a post hoc Bonferroni test to compare the average between each conditions. The akinesia level defined as the bar test score was compared in the same 4 conditions as above using a nonparametric one-way analysis of variance on ranks for repeated measures (Kruskall–Wallis test) with post hoc Dunn test.

Histology

Following the final recording, the rats were given a lethal dose of sodium pentobarbitone (Provet NZ, Auckland, New Zealand). Immediately after the injection, electrical microlesions (30 μA, 5–10 s) were induced by passing an anodal current through one electrode at each stimulation site. Sagittal brain sections (50 μm) were cut and those encompassing the STN were mounted on slides to verify the placement of the electrodes. These slices were stained with cresyl violet for structural identification. The electrode tracks and stimulation sites were then established by reconstructing the marks left by the electrode and the electrolesion. In the 9 animals both stimulation sites were located in the STN region (Supplementary Fig. S3), with 16 found in the STN and 2 at the interface between STN and substantia nigra pars reticulata (SNr). Although the electrode contacts span the rat STN (Supplementary Fig. S3a), this is similar to the electrodes used in human therapy, which are also relatively large compared with the size of the human STN.

Results

Antidromically Evoked Potential

The electrical stimulation of the STN evoked polyphasic responses in the cortex (Fig. 1*A*) with an early peak at a latency of 1.9 ± 0.09 ms and a late peak at 11.2 ± 0.41 ms. The early response occurred in a time range close to the conduction time from stimulus site to cortex and therefore likely corresponds to the antidromic response recently characterized with similar stimulation parameters in anaesthetized rats (Li et al. 2007). The latency of the late response is consistent with the activation of synaptic connections. It could be elicited by the antidromic invasion of intracortical axonal branches and/or by stimulating direct cortical afferents. At a stimulation frequency of 130 Hz the late component is obscured by the occurrence of the early component induced by stimulus n+1 (Fig. 1*B*). The cortical response appeared at an average threshold applied current of 81.85 ± 10.22 μA at 130 Hz and its amplitude grew linearly with increasing intensities (Fig. 1*C*). The chronaxie for the fibers producing the cortical effect (Fig. 1*D*) ranged from 40 to 75 μs, consistent with activation of myelinated fibers (Ranck 1975). In contrast, direct motor manifestations of stimulation occurred at an average threshold of 210.5 ± 21.75 μA at 130 Hz, starting with slight forepaw movement and developing into severe dystonia. The threshold for evoking a cortical response was significantly below the motor threshold (Wilcoxon test, $P = 0.0001$) and there was no clear relation between the amplitude of the cortical response and the motor threshold for each animal. All following experiments were performed at and below 80% of the motor threshold so that the stimulation did not directly induce movements of any kind.

In addition to being intensity dependent, we found that the amplitude of the early peak of the cortical evoked potential was also a function of the frequency of the stimulation (one-way RM ANOVA, $F_{2,17} = 30.56$, $P < 0.0001$; Fig. 1*E*). When stimulating unilaterally, the ipsilateral early peak amplitude was significantly larger at 130 Hz than at 60 Hz (respectively, 3.54 ± 0.39 μV and 1.60 ± 0.34 μV, Bonferroni $P < 0.0001$). Furthermore, there was an increased effect of simultaneously stimulating the contralateral STN. The potential evoked in cortex by a bilateral stimulation (4.95 ± 0.46 μV) was significantly higher than one evoked by a stimulation applied unilaterally with the same intensity (Bonferroni test, $P < 0.01$). This effect was perhaps due to contralateral effects of the stimuli that were confirmed in contralateral 60-Hz stimulation experiments, which elicited a small late component in the ipsilateral EEG (Fig. 1*F*).

Stimulation Has No Effect on Behavior and EEG Power Spectrum before Drug Treatment

As shown in Figure 2*A*, in the absence of drug-induced catalepsy, the STN-DBS had no significant effect on the animal's overall activity level during 10 min (one-way RM ANOVA, $F_{3,17} = 88.37$, $P > 0.05$) or bar test performance (Kruskall–Wallis test, $P > 0.05$). Similarly, prior to drug administration DBS had no significant effect on the oscillatory activity of the EEG in the beta band between 12 and 30 Hz (Fig. 3, one-way RM ANOVA, $F_{3,17} = 16.51$, $P > 0.05$).

D1/D2 Antagonism Produces Akinesia and Increases Cortical EEG Beta Power

Administration of the combined D1/D2 antagonist resulted in a cataleptic state characterized by strong akinesia and rigidity. The activity of the animal was markedly reduced in the next 10 min (Fig. 2). This drug effect can be seen shortly after the

