High-Frequency Deep Brain Stimulation of the Nucleus Accumbens Region Suppresses Neuronal Activity and Selectively Modulates Afferent Drive in Rat Orbitofrontal Cortex *In Vivo*

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High-frequency deep-brain stimulation (DBS) of the nucleus accumbens (NAc) region is an effective therapeutic avenue for patients with treatment-resistant obsessive–compulsive disorder (OCD). Imaging studies suggest that DBS acts by suppressing the aberrant metabolism in the orbitofrontal cortex (OFC) that is a hallmark of OCD; however, little is known about the mechanisms by which this occurs. We examined the effects of 30 min NAc DBS at 130 Hz on spontaneously active OFC neurons and local field potentials (LFPs) in addition to evoked responses elicited by single-pulse stimulation of the NAc or mediodorsal thalamus (MD) in urethane-anesthetized rats. NAc DBS reduced the mean firing rate of OFC neurons, although neurons receiving monosynaptic input from MD were less affected and some putative interneurons were excited by DBS. Single-pulse stimulation of the NAc produced a robust inhibition in OFC neurons that was attenuated after DBS, whereas excitatory responses were unchanged. In contrast, after DBS inhibitory responses evoked from MD were unchanged, whereas excitatory responses were enhanced. NAc-evoked LFP responses were potentiated after DBS, whereas MD-evoked LFP responses were unchanged. NAc DBS also enhanced OFC spontaneous LFP oscillatory activity in the slow (0.5–4 Hz) frequency band. These results suggest that DBS of the NAc region may alleviate OCD symptoms by reducing activity in subsets of OFC neurons, potentially by driving recurrent inhibition through antidromic activation of corticostriatal axon collaterals. Moreover, selective potentiation of input to these inhibitory circuits may also contribute to the therapeutic effects produced by DBS in OCD patients.

Key words: electrical stimulation; nucleus accumbens; prefrontal; thalamus; electrophysiology; obsessive–compulsive

Introduction

High-frequency (HF) electrical stimulation of specific subcortical structures, known as deep-brain stimulation (DBS), has attracted substantial attention for treatment of severe neurological and psychiatric disorders that fail to respond to pharmacotherapeutic intervention. Thus, DBS of thalamic and subthalamic nuclei is a relatively safe and efficacious alternative to ablative neurosurgery for Parkinson's disease and other movement disorders (Benabid et al., 1991, 1994; Krack et al., 2003; Rehncrona et al., 2003; Rodriguez-Oroz et al., 2005; Deuschl et al., 2006; Perlmuter and Mink, 2006). More recently, DBS of the ventral anterior internal capsule and ventral striatum has proven to be an effective therapeutic approach for treatment-resistant obsessive–compulsive disorder (OCD) (Nuttin et al., 1999; Anderson and Ahmed, 2003; Gabriels et al., 2003; Nuttin et al., 2003; Sturm et al., 2003;

Abelson et al., 2005; Aouizerate et al., 2005; Greenberg et al., 2006). However, the neuronal mechanisms underlying the therapeutic actions of DBS in OCD remain unclear.

Imaging studies have provided insight into the brain systems involved in OCD and its treatment. Metabolic hyperactivity in the striatum, medial thalamus, and, in particular, the orbitofrontal cortex (OFC) has been consistently associated with OCD patients at rest (Baxter et al., 1988; Swedo et al., 1989) and is accentuated after symptom provocation (McGuire et al., 1994; Rauch et al., 1994; Breiter et al., 1996). Moreover, successful pharmacological (Swedo et al., 1992), cognitive-behavioral (Schwartz et al., 1996), and neurosurgical (Mindus et al., 1986) treatment of OCD have all been associated with reductions in activity in these same regions. Significantly, studies using DBS for OCD have also shown that successful treatment correlates with lowered activity in frontal cortical regions (Nuttin et al., 2003; Abelson et al., 2005; Van Laere et al., 2006).

The cellular mechanisms by which DBS produces therapeutic effects in OCD are not known. Drawing from the Parkinson's disease and movement disorders literature, DBS is proposed to act by decreasing neuronal activity within the stimulated nucleus, which is postulated to occur either by depolarization blockade or increase in local GABAergic transmission (Boraud et al., 1996; Benazzouz et al., 2000; Dostrovsky et al., 2000; Beurrier et al.,

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2001; Kiss et al., 2002; Magarinos-Ascone et al., 2002; Lian et al., 2003). However, given that electrical stimulation preferentially activates axons as opposed to cell bodies (Nowak and Bullier, 1998a,b; McIntyre and Grill, 1999), it has been proposed that DBS may produce inhibition of the stimulated area but activation of efferent and afferent axons (Vitek, 2002; McIntyre et al., 2004a,b). Thus, characterizing the effects of HF stimulation on nuclei upstream and downstream from the stimulation site is necessary for clarifying the system-level actions of DBS. The purpose of the present study was to investigate the effects of HF electrical stimulation of the nucleus accumbens (NAc) region on spontaneous and evoked neuronal and local field potential (LFP) activity in the OFC *in vivo*.