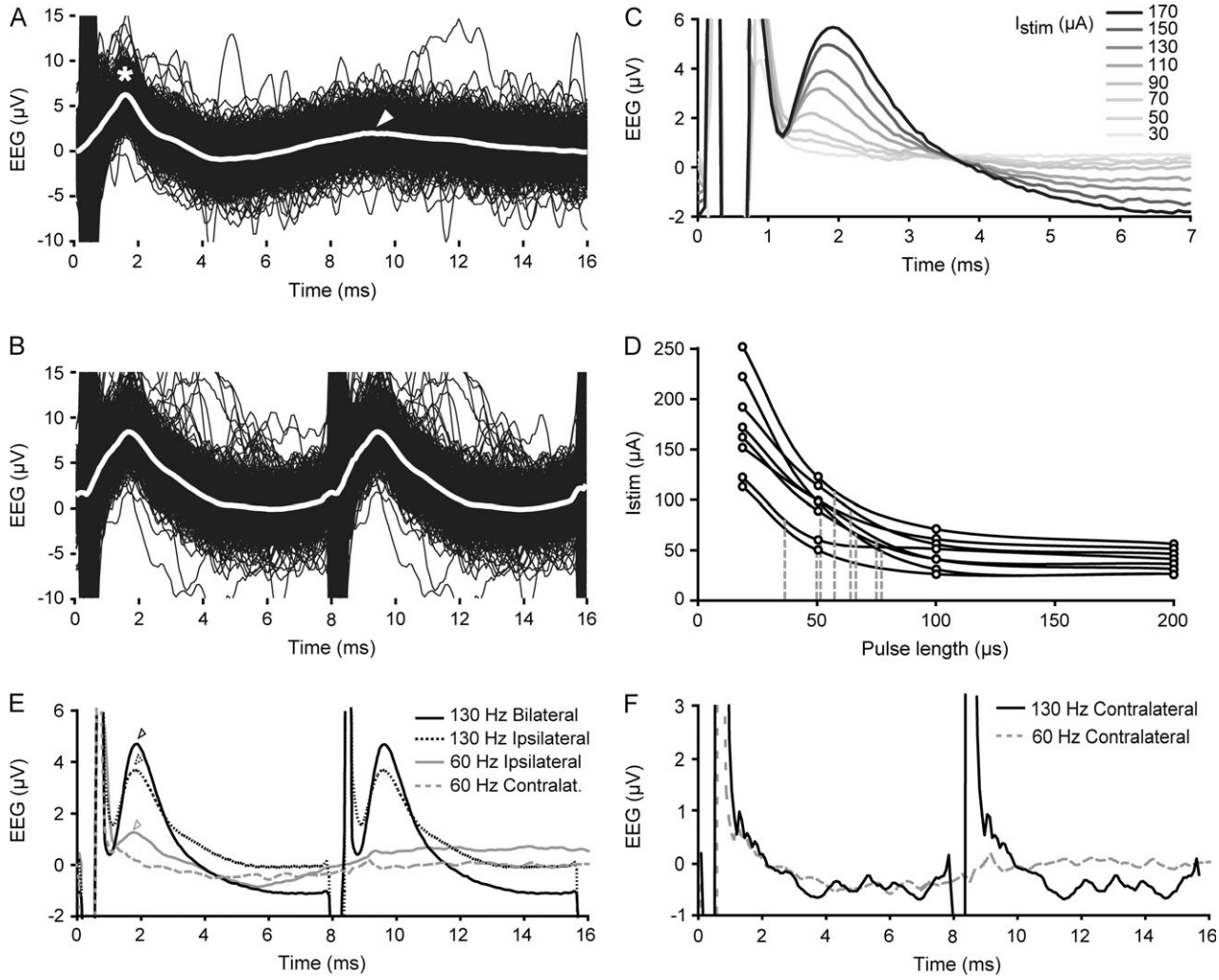

Figure 1. Evoked potentials in the cortex following STN-DBS. (*A*) The top panel shows 600 superimposed cortical EEG traces triggered by stimulation in the STN ($t = 0$). In this example stimuli were given every 16.7 ms (60 Hz). The white line represent the average evoked potential. STN stimulation elicits a polyphasic response in the cortex with an early (asterisk) and a late (arrowhead) positive component. (*B*) EEG responses with stimulation rate of 130 Hz. (*C*) Effect of stimulus intensity on response amplitude, illustrated for one rat. Lines show mean evoked cortical potentials under different intensities at 130 Hz. In this example linear regression analysis shows that amplitude of the evoked potential is significantly correlated to the current applied ($R^2 = 0.9757$). (*D*) Strength–duration curves and chronaxies. Points show threshold intensity for evoked cortical response at different pulse durations. Chronaxie was defined as the pulse length at which estimated threshold intensity was 2× the threshold at the longest pulse width (gray dashed lines). (*E*) Mean cortical evoked potential under different stimulation parameters: unilateral versus bilateral and 60 versus 130 Hz, as well as contralateral at 60 Hz with a fixed stimulus intensity (150 μA). Time base allows display of a single stimulus and response at 60 Hz (solid and doted gray line) and 2 stimulus artifacts and responses at 130 Hz (black and dotted lines). Unilateral stimulation at 60 Hz produces a small evoked potential (open gray arrow), which is enlarged with 130-Hz stimulation (dotted black arrow), and further enhanced with bilateral stimulation (filled black arrow). Contralateral stimulation induces no early response. In this animal, bilateral 130-Hz stimulation, that produced the illustrated maximum amplitude response, reduced the bar test akinesia score from 124 to 2 s. (*F*) The panel illustrates the effect of contralateral stimulation at 60 and 130 Hz in the same animal as in (*E*). Although no detectable increases in the early potentials are visible a small late rebound occurs after 8 ms at 60-Hz stimulation. There is no obvious increase in the earlier components of the response at 130 Hz. Such stimulation increased the potential recorded when stimulation of the ipsilateral STN was included (as shown in E). Note that the voltage scale is half the size in (*F*) as in (*E*).

injection as the record of any sort of movement drops to nil after 81.82 ± 11.95 s. The locomotor activity over the whole 10-min postinjection period was significantly decreased compared with the 10 min preceding injection (one-way RM ANOVA, $F_{3,17} = 88.37$, $P < 0.001$). The akinesia was confirmed by the bar test score (Fig. 2) which showed a significant increase following the treatment (Kruskall–Wallis test, $P < 0.0001$). The blockade of the dopaminergic system also influenced the EEG (one-way RM ANOVA, $F_{3,17} = 16.51$, $P < 0.001$; Fig. 3). Injections induced a significant increase of the oscillatory activity in the beta band (Bonferroni test, $P < 0.001$). The detailed time course of changes in beta frequency power shows that power increases are detectable 2 min after the injection (Fig. 3*B*).

STN-DBS Reverses Behavioral Impairments Induced by D1/D2 Blockade

As shown in Figure 2, locomotor activity after drug injection was significantly higher in sessions where STN-DBS was applied at 130 Hz, compared with the nonstimulated condition (one-way RM ANOVA, $F_{3,17} = 88.37$, $P < 0.001$). The overall activity level did not completely recover to predrug levels, remaining significantly below that observed before the injection (Bonferroni test, $P < 0.001$). In contrast

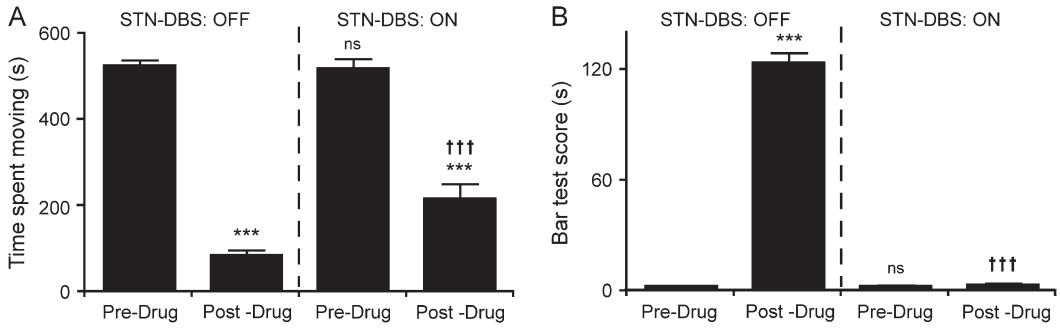

Figure 2. Effect of STN-DBS on D1/D2 antagonist induced akinesia. (*A*) Total movement. The histogram displays the mean (±SEM) time spent moving by animals over 10 min before (Pre-Drug) and after (Post-Drug) drug administration under control (STN-DBS: OFF) and stimulated conditions (STN-DBS: ON). ***$P < 0.001$ postdrug compared with before drug; †††$P < 0.001$ postdrug stimulated compared with postdrug nonstimulated; ns, $P > 0.05$ predrug stimulated compared with predrug nonstimulated (one-way ANOVA, Bonferroni post hoc tests, $n = 9$ animals in all the conditions). (*B*) Bar test scores. ***$P < 0.001$ postdrug compared with before drug, nonstimulated; †††$P < 0.001$ postdrug stimulated compared with postdrug nonstimulated; ns, $P > 0.05$ predrug stimulated versus predrug nonstimulated (one-way ANOVA, Bonferroni post hoc tests $n = 9$ animals in all the conditions).

akinesia as assessed by the bar test score was completely reversed by STN-DBS (Fig. 2*B*). The bar test score in the stimulated condition was significantly lower than the non-stimulated condition (Kruskall–Wallis test, $P < 0.0001$, Dunn's post hoc test $P < 0.001$) and not significantly different from values obtained in the absence of drug (Dunn test, $P > 0.05$ for both the nonstimulated and stimulated drug-free sessions). After the stimulation was turned off animals became cataleptic again as soon as they could be tested on the bar (data not shown). The effect required high-frequency stimulation because 60-Hz stimulation was not able to reverse akinesia. The time spent on the bar under stimulation at this frequency (126 ± 7.6 s) was not significantly lower than in that in the absence of stimulation (Dunn test, $P > 0.05$).

Analysis of the relationship between effect of STN-DBS on behavior, and the amplitude of the cortical potentials evoked by the stimulation is illustrated by the example data in Figure 4*A*. Normalization of the behavior was dependent on the stimulation producing a cortical evoked potential, and scaled with the potential amplitude. Across all experiments (Fig. 4*B*) there was a strong inverse relationship between the level of akinesia, as assessed with a bar test, and the amplitude of the evoked potential (Fig. 4*B*, inset, $R^2 = 0.84$). Thus the positive behavioral effect of the STN-DBS is a function of its impact on the cortex.

Cortical Correlates of Behavioral Recovery

The improvement of the animal's behavior induced by STN-DBS was also coupled with changes in the cortical EEG in the frequency domain. The increase of the oscillatory activity in the beta band induced by the antagonists was completely abolished by STN-DBS (one-way RM ANOVA, $F_{3,17} = 16.51$, $P < 0.0001$; Fig. 3). On average, the level of 12- to 30-Hz oscillation was 150% higher after drug injection in the nonstimulated condition than in the stimulated condition (Bonferroni $P < 0.001$). Moreover this latter value was not different from that before the injection in the nonstimulated or the stimulated conditions (Bonferroni test, $P > 0.05$ for both) indicating that beta oscillations level remains at its initial level in spite of the drug treatment, when the cortex is activated by STN-DBS. The analysis of the time course of this effect (Fig. 3*B*) shows that the increase in power in the beta frequencies observed 2 min after the drug injection is absent during STN-DBS as beta band area is significantly diminished in the stimulated condition compared with corresponding time blocks in the non stimulated condition (one-way RM ANOVA, $F_{39,19} = 19.32$, $P < 0.05$).

Discussion

The main results of this study are that 1) STN-DBS in conscious rats evokes a cortical response at short latency consistent with antidromic activation; 2) Combined D1/D2 blockade produces an increase in cortical beta oscillations characteristic of PD; 3) STN-DBS normalizes the oscillations in the beta band; 4) the stimulation effective for 1) and 3) also produces therapeutic effect, which is correlated with the amplitude of the evoked response.

STN-DBS Evokes a Cortical Antidromic Response in Freely Moving Rat

In this study stimulation in the region of STN produced a short latency positive going wave recorded on the surface of the cortex, as has been previously reported for anesthetized rats (Li et al. 2007). In that study the positive wave was closely associated with the antidromic driving of deep cells in the cortex of the rat and the source of the wave was established as layer V by current-source density analysis. Thus, in the anesthetized animals we can be sure that the potential is a consequence of antidromic activation of the layer V cortico-fugal axons coursing past the STN (Li et al. 2007). The response peak time in the present study (1.9 ms) is almost identical to that for antidromic responses identified in anesthetized animals (2.5 ms). The waveforms in the rat are similar to cortical EEG responses to STN stimulation recorded in human patients (Ashby et al. 2001), where the latency (3 ms) was slightly longer, as would be expected for antidromic responses in the larger human brain. Further, the measured chronaxie values here and in the human data (Ashby et al. 2001), match those expected for large myelinated fibers (Ranck 1975) and are not compatible with activation of large cell bodies. Together, the match of the characteristics of the evoked potentials recorded here to those definitely identified as antidromic suggest that they are due to activation of myelinated corticofugal fibers passing in the vicinity of the STN.