Materials and Methods

Animals and surgery. Male Sprague Dawley rats (275–400 g) were anesthetized with urethane (1.5 g/kg, i.p.) and placed in a stereotaxic frame. Body temperature was maintained at 37°C with a temperature-controlled heating pad. In all surgical preparations, the scalp was exposed, and burr holes were drilled in the skull overlying the lateral OFC, the NAc core, and the mediodorsal thalamus (MD). Concentric bipolar stimulating electrodes (NEX-100; David Kopf Instruments, Tujunga, CA) were placed according to the following coordinates: NAc electrode: anteroposterior (AP), +1.2 mm (from bregma); mediolateral (ML), +2.0 mm; dorsoventral (DV), –6.9 mm (from skull); MD electrode: AP, –3.2 mm; ML, +0.7 mm; DV, –5.5 mm. All procedures were performed in accordance with the guidelines outlined in the National Institutes of Health *Guide for the Care and Use of Laboratory Animals* and were approved by the Institutional Animal Care and Use Committee of the University of Pittsburgh.

Single-unit recordings. Extracellular recording microelectrodes were constructed from borosilicate glass tubing using a vertical microelectrode puller (Narishige, Tokyo, Japan), with the tip broken back under microscopic control and filled with 2% pontamine sky blue dye dissolved in 2 M NaCl (impedance measured *in situ* ranged between 6 and 14 M Ω). A burr hole was drilled over the OFC, the dura was resected, and a recording electrode was lowered slowly into the OFC (AP, +3.2 mm; ML, +3.5 mm; DV, 4.7–6.2 mm from skull) using a hydraulic micromanipulator. Signals from the recording electrode were amplified by a head stage connected to a preamplifier before being amplified and filtered (0.05–16 kHz) by a window discriminator/amplifier unit (Fintronics, Orange, CT). Signals were also sent to an audio monitor (AM8; Grass Instruments, Quincy, MA) and displayed on an oscilloscope (Tektronics, Wilsonville, OR). The data were acquired, stored, and analyzed using custom-designed computer software (Neuroscope) with a data acquisition board interface (Microstar Laboratories, Bellevue, WA).

To identify OFC neurons responsive to single-pulse stimulation of the NAc or MD electrode, the microelectrode was lowered slowly through the OFC while stimuli were delivered alternately to the NAc and MD electrodes (1000 μ A) at 2 s intervals (i.e., each area was stimulated at 0.25 Hz). Cathodal constant current pulses (0.2 ms duration) were given using a Grass Instruments S88 stimulator and a Grass Instruments photoelectric stimulus isolation unit. When a responsive neuron was identified, 5 min of baseline activity were recorded, after which peristimulus time histograms were constructed for 50 stimulations from each electrode. Two seconds of data were collected before and after the stimulus for each stimulus “sweep.” Both inhibitory and excitatory responses were observed. Single-pulse stimulation of the NAc electrode frequently resulted in antidromic spikes recorded in OFC; however, because our aim in this study was to characterize the effects of DBS on spontaneous activity, the responses of antidromically activated OFC neurons to NAc DBS were not examined because of potential confounds as a consequence of this activation. Responsive neurons were classified as either putative pyramidal neurons or putative projection neurons based on the spike duration frequency histogram constructed from all OFC neurons recorded. Spike duration has proven to be a reliable measure for classifying neuron types in the frontal cortex *in vivo* (Tierney et al., 2004; Tseng et al., 2006).

In this study, neurons with spike durations of <0.9 ms were classified as putative interneurons, and neurons with spike durations >1.1 ms were classified as putative pyramidal neurons.

Inhibitory responses before and after DBS were characterized according to the following: (1) the latency until inhibition onset; (2) duration of inhibition; and (3) changes in the magnitude of inhibition after DBS. The change in magnitude of inhibition after DBS was evaluated in two ways: (1) for a raw measure, the number of spikes discharged in the first 200 ms after stimulus was determined; and (2) for a normalized measure, the average percentage of baseline firing in the first 200 ms was calculated using 25 ms bins.

Excitatory responses were considered monosynaptic and presumed orthodromic if the response occurred within 15 ms of the stimulus, displayed spike “jitter” of at least 2 ms and a shift in spike latency with increasing current amplitude, and failed to follow 400 Hz paired-pulse stimulation (otherwise characterized as antidromic). Excitation was also quantified using complementary measures, including calculation of spike probability (i.e., the percentage of stimulations that result in an evoked spike), the number of spikes occurring within the first 25 ms after stimulus, and the percentage of baseline firing in the first 25 ms when calculated using 25 ms bins. With regard to MD-evoked responses, it has been suggested that some longer-latency excitatory responses in the prefrontal cortex (PFC) may represent antidromic activation of corticothalamic afferents that invades local PFC recurrent collaterals (Pirot et al., 1994). Because the OFC has reciprocal connections with MD in a manner analogous to the medial PFC (mPFC) (Krettek and Price, 1977; Groenewegen, 1988), latencies longer than 15 ms for MD→OFC excitatory responses were not included in the analysis to rule out this class of response (Pirot et al., 1994).