STN-DBS also evokes a later component at 11.2 ms following stimulus and this component seems to be the source of

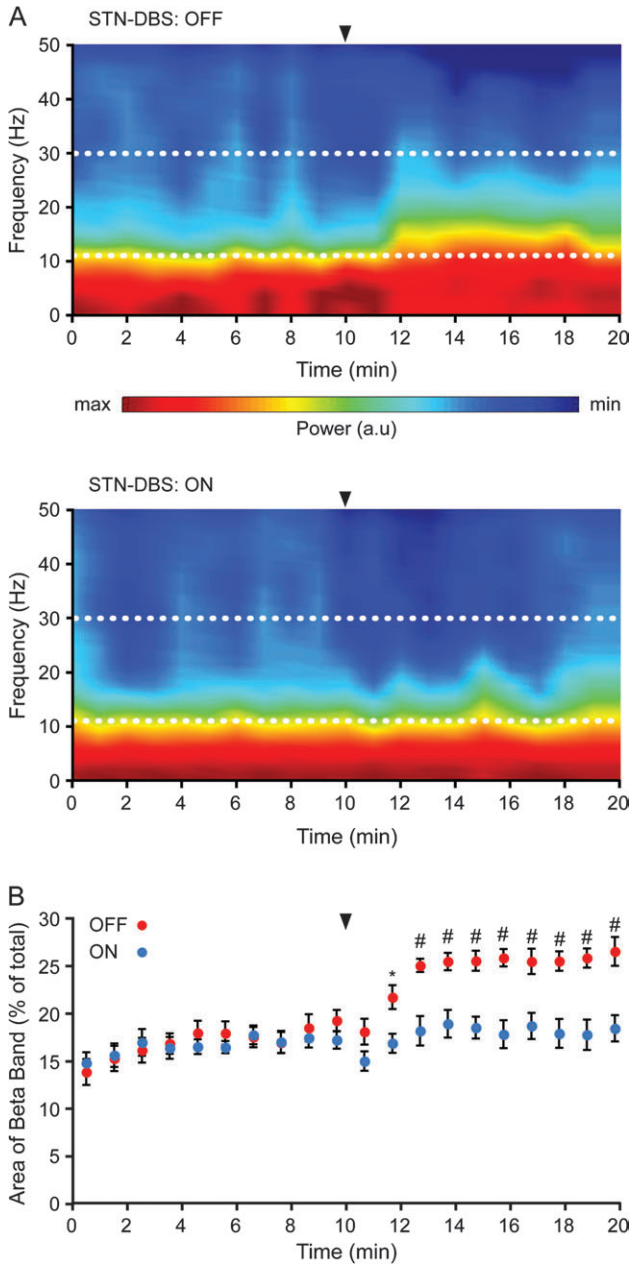

Figure 3. Effect of STN-DBS on change in frequency components of EEG induced by D1/D2 antagonists. (*A*) Example of PSD across time for the EEG in an animal treated with D1 and D2 antagonists, in nonstimulated (top panel) and stimulated (130 Hz, 100 μA, bottom panel) conditions. Drug injections happened half way through the records, at the triangular arrow, in both stimulated and unstimulated conditions. Power at each frequency represented by color scale. The white dotted lines delineate the margins of the beta band defined for this study (12–30 Hz). (*B*) Average oscillatory activity in the beta band from all 9 animals (18 electrodes) before and after D1/D2 antagonist injection in 2 conditions: nonstimulated (OFF, red dots) and stimulated (ON, blue dots). Points show the mean area of the PSD histogram in the beta band calculated over 1-min blocks. $*P < 0.05$; $\#P < 0.001$, comparing STN-DBS ON and OFF situations. There is no difference between the power spectra before drug application in animals.

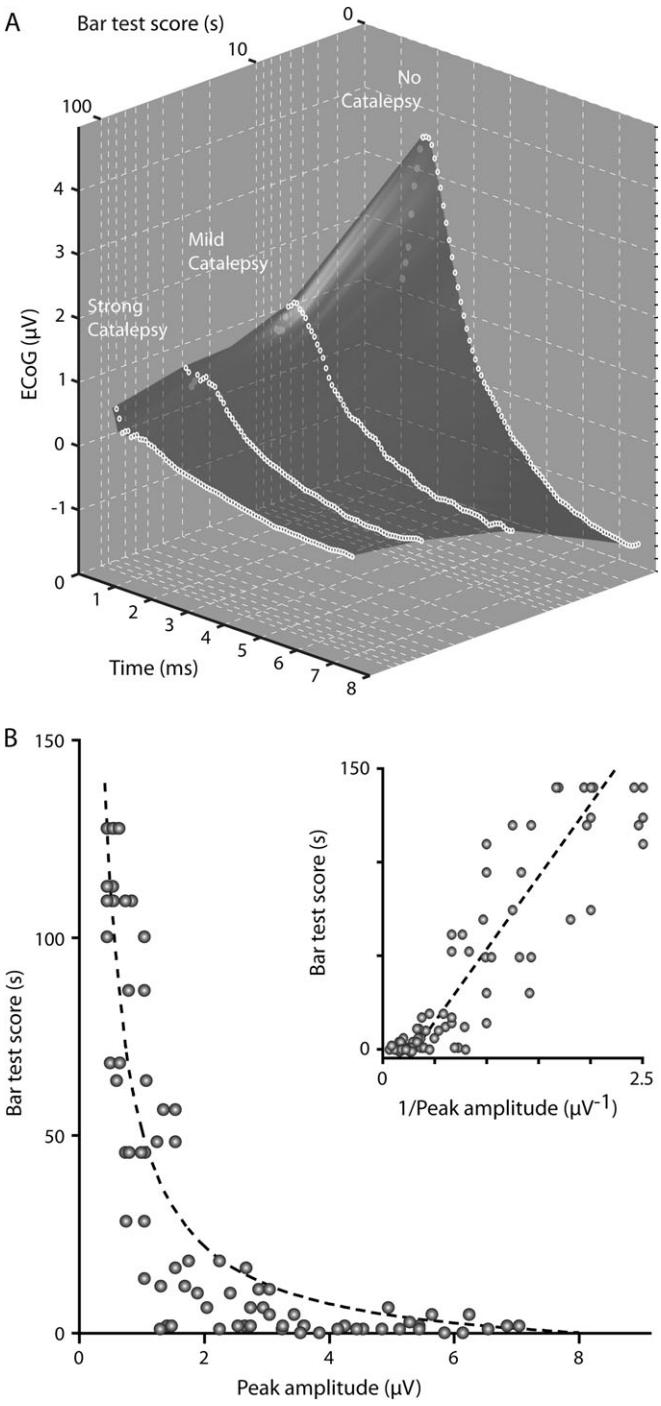

Figure 4. Relief from parkinsonian symptoms is correlated with the effect of STN-DBS on amplitude of cortical evoked potential. (*A*) Surface plot shows relationship between cortical evoked potential trace and bar test score (log scale) for 4 example recordings from one animal. In this plot, time zero indicates the end of the stimulus artifact. Traces were obtained from the same animal with differing levels of stimulus intensity and frequency. (*B*) Group data. Points show bar test score as a function of the peak amplitude of the evoked response evoked in the cortex for all 86 recording sessions in which bar test score and EEG were both recorded. Data obtained from 9 animals (18 hemispheres). The inset shows linear regression calculated from the same data with the bar tests score plotted against 1/peak evoked potential amplitude ($R^2 = 0.84$).

resonance effect at high-frequency stimulation. This wave could be triggered from a multitude of possible pathways through the basal ganglia and thalamus. However, its ability to support resonance at high frequencies makes most polysynaptic pathways less likely, because multiple synaptic junctions would be expected to show failure of transmission at high frequencies. The simplest explanation would thus be activation of intracortical or thalamocortical connections from branches of the antidromically activated corticofugal axons.

STN-DBS Reverses the Increase in Beta Oscillations Induced by Dopamine Receptor Antagonists

We used a combined D1/D2 receptor antagonist protocol to rapidly produce a marked, reversible akinesia and rigidity, as previously described (Degos et al. 2005). Although it does not mimic the pathology of PD, catalepsy induced by dopamine antagonists in rats has been shown to produce similar patterns of rigidity to those seen in parkinsonism (Wu et al. 2007). These considerations suggest that inadequate stimulation of dopamine receptors underlies similar motor symptoms, whether caused by pharmacological blockade or lack of dopamine.

We found that drug-induced akinesia was associated with an increase in the oscillatory activity in the beta band of the EEG. This increase agrees with observations with D1 or D2 antagonists administered separately (Sebban et al. 1999) and in local field potentials we have recorded from electrodes located in the globus pallidus (Hyland et al., 2008). In contrast, another study found no specific enhancement at beta frequencies in acutely drug treated animals (Mallet et al. 2008). The reason for this difference is not clear, but may relate to the relatively restricted frequency band analyzed in the latter study (only down to 19 Hz, compared with a lower bound of 12 Hz in the other studies). Importantly the effect on the EEG power spectrum is comparable to that seen in the cortex and basal ganglia of chronic animal models of PD with selective lesions of dopamine pathways, and in patients (Bergman et al. 1994; Nini et al. 1995; Brown and Marsden 1999; Goldberg et al. 2002; Levy et al. 2002; Belluscio et al. 2003; Sharott et al. 2005; Kuhn et al. 2006; Dejean et al. 2008). Like (Mallet et al. 2008) we also found no distinct peak in the raw EEG, however, our analysis of the changes in EEG power does show an increase in this frequency band (Supplementary Fig. S2). It has been suggested that increased beta band oscillations may be causal in Parkinsonian akinesia (Brown 2003) and it has been shown that induction of beta band activity by direct STN stimulation slows movement in humans (Chen et al. 2007), and induces tremor in monkeys (Boraud et al. 2007).

STN-DBS Reverses the Akinesia Induced by Dopamine Receptor Blockade

STN-DBS induced a dramatic recovery from the drug-induced restriction of movement. This effect fits with results from 6-OHDA lesioned rat (Darbaky et al. 2003; Lehmkuhle et al. 2007), other chronic animal models (Benazzouz et al. 1993) and PD patients (Benabid et al. 1994). Importantly, we show that animals that benefit from behavioral improvement also show normalization of cortical EEG. This is the first demonstration that STN-DBS is also able to reverse changes in cortical beta oscillations induced by pharmacological blockade of dopaminergic transmission in the rat. This confirms data collected in studies with patients and nonhuman primate models of PD showing that EEG is normalized by effective therapeutic intervention with STN-DBS (Brown et al. 2004; Silberstein et al. 2005; Wingeier et al. 2006; Kuhn et al. 2008) (but see also Foffani et al. 2006) and also L-DOPA treatment (Heimer et al. 2006; Kuhn et al. 2006; Wingeier et al. 2006).

Antidromic Activation of the Cortex during Therapeutic STN-DBS

In this study we have shown that STN-DBS can effectively rescue motility in the rat, together with a normalization of cortical beta rhythms. In addition, however, we show that the behavioral amelioration is directly correlated with the amplitude of evoked response in the cortex. These data lead to the hypothesis that the cortical activation may itself be responsible for the behavioral improvement, perhaps through normalization of rhythmic cortical activity.

Li and colleagues (Li et al. 2007) showed that this stimulation reduces cortical slow anesthetic-induced rhythms. These authors also observed that the reduction in oscillatory activity was associated with the generation of the antidromic response in cortical cells. Such cortical antidromic activation is a likely suppressor of oscillatory activity. However, anesthetic-induced slow waves are generated in the thalamocortical network (Steriade 1999), whereas PD beta rhythms originate in cortex–basal ganglia networks (Bergman et al. 1998; Bevan et al. 2002; Brown 2003; Sharott et al. 2005). Thus both the frequency and the underlying mechanisms for the generation of these 2 EEG rhythms are different. In our unanesthetized, akinetic, animals STN-DBS that evoked antidromic responses in the cortex also reduced excess EEG power in the beta band. This suggests that the cortical activation is also effective against beta oscillations of PD.

Cortical Resonance as a Mechanism of STN-DBS

It is a repeated observation that frequencies >100 Hz are necessary for effective STN-DBS. Li et al. (2007) suggested that the importance of the higher frequencies of stimulation is a consequence of the resonance effects that they observed. At high frequencies, responses from one stimulation are still occurring when the next arrives, allowing the development of resonant increases in potential. The present study supports their postulate by showing a similar potentiation of the effect of STN-DBS at 130-Hz stimulation compared with 60 Hz. Moreover we show that contralateral stimulation is able to help activate ipsilateral cortex and that bilateral stimulation is more efficient than unilateral stimulation in activating the cortex. This might reflect additional interhemispheric resonance with responses carried by the callosal connections, which are prominent in frontal cortical areas.