After recording evoked activity under baseline conditions, neurons were allowed to equilibrate for 3–5 min. An additional 5 min of baseline activity was then collected before recording with DBS-on for 30 min. The DBS parameters used (0.1–0.4 mA, 100 μ s pulse duration, 130 Hz) have been shown to be efficacious in rat Parkinson’s models (Chang et al., 2003; Degos et al., 2005) and are reported to cause negligible trauma to the stimulated area. This DBS protocol produced no visible lesions in the NAc under 25 $\times$ light microscopy with cresyl violet staining. After 30 min of recording with DBS-on, baseline activity was recorded for an additional 5 min, after which evoked activity was reassessed.

LFPs. When filter settings were adjusted to allow preferential passage of low-frequency (LF) signals (i.e., 0.1–1000 Hz), single-pulse stimulation of either the NAc or MD resulted in large-amplitude LFP responses in the OFC. To determine the relative contributions of GABA and glutamate to these evoked LFP responses, evoked LFPs were recorded using a chemotrode (Plastics One, Roanoke, VA) that also allowed local infusion of drugs. The chemotrode consisted of two individually polyimide-insulated stainless steel wires (0.2 mm diameter) attached to an insulated stainless steel 26 gauge guide cannula. The wires extended 1 mm past the end of the guide cannula; when inserted, the tip of the injection cannula used was flush with the recording surface of the electrode. LFP responses were assessed after infusion of the GABA_A receptor antagonist (–)-bicuculline methiodide or the broad-spectrum ionotropic glutamate receptor antagonist kynurenic acid. Drugs or vehicle [Dulbecco’s PBS (DPBS); Sigma, St. Louis, MO] were administered over 2 min using a 30 gauge injection cannula connected to a Hamilton syringe (bicuculline, 0.2 μ g in 0.5 μ l of DPBS; kynurenic acid, 10 μ g in 0.5 μ l of DPBS; vehicle, 0.5 μ l of DPBS). In a separate set of animals, using low-impedance glass microelectrodes (1–4 M Ω), baseline input–output curves were constructed for these responses (0.2–1.0 mA, 10 stimulations at each current intensity, stimulation at 0.4 Hz), then reassessed 5 and 90 min after HF (130 Hz) or LF (10 Hz) DBS. Spontaneous LFP activity was recorded immediately before and after 30 min DBS and occasionally during the first 5 min and last 5 min of DBS-on. We also examined the effects of the NMDA receptor antagonist (+)-5-methyl-10,11-dihydro-5H-dibenzo [a,d] cyclohepten-5,10-imine maleate (MK-801) on evoked LFPs before and after DBS. MK-801 (Sigma) was dissolved in vehicle (DPBS) and administered intraperitoneally.

Data analysis. Data are presented as mean $\pm$ SEM. Spontaneous unit activity was assessed in terms of firing rate and the proportion of spikes

Figure 1. *A*, Recording sites in the OFC and stimulation sites in NAc and MD. For clarity, only representative nonoverlapping samples are shown. Numbers represent anterior/posterior distance from bregma. *B*, Raw trace of neuronal firing with DBS-on. Arrows indicate spikes. Note that the spike on the right can be effectively discriminated both before and after the stimulus artifact. Calibration, 5 ms.

fired in a bursting pattern. Bursts were defined as the occurrence of two spikes with an interspike interval (ISI) of <45 ms; this value was generated by fitting the ISI histogram of PFC neurons with the sum of two inverse Gaussian probability density functions as described previously (Laviolette et al., 2005).

For analysis of spontaneous LFP spectral density, LFP signals were filtered with a high cutoff of 100 Hz, and fast Fourier transform-based periodograms were generated using 2 min of recorded LFP activity. The power spectral density data were binned into the following discrete frequency bands for analysis: slow/delta (0.5–4 Hz), theta (4–12 Hz), beta (15–30 Hz), and gamma (35–80 Hz). Values for each frequency band were also normalized to total power (to 100 Hz). To assess LFP effects over time, spectral time-frequency plots were constructed using a continuous wavelet transform with a Morlet wavelet (wave number, 8) with the AutoSignal software platform (SysStat, San Jose CA).