Numerous studies have shown that when cortical neurons oscillate synchronously they exert a powerful rhythmic drive on the basal ganglia (Stern et al. 1997; Magill et al. 2000; Mahon et al. 2001; Dejean et al. 2007) and this phenomenon is exacerbated in pathological conditions (Magill et al. 2001; Belluscio et al. 2003; Dejean et al. 2008). Interrupting cortical beta oscillations would stop their spread through the cortex–basal ganglia loops and might pull the system away from the dysfunctional state towards a more physiological condition. The tight correlation of antidromic potential size with behavioral outcome shown in this study certainly encourages this suggestion.

An action on cortex is consonant with the suggestion in the introduction that the effect of STN-DBS might be on fibers rather than cell bodies. Pallidal efferents seem less likely in view of the clinical literature suggesting that STN-DBS is effective even in patients with antecedent lesions of the pallidum (Revilla et al. 2002; Kleiner-Fisman et al. 2004; Ondo et al. 2006). Thus an action on cortical efferent fibers appears the most plausible. If cortical activation is the most important factor for STN-DBS action then direct cortical stimulation might also be efficacious. Indeed, monkeys given high-frequency stimulation through electrodes lying above the

dura along the motor cortical areas were reported to be relieved of 1-methyl 4-phenyl 1,2,3,6-tetrahydropyridine (MPTP) induced parkinsonism (Drouot et al. 2004). Although trials with epidural motor cortical stimulation in patients have not been as successful (Priori and Lefaucheur 2007), this may relate to the fact that selective activation of layer V cells (a property of antidromic activation) might be hard to elicit from a surface electrode. Magnetic stimulation, in contrast, is capable of targeting deep layers and has been shown to have a beneficial effect in several studies (Lefaucheur et al. 2004; Fregni et al. 2005; Fregni and Pascual-Leone 2007).

Supplementary Material

Supplementary material can be found at: http://www.cercor.oxfordjournals.org/

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Notes

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References

Ashby P, Paradiso G, Saint-Cyr JA, Chen R, Lang AE, Lozano AM. 2001. Potentials recorded at the scalp by stimulation near the human subthalamic nucleus. Clin Neurophysiol. 112:431–437.

Ashby P, Strtafella A, Dostrovsky JO, Lozano A, Lang AE. 1998. Immediate motor effects of stimulation through electrodes implanted in the human globus pallidus. Stereotact Funct Neurosurg. 70:1–18.

Belluscio MA, Kasanetz F, Riquelme LA, Murer MG. 2003. Spreading of slow cortical rhythms to the basal ganglia output nuclei in rats with nigrostriatal lesions. Eur J Neurosci. 17:1046–1052.

Benabid AL, Pollak P, Gross C, Hoffmann D, Benazzouz A, Gao DM, Laurent A, Gentil M, Perret J. 1994. Acute and long-term effects of subthalamic nucleus stimulation in Parkinson's disease. Stereotact Funct Neurosurg. 62:76–84.

Benazzouz A, Gross C, Féger J, Boraud T, Bioulac B. 1993. Reversal of rigidity and improvement in motor performance by subthalamic high frequency stimulation in MPTP-treated monkeys. Eur J Neurosci. 5:382–389.

Bergman H, Raz A, Feingold A, Nini A, Nelken I, Hansel D, Ben-Pazi H, Reches A. 1998. Physiology of MPTP tremor. Mov Disord. 13:29–34.

Bergman H, Wichmann T, DeLong MR. 1990. Reversal of experimental parkinsonism by lesions of the subthalamic nucleus. Science. 249:1436–1438.

Bergman H, Wichmann T, Karmon B, DeLong MR. 1994. The primate subthalamic nucleus. II. Neuronal activity in the MPTP model of parkinsonism. J Neurophysiol. 72:507–520.

Bevan M, Magill P, Terman D, Bolam J, Wilson C. 2002. Move to the rhythm: oscillations in the subthalamic nucleus-external globus pallidus network. Trends Neurosci. 25:525–531.

Boraud T, Brown T, Goldberg JA, Graybiel AM, Magill PJ. 2005. Oscillations in the basal banglia: the good, the bad and the unexpected. In: Bolam JP, Ingham CA, Magill PJ, editors. The basal ganglia viii. New York: Springer. p. 3–24.

Boraud T, Taillade M, Baufreton J, Gross C, Benazzouz A. 2007. Beta oscillatory activity in the subthalamic nucleus: role in the pathophysiology of Parkinson's disease IBAGS IX Abstract O-12. In: Proceedings of the IX International Basal Ganglia Society Meeting, Egmond Aan Zee, the Netherlands.

Brown P. 2003. Oscillatory nature of human basal ganglia activity: relationship to the pathophysiology of Parkinson's disease. Mov Disord. 18:357–363.

Brown P, Marsden CD. 1999. Bradykinesia and impairment of EEG desynchronization in Parkinson's disease. Mov Disord. 14:423–429.

Brown P, Mazzone P, Oliviero A, Altibrandi MG, Pilato F, Tonali PA, Di Lazzaro V. 2004. Effects of stimulation of the subthalamic area on oscillatory pallidal activity in Parkinson's disease. Exp Neurol. 188:480–490.

Brown P, Williams D. 2005. Basal ganglia local field potential activity: character and functional significance in the human. Clin Neurophysiol. 116:2510–2519.

Chen CC, Litvak V, Gilbertson T, Kuhn A, Lu CS, Lee ST, Tsai CH, Tisch S, Limousin P, Hariz M, Brown P. 2007. Excessive synchronization of basal ganglia neurons at 20 Hz slows movement in Parkinson's disease. Exp Neurol. 205:214–221.

Darbaky Y, Forni C, Amalric M, Baunez C. 2003. High frequency stimulation of the subthalamic nucleus has beneficial antiparkinsonian effects on motor functions in rats, but less efficiency in a choice reaction time task. Eur J Neurosci. 18:951–956.

Degos B, Deniau JM, Thierry AM, Glowinski J, Pezard L, Maurice N. 2005. Neuroleptic-induced catalepsy: electrophysiological mechanisms of functional recovery induced by high-frequency stimulation of the subthalamic nucleus. J Neurosci. 25:7687–7696.

Dejean C, Gross CE, Bioulac B, Boraud T. 2007. Synchronous high-voltage spindles in the cortex-basal ganglia network of awake and unrestrained rats. Eur J Neurosci. 25:772–784.

Dejean C, Gross CE, Bioulac B, Boraud T. 2008. Dynamic changes in the cortex-basal ganglia network after dopamine depletion in the rat. J Neurophysiol. 100:385–396.

Drouot X, Oshino S, Jarrya B, Besret L, Kishima H, Remy P, Dauguet J, Lefaucher JP, Dolle F, Conde F, et al. 2004. Functional recovery in a primate model of Parkinson's disease following motor cortex stimulation. Neuron. 44:769–778.

Foffani G, Ardolino G, Egidi M, Caputo E, Bossi B, Priori A. 2006. Subthalamic oscillatory activities at beta or higher frequency do not change after high-frequency DBS in Parkinson's disease. Brain Res Bull. 69:123–130.

Fregni F, Pascual-Leone A. 2007. Technology insight: Noninvasive brain stimulation in neurology—perspectives on the therapeutic potential of RTMS and TDCS. Nat Clin Pract Neurol. 3:383–393.

Fregni F, Simon DK, Wu A, Pascual-Leone A. 2005. Non-invasive brain stimulation for Parkinson's disease: a systematic review and meta-analysis of the literature. J Neurol Neurosurg Psychiatr. 76:1614–1623.

Garcia L, Audin J, D'Alessandro G, Bioulac B, Hammond C. 2003. Dual effect of high-frequency stimulation on subthalamic neuron activity. J Neurosci. 23:8743–8751.

Goldberg JA, Boraud T, Maraton S, Haber SN, Vaadia E, Bergman H. 2002. Enhanced synchrony among primary motor cortex neurons in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine primate model of Parkinson's disease. J Neurosci. 22:4639–4653.

Hammond C, Bergman H, Brown P. 2007. Pathological synchronization in Parkinson's disease: networks, models and treatments. Trends Neurosci. 30:357–364.

Hashimoto T, Elder CM, Okun MS, Patrick SK, Vitek JL. 2003. Stimulation of the subthalamic nucleus changes the firing pattern of pallidal neurons. J Neurosci. 23:1916–1923.

Hauber W, Munkle M. 1995. Stimulation of adenosine a2a receptors in the rat striatum induces catalepsy that is reversed by antagonists of n-methyl-d-aspartate receptors. Neurosci Lett. 196:205–208.

Heimer G, Rivlin-Etzion M, Bar-Gad I, Goldberg JA, Haber SN, Bergman H. 2006. Dopamine replacement therapy does not restore the full spectrum of normal pallidal activity in the 1-methyl-4-phenyl-1,2,3,6-tetra-hydropyridine primate model of parkinsonism. J Neurosci. 26:8101–8114.

Hyland B, Dejean C, Sheerin A, Arbuthnott G, Wickens J. 2008. Gamma- and beta-oscillations in rat globus pallidus are differentially modulated during immobility induced by dopamine D2- or D1-receptor antagonists. FENS Abstr. 222.15.

Hutchison WD, Dostrovsky JO, Walters JR, Courtemanche R, Boraud T, Goldberg J, Brown P. 2004. Neuronal oscillations in the basal ganglia