Histology. At the end of each experiment, the recording site in the OFC was marked via electrophoretic ejection of pontamine sky blue dye from the tip of the recording electrode. Stimulation sites were marked by passing direct current through the stimulating electrode. After dye ejection, animals were decapitated, and brains were rapidly removed and fixed in formalin containing 0.1% potassium ferricyanide (to stain for stimulating electrode deposits) for a minimum of 24 h. Brains were then sectioned into 50 μ m coronal slices and stained with cresyl violet to determine recording and stimulation sites (Fig. 1). In a subset of animals, the NAc stimulating electrode was not marked at the end of the experiment to evaluate the presence and extent of tissue damage produced by the DBS stimulation protocol.

Statistics. Spontaneous neuronal activity data collected during DBS was grouped into 5 min bins and analyzed by one-way repeated-measures ANOVA with the Student–Newman–Kewls *post hoc* test. Comparisons of pre- and post-DBS measures of evoked inhibition and excitation were performed using paired *t* tests. Data that failed normality or equal variance testing were analyzed using the appropriate nonparametric tests (repeated-measures ANOVA for ranks, Wilcoxon signed-rank test). All analyses were performed using the SigmaStat software platform (SysStat).

Results

Spontaneous activity was sampled from 86 OFC neurons from 47 rats. The average firing rate of these neurons was 2.6 ± 0.4 Hz (mean $\pm$ SEM). A total of 30 neurons responsive to single-pulse stimulation of the NAc were recorded for the duration of the

DBS experiment. Pure inhibitory responses were seen in 80% (23 of 30) of neurons; one neuron showed a short-latency (<15 ms) excitatory response only, and six neurons showed short-latency excitation followed by inhibition. The average latency of the short-latency excitatory responses was 8.3 ± 1.1 ms. Of the neurons showing excitation to acute NAc stimulation, 57% (four of seven) were putative interneurons based on spike duration. Many NAc-responsive neurons (77%; 23 of 30) also responded to MD stimulation. These neurons responded to MD stimulation with inhibition only (43%; 10 of 23), short-latency excitation only (27%; 6 of 23), or excitation followed by inhibition (30%; 7 of 23). The average latency of the excitatory responses was 9.8 ± 1.0 ms, which is consistent with a monosynaptic innervation of OFC based on analogous studies of thalamocortical latencies in the mPFC (Floresco and Grace, 2003). Of the neurons showing excitation to acute MD stimulation, 38% (5

of 13) were putative interneurons. Three putative interneurons were excited by stimulation of both NAc and MD. A number of NAc-responsive cells showed excitatory responses to MD stimulation at latencies of 15–25 ms. Given the long latency of the excitatory response, these neurons were not considered to be monosynaptically driven by thalamocortical fibers but instead may have been activated via antidromic activation of local recurrent collaterals from corticothalamic fibers (Pirot et al., 1994; Floresco and Grace, 2003).

Effects of DBS on spontaneous OFC neuronal firing

The effect of NAc DBS on OFC neuron firing was examined by recording 5 min of baseline activity, followed by 30 min with DBS-on, followed by another 5 min with DBS-off (Fig. 2). In the first 5 min of stimulation, 57% (17 of 30) of neurons were inhibited ($>25\%$ decrease from baseline), 17% (5 of 30) were excited ($>25\%$ increase from baseline), whereas 27% (8 of 30) were relatively unaffected. A subset (30%; 9 of 30) of the neurons showed a complete or almost complete cessation of firing in the first few minutes of DBS. However, these initial effects were often transient and did not reflect the firing rate across the entire 30 min DBS (Fig. 2*A1*). Firing rate data were analyzed by grouping into 5 min bins for analysis across the DBS period. The mean firing rate of OFC neurons was significantly suppressed during the period of DBS ($\chi^2 = 24.15$; $df = 7$; $p < 0.001$) (Fig. 2*A*). Differential effects of NAc DBS were seen when cells were classified as putative interneurons and principal neurons according to spike duration, such that putative pyramidal neurons ($n = 20$) were significantly inhibited by DBS ($\chi^2 = 19.08$; $df = 7$; $p < 0.01$) (Fig. 2*B*), whereas the mean firing rate of putative interneurons ($n = 7$) was not affected by NAc DBS ($\chi^2 = 13.19$; $df = 7$; NS) (Fig. 2*B*). However, 75% (three of four) of putative interneurons that were driven by acute NAc stimulation showed initial excitatory responses to DBS. Neurons that received monosynaptic excitatory MD input ($n = 13$) were also relatively unaffected by DBS ($\chi^2 = 9.55$; $df = 7$; NS) (Fig. 2*C*) compared with neurons that did not receive MD input [i.e., all other cells, $n = 17$ ($\chi^2 = 16.90$; $df = 7$; $p < 0.05$)] (Fig. 2*C*). It should be noted that four of seven putative

interneurons also were driven by MD. NAc DBS produced no significant changes in the percentage of spikes fired in bursts in any OFC neuronal subpopulation (data not shown).

Evoked unit activity

Inhibition

We examined the responses of OFC neurons to single-pulse stimulation of the NAc and MD before and after DBS (Fig. 3). Almost all neurons recorded (29 of 30) responded to NAc stimulation with an inhibition of firing, with five of these neurons showing a short-latency excitation followed by inhibition. The mean onset of inhibition by NAc stimulation was not different before and after DBS (26.0 ± 6.7 vs 31.9 ± 6.2 ms; NS) (Fig. 3A), whereas the mean duration of inhibition was significantly reduced after DBS (258.7 ± 24.5 vs 154.0 ± 15.5 ms; $p < 0.05$). The magnitude of inhibition was also significantly reduced after DBS, when measured both by the mean total number of spikes in the first 200 ms after stimulus (6.6 ± 2.1 vs 11.2 ± 3.3 spikes; $p < 0.05$) and the average percentage of baseline firing in the first 200 ms (21.4 ± 5.0 vs $37.6 \pm 7.6\%$; $p < 0.05$). These effects contrast with the effects of NAc DBS on MD-evoked inhibition, in which no changes were seen in mean onset of inhibition (46.3 ± 10.0 vs 46.0 ± 9.1 ms; NS), duration of inhibition (95.4 ± 18.7 vs 93.3 ± 28.3 ms; NS), number of spikes (27.2 ± 8.9 vs 36.6 ± 9.7 spikes; NS), or percentage of baseline firing (67.2 ± 25.9 vs $76.6 \pm 29.4\%$; NS) in the first 200 ms after stimulus after 30 min of NAc DBS (Fig. 3B).

The effects of DBS on NAc-evoked inhibition varied according to neuronal subpopulation in a manner similar to the effects of DBS on spontaneous activity. Specifically, putative interneurons and neurons excited by MD showed less suppression of inhibition after DBS than putative pyramidal neurons or neurons that did not receive excitatory monosynaptic input from MD (Table 1).

Excitation

Mean excitatory responses evoked by single-pulse NAc stimulation were unchanged after 30 min NAc DBS ($n = 7$) (Fig. 4A). No significant differences were seen in evoked spike probability (37.1 ± 14.2 vs $34.6 \pm 12.3\%$; NS), number of evoked spikes (51.3 ± 19.1 vs 46.4 ± 19.4 ; NS), or percentage of baseline firing (2976.2 ± 1199.1 vs $560.0 \pm 150.4\%$; NS) in the first 25 ms after stimulus. However, when grouped according to cell type, four of four putative interneurons showed an increase in evoked spike probability. In contrast, after NAc DBS, MD-evoked short-latency responses ($n = 13$) (Fig. 4B) were strongly enhanced. This occurred as significant increases in evoked spike probability (37.8 ± 4.2 vs $55.7 \pm 5.9\%$; $p < 0.05$), number of spikes in the first 25 ms after stimulus (14.4 ± 3.2 vs 23.3 ± 4.3 ; $p < 0.05$), and percentage of baseline firing in the first 25 ms after stimulus

Figure 2. Thirty minutes of DBS produces a general inhibition of OFC neuronal firing. The open bar indicates DBS-on. **A1**, Top, Summed histogram showing DBS effects on all recorded neurons ($n = 30$; 10 s bins). Bottom, DBS effects on OFC activity, grouped in 5 min bins. **A2**, Firing rate histograms for four individual neurons (10 s bins). The bottom panel is a putative interneuron. **B1**, Top, NAc DBS effects on putative interneurons in OFC (10 s bins; $n = 7$). Bottom, Five minute bins. **B2**, Top, NAc DBS effects on putative pyramidal neurons in OFC (10 s bins; $n = 20$). Bottom, Five minute bins. **C1**, Top, NAc DBS effects on OFC neurons receiving monosynaptic MD input (10 s bins; $n = 13$). Bottom, Five minute bins. **C2**, Top, NAc DBS effects on OFC neurons not excited by MD (10 s bins; $n = 17$). Bottom, Five minute bins. Error bars represent SEM. * $p < 0.05$.

(435.0 ± 95.1 vs 693.3 ± 117.1 ; $p < 0.05$). Both putative interneurons and putative pyramidal neurons showed this enhancement of excitation. To examine the source of the evoked responses, the effects of an electrolytic lesion of the NAc stimulation site on MD-evoked excitation was examined. Lesions of the NAc stimulation site did not affect any measure of MD-evoked excitation ($n = 4$). Two of these neurons had been driven by both NAc and MD stimulation; after a NAc lesion, only the NAc responses were abolished, indicating that NAc-evoked effects are not attributable to stimulation of ascending MD→OFC fibers.