and movement disorders: evidence from whole animal and human recordings. J Neurosci. 24:9240–9243.
Kita H, Kitai ST. 1994. The morphology of globus pallidus projection neurons in the rat: an intracellular staining study. Brain Res. 636:308–319.
Kitai ST, Deniau JM. 1981. Cortical inputs to the subthalamus: Intracellular analysis. Brain Res. 214:411–415.
Kleiner-Fisman G, Fisman DN, Zamir O, Dostrovsky JO, Sime E, Saint-Cyr JA, Lozano AM, Lang AE. 2004. Subthalamic nucleus deep brain stimulation for Parkinson's disease after successful pallidotomy: clinical and electrophysiological observations. Mov Disord. 19:1209–1214.
Kuhn AA, Kempf F, Brucke C, Gaynor Doyle L, Martinez-Torres I, Pogosyan A, Trottenberg T, Kupsch A, Schneider G-H, Hariz MI, et al. 2008. High-frequency stimulation of the subthalamic nucleus suppresses oscillatory {beta} activity in patients with Parkinson's disease in parallel with improvement in motor performance. J Neurosci. 28:6165–6173.
Kuhn AA, Kupsch A, Schneider G-H, Brown P. 2006. Reduction in subthalamic 8-35 Hz oscillatory activity correlates with clinical improvement in Parkinson's disease. Eur J Neurosci. 23:1956–1960.
Lefaucheur JP, Drouot X, Von Raison F, Menard-Lefaucheur I, Cesaro P, Nguyen JP. 2004. Improvement of motor performance and modulation of cortical excitability by repetitive transcranial magnetic stimulation of the motor cortex in Parkinson's disease. Clin Neurophysiol. 115:2530–2541.
Lehmkuhle MJ, Bhangoo SS, Kipke DR. 2007. The electrocorticogram signal can be modulated with deep brain stimulation of the subthalamic nucleus in the hemi-parkinsonian rat. Soc Neurosci Abstr. 855:13.
Levy R, Hutchison WD, Lozano AM, Dostrovsky JO. 2002. Synchronized neuronal discharge in the basal ganglia of parkinsonian patients is limited to oscillatory activity. J Neurosci. 22:2855–2861.
Li S, Arbuthnott GW, Jutras MJ, Goldberg JA, Jaeger D. 2007. Resonant antidromic cortical circuit activation as a consequence of high-frequency subthalamic deep-brain stimulation. J Neurophysiol. 98:3525–3537.
Magarinos-Ascone C, Pazo JH, Macadar O, Buno W. 2002. High-frequency stimulation of the subthalamic nucleus silences subthalamic neurons: a possible cellular mechanism in Parkinson's disease. Neuroscience. 115:1109–1117.
Magill PJ, Bolam JP, Bevan MD. 2000. Relationship of activity in the subthalamic nucleus-globus pallidus network to cortical electroencephalogram. J Neurosci. 20:820–833.
Magill PJ, Bolam JP, Bevan MD. 2001. Dopamine regulates the impact of the cerebral cortex on the subthalamic nucleus-globus pallidus network. Neuroscience. 106:313–330.
Mahon S, Deniau JM, Charpier S. 2001. Relationship between EEG potentials and intracellular activity of striatal and cortico-striatal neurons: an in vivo study under different anesthetics. Cereb Cortex. 11:360–373.
Mallet N, Pogosyan A, Sharott A, Csicsvari J, Bolam JP, Brown P, Magill PJ. 2008. Disrupted dopamine transmission and the emergence of exaggerated beta oscillations in subthalamic nucleus and cerebral cortex. J Neurosci. 28:4795–4806.
Maurice N, Thierry AM, Glowinski J, Deniau JM. 2003. Spontaneous and evoked activity of substantia nigra pars reticulata neurons during high-frequency stimulation of the subthalamic nucleus. J Neurosci. 23:9929–9936.
McIntyre CC, Grill WM, Sherman DL, Thakor NV. 2004. Cellular effects of deep brain stimulation: model-based analysis of activation and inhibition. J Neurophysiol. 91:1457–1469.
Meissner W, Guigoni C, Cirilli L, Garret M, Bioulac BH, Gross CE, Bezard E, Benazzouz A. 2007. Impact of chronic subthalamic high-frequency stimulation on metabolic basal ganglia activity: a 2-deoxyglucose uptake and cytochrome oxidase mRNA study in a macaque model of Parkinson's disease. Eur J Neurosci. 25:1492–1500.
Meissner W, Leblois A, Hansel D, Bioulac B, Gross CE, Benazzouz A, Boraud T. 2005. Subthalamic high frequency stimulation resets subthalamic firing and reduces abnormal oscillations. Brain. 128:2372–2382.
Nini A, Feingold A, Slovin H, Bergman H. 1995. Neurons in the globus pallidus do not show correlated activity in the normal monkey, but phase-locked oscillations appear in the MPTP model of parkinsonism. J Neurophysiol. 74:1800–1805.
Ondo WG, Silay Y, Almaguer M, Jankovic J. 2006. Subthalamic deep brain stimulation in patients with a previous pallidotomy. Mov Disord. 21:1252–1254.
Paxinos G, Watson C. 1986. The rat brain in stereotaxic coordinates. New York: Academic Press.
Priori A, Lefaucheur JP. 2007. Chronic epidural motor cortical stimulation for movement disorders. Lancet Neurol. 6:279–286.
Ranck JB, Jr. 1975. Which elements are excited in electrical stimulation of mammalian central nervous system: a review. Brain Res. 98:417–440.
Revilla FJ, Mink JW, Rich KM, Dowling JL, Loepker A, Perlmutter JS. 2002. Clinical outcome of bilateral subthalamic nucleus stimulation in patients with Parkinson's disease and previous pallidotomy. Mov Disord. 17S5 7th International Congress of Parkinson's Disease and Movement Disorders P600, s189–s190.
Sebban C, Zhang XQ, Tesolin-Decros B, Millan MJ, Spedding M. 1999. Changes in EEG spectral power in the prefrontal cortex of conscious rats elicited by drugs interacting with dopaminergic and noradrenergic transmission. Br J Pharmacol. 128:1045–1054.
Sharott A, Magill PJ, Harnack D, Kupsch A, Meissner W, Brown P. 2005. Dopamine depletion increases the power and coherence of beta-oscillations in the cerebral cortex and subthalamic nucleus of the awake rat. Eur J Neurosci. 21:1413–1422.
Shi LH, Luo F, Woodward DJ, Chang JY. 2006. Basal ganglia neural responses during behaviorally effective deep brain stimulation of the subthalamic nucleus in rats performing a treadmill locomotion test. Synapse. 59:445–457.
Silberstein P, Pogosyan A, Kuhn AA, Hotton G, Tisch S, Kupsch A, Dowsey-Limousin P, Hariz MI, Brown P. 2005. Cortico-cortical coupling in Parkinson's disease and its modulation by therapy. Brain. 128:1277–1291.
Steriade M. 1999. Coherent oscillations and short-term plasticity in corticothalamic networks. Trends Neurosci. 22:337–345.
Stern EA, Kincaid AE, Wilson CJ. 1997. Spontaneous subthreshold membrane potential fluctuations and action potential variability of rat corticostriatal neurons in vivo. J Neurophysiol. 77:1697–1715.
Taï CH, Boraud T, Bezard E, Bioulac B, Gross CE, Benazzouz A. 2003. Electrophysiological and metabolic evidence that high frequency stimulation of the subthalamic nucleus bridles neuronal activity in the subthalamic nucleus and the substantia nigra reticulata. FASEB J. 17:1820–1830.
Wadenberg ML, Seeman P. 1999. Clozapine pre-treatment enhances raclopride catalepsy. Eur J Pharmacol. 377:R1–R2.
Windels F, Bruet N, Poupard A, Urbain N, Chouvet G, Feuerstein C, Savasta M. 2000. Effects of high frequency stimulation of subthalamic nucleus on extracellular glutamate and GABA in substantia nigra and globus pallidus in the normal rat. Eur J Neurosci. 12:4141–4146.
Windels F, Carcenac C, Poupard A, Savasta M. 2005. Pallidal origin of GABA release within the substantia nigra pars reticulata during high-frequency stimulation of the subthalamic nucleus. J Neurosci. 25:5079–5086.
Wingeier B, Tcheng T, Koop MM, Hill BC, Heit G, Bronte-Stewart HM. 2006. Intra-operative STN DBS attenuates the prominent beta rhythm in the STN in Parkinson's disease. Exp Neurol. 197:244–251.
Wu YN, Hyland BI, Chen JJ. 2007. Biomechanical and electromyogram characterization of neuroleptic-induced rigidity in the rat. Neuroscience. 147:183–196.