Spontaneous LFP activity

Spontaneous oscillatory LFP activity was quantified in a number of frequency bands before, during [early (in the first 5 min of DBS) and late (after 25 min)], and after HF (130 Hz) or LF (10 Hz) DBS. HF DBS produced a significant increase in the raw power of LF (0.5–4 Hz, slow/delta) LFP oscillations ($F_{(3,24)} = 6.33$; $p = 0.008$; $n = 9$) (Fig. 5A), as well as in the power in this frequency band when expressed as a percentage of total power ($\chi^2 = 11.93$; $df = 3$; $p = 0.008$; $n = 9$). *Post hoc* analysis revealed that both raw and normalized power of these LF oscillations was

Figure 3. NAc DBS selectively attenuates NAc-evoked inhibition of OFC neurons. **A**, Peristimulus time histogram (PSTH) of an OFC neuron showing NAc-evoked inhibition before (top) and after (bottom) 30 min NAc DBS. PSTHs were constructed from 50 sweeps. The dashed line indicates time of stimulation. **B**, PSTH of a representative OFC neuron showing MD-evoked inhibition before (top) and after (bottom) 30 min NAc DBS. The dashed line indicates time of stimulation.

Table 1. Effect of NAc DBS on single-pulse NAc-evoked inhibition

	Onset (ms)			Duration (ms)			Spikes (first 200 ms)			Percentage of BL (first 200 ms)		
	Pre-DBS	Post-DBS	<i>p</i> value	Pre-DBS	Post-DBS	<i>p</i> value	Pre-DBS	Post-DBS	<i>p</i> value	Pre-DBS	Post-DBS	<i>p</i> value
Putative interneuron (<i>n</i> = 7)	28.57 (7.46)	41.78 (12.90)	0.098	196.58 (44.13)	125.07 (32.31)	0.066	11.43 (6.43)	11.86 (5.6)	0.92	18.15 (6.1)	25.76 (9.93)	0.117
Putative pyramidal neuron (<i>n</i> = 20)	25.61 (9.09)	29.49 (7.64)	0.210	280.20 (29.56)	164.26 (18.39)	0.001	5.24 (11.23)	11.43 (4.16)	0.038	17.42 (5.34)	29.64 (6.91)	0.033
Excited by MD (<i>n</i> = 13)	39.09 (12.31)	41.29 (10.08)	0.278	227.38 (38.03)	132.28 (23.58)	0.005	12.00 (3.95)	17.71 (6.22)	0.414	23.77 (5.74)	66.25 (29.29)	0.089
Not excited by MD (<i>n</i> = 17)	13.71 (4.87)	23.12 (7.49)	0.047	288.05 (30.54)	174.18 (19.55)	0.001	1.47 (0.47)	5.20 (1.50)	0.040	9.34 (5.61)	22.13 (6.17)	0.018

Values represent mean (SEM). Significant *p* values are in bold type. BL, Baseline.

Figure 4. NAc DBS augments MD-evoked excitation in OFC without affecting NAc-evoked excitation. **A**, PSTH of an OFC neuron showing NAc-evoked excitation before (top) and after (bottom) 30 min NAc DBS. PSTHs were constructed from 50 sweeps. The dashed line indicates time of stimulation. **B**, PSTH of a representative OFC neuron showing MD-evoked excitation before (top) and after (bottom) 30 min NAc DBS. PSTHs were constructed from 50 sweeps. The dashed line indicates time of stimulation.

significantly elevated after DBS. There was a trend ($p = 0.08$) toward an increase in power in the last 5 min of DBS, suggesting that this effect developed over the course of the DBS-on period as opposed to being a compensatory change after DBS. No changes in raw or normalized power were observed in any other frequency band (i.e., theta, beta, gamma). These results contrast with those obtained with LF DBS [known to be ineffective for treating most neurological and psychiatric disorders (Perlmutter and Mink, 2006)], in which no significant changes in power were seen in any frequency band ($n = 5$) (Fig. 5B).

Evoked LFP activity

Stimulation of either the NAc or MD produced robust short-latency LFP responses in OFC. Both of these responses were characterized by a large negative-going voltage deflection (mean latency to peak: NAc evoked, 4.35 ± 0.16 ms; MD evoked, 6.11 ± 0.14 ms). Local infusion of kynurenic acid almost completely abolished the negative-going component of the LFP response evoked from either NAc or MD ($n = 3$) (Fig. 6A1), suggesting that this component is primarily glutamatergic. Conversely, local infusion of bicuculline virtually eliminated the positive-going component of the LFP response evoked from either region ($n = 3$) (Fig. 6A2), producing instead a secondary large-amplitude (presumably excitatory) negative-going component. Vehicle infusions had no effects on the evoked LFP responses.

The NAc-evoked responses likely correspond to antidromic activation of local recurrent corticostriatal fiber collaterals, because there are projections from the OFC that terminate in this region (Gabbott et al., 2005) and there are no known direct projections from NAc to OFC. The MD-evoked responses likely reflect orthodromic and monosynaptic activation of OFC neurons, because the latency of the peak field response corresponds roughly to reported thalamocortical (as opposed to corticothalamic) conduction velocities [i.e., ~ 5 ms (Pirou et al., 1994)].

To assess the effects of NAc DBS on these evoked LFP re-

Figure 5. HF but not LF NAc DBS enhances spontaneous LFP slow oscillatory activity in OFC. **A1**, Top, OFC voltage trace before (top) and after (bottom) 30 min 130 Hz NAc DBS. Bottom left, Periodogram constructed from 2 min of spontaneous OFC LFP activity before (gray) and after (black) 30 min NAc DBS. Bottom right, Spectrograms showing changes in OFC oscillatory activity across time. Spectrograms were constructed from 2 min of spontaneous OFC LFP activity before (top) and after (bottom) 30 min NAc DBS. **A2**, Left, Total raw power in the 0.5–4 Hz frequency band before DBS, during the first 5 min of DBS-on, during the last 5 min of DBS-on (i.e., minutes 26–30), and after DBS ($n = 7$). Right, Power in the 0.5–4 Hz band expressed as percentage of total power before DBS, during the first 5 min of DBS-on, during the last 5 min of DBS-on (i.e., minutes 26–30), and after DBS ($n = 7$). $*p < 0.05$. **B1**, Top, OFC voltage trace before (top) and after (bottom) 30 min 10 Hz NAc DBS. Bottom left, Periodogram constructed from 2 min of spontaneous OFC LFP activity before (gray) and after (black) 30 min NAc DBS. Bottom right, Spectrograms showing changes in OFC oscillatory activity across time. Spectrograms were constructed from 2 min of spontaneous OFC LFP activity before (top) and after (bottom) 30 min 10 Hz NAc DBS ($n = 5$). **B2**, Left, Total raw power in the 0.5–4 Hz frequency band before and after 10 Hz NAc DBS. Right, Power in the 0.5–4 Hz band expressed as percentage of total power, before and after 10 Hz NAc DBS ($n = 5$). Error bars indicate SEM.

sponses, input–output curves from each electrode were generated before DBS and both 5 and 90 min after HF DBS and LF DBS (Fig. 7). Two-way ANOVA with current intensity as a repeated measure revealed a main effect of time after DBS ($F_{(2,48)} = 4.29$; $p = 0.03$) and current intensity ($F_{(2,48)} = 51.864$; $p < 0.001$) with no interaction between time after DBS and intensity ($F_{(2,48)} = 1.01$; NS). *Post hoc* analysis revealed that HF DBS produced a significant potentiation of NAc-evoked LFP amplitude both 5 and 90 min after DBS at all, except for the lowest, stimulation intensity. MD-evoked responses were unaffected at all time points. Conversely, LF DBS failed to produce an effect on evoked responses from either region at any stimulation intensity or time point. Given the reliance of long-term potentiation (LTP)-like processes on NMDA receptors, we also assessed the effects of HF DBS on evoked LFP activity in the presence of the NMDA antagonist MK-801. Pretreatment with MK-801 (1.0 mg/kg, i.p.) 30 min before DBS did not affect the LFP evoked from either NAc or

MD but completely blocked the potentiating effects of HF DBS on NAc-evoked LFP activity ($n = 4$) (Fig. 7).

Discussion

NAc DBS, delivered at clinically effective frequencies and intensities, reduces OFC neuronal firing, selectively modulates afferent input to OFC measured by single-unit and evoked LFPs, and alters OFC LFP oscillatory activity *in vivo*. We propose that this occurs via activation of recurrent inhibitory processes within the OFC that are selectively potentiated during DBS.

Parallels between rodent DBS and therapeutic approaches in humans

Successful DBS treatment of OCD patients is associated with reductions in aberrant metabolism in the OFC (Nuttin et al., 2003; Abelson et al., 2005). Studies suggest that the rat and human OFC are functionally analogous based on connectivity (Leonard, 1969;

Figure 6. Effects of ionotropic GABA or glutamate receptor blockade on NAc-evoked (**A1**) and MD-evoked (**A2**) LFP responses. Blockade of fast glutamatergic transmission with kynurenic acid greatly attenuated the LFP evoked from either NAc or MD stimulation. In contrast, blockade of ionotropic GABA receptors with bicuculline eliminated the positive-going component of the LFP response and instead produced a large-amplitude secondary negative-going component. Arrowheads indicate time of stimulation. Calibration: 10 ms, 30 mV.

Krettek and Price, 1977; Groenewegen, 1988). Although some debate exists, the area consisting of the ventral orbital (VO), lateral orbital (LO), and agranular insular (AI) cortices is reported to be most homologous to the primate OFC (Ongur and Price, 2000; Schoenbaum et al., 2006). We recorded from neurons in LO and ventral AI because these areas are the source of OFC→NAc fibers, with VO having relatively sparse projections to the NAc (Gabbott et al., 2005). The stimulating electrode was targeted to the dorsal NAc core. A common DBS target in human OCD patients is the ventral anterior internal capsule (Nuttin et al., 2003; Abelson et al., 2005; Greenberg et al., 2006); however, recently therapeutic responses have been achieved by targeting the NAc (Sturm et al., 2003; Aouizerate et al., 2005), supporting the validity of our stimulation target in the rat. Although difficult to precisely replicate human parameters, current intensities were modeled after the human literature, and in the range used effectively in animal models of Parkinson's disease (Chang et al., 2003; Degos et al., 2005). Moreover, these stimulation parameters produced profound effects on neuronal firing without observable tissue trauma. The dearth of robust animal models of OCD makes it difficult to judge whether these intensities have beneficial behavioral effects; nonetheless, we feel the present results yield pertinent data regarding the effects of DBS on neuronal activity. Indeed, whereas the current study was performed in animals with no obvious pathology, we believe that the plastic changes induced by direct stimulation are likely to produce the same circuit-level effects as those elicited in the clinic.

Spontaneous neuronal activity

The mean firing rate of OFC neurons was reduced during NAc DBS. This effect was most pronounced in putative pyramidal neurons; some putative interneurons showed excitatory responses to DBS. Moreover, single-pulse stimulation of the NAc DBS site resulted in a profound, rapid-onset inhibition of firing in almost every OFC neuron encountered, with many of these neurons exhibiting antidromic activation from the NAc. The rapid onset of inhibition (i.e., >50% of neurons showed total inhibition within 15 ms of stimulation) suggests that this acute inhibition does not arise from a polysynaptic feedforward effect. Furthermore, there are no direct projections from NAc to OFC, as opposed to the substantial OFC→NAc projection (Gabbott et al., 2005). Finally, given that an electrolytic lesion of the DBS site does not interrupt MD-evoked responses in OFC, it is unlikely

Figure 7. HF but not LF NAc DBS selectively potentiates NAc-evoked LFP responses in OFC. **A1**, Voltage trace showing a NAc-evoked LFP response before (gray) and after (black) 30 min NAc DBS. Arrowheads indicate time of stimulation. Calibration: 10 ms, 30 mV. **A2**, Input–output curves for NAc-evoked OFC LFP responses before DBS, 5 min after DBS, and 90 min after DBS ($p < 0.05$ for pre-DBS vs 20 min post-DBS; $+p < 0.05$ for pre-DBS vs 5 min post-DBS; $n = 7$). **A3**, Input–output curves for NAc-evoked LFP responses before 10 Hz DBS, 5 min after 10 Hz DBS, and 90 min after 10 Hz DBS ($n = 5$). **A4**, Input–output curves for NAc-evoked LFP responses at baseline, 20 min after 1.0 mg/kg MK-801, and 5 min after DBS (130 Hz) ($n = 4$). **B1**, The voltage trace showed an MD-evoked OFC LFP response before (gray) and after (black) 30 min NAc DBS. Calibration: 10 ms, 30 mV. **B2**, Input–output curves for MD-evoked LFP responses before DBS, 5 min after DBS, and 90 min after DBS ($n = 7$). **B3**, Input–output curves for MD-evoked LFP responses before 10 Hz DBS, 5 min after 10 Hz DBS, and 90 min after 10 Hz DBS ($n = 5$). **B4**, Input–output curves for MD-evoked LFP responses at baseline, 20 min after 1.0 mg/kg MK-801, and 5 min after 130 Hz DBS ($n = 4$).

that the acute inhibitory response reflects activation of MD→OFC fibers traversing the NAc. Thus, these data are consistent with NAc stimulation driving recurrent inhibition in OFC via antidromic activation of corticostriatal axons. We focused exclusively on neurons that responded to acute NAc stimulation, because assessing the effects of DBS on evoked activity requires an appreciable level of responsivity to stimulation. Moreover, by limiting our analysis to neurons exhibiting some evoked activity, we ensured that we were in the appropriate projection field for the neuron under investigation.

Antidromically driven recurrent inhibition is a well characterized phenomenon that has been documented in several cortical regions, including motor cortex (Phillips, 1959), visual cortex (Feeney and

Orem, 1971), and hippocampus (Matsuda and Fujimura, 1996). In layer V pyramidal neurons of the motor cortex, antidromic activation of efferent fiber tracts produces predominantly IPSPs mediated by recurrent collaterals (Phillips, 1959; Stefanis and Jasper, 1964). Whereas demonstration of NAc stimulation-mediated excitation is limited in the current study because of the small number of putative interneurons recorded, a subset of these putative interneurons did exhibit reliable excitatory responses to acute NAc stimulation, and an increase in firing to NAc DBS.

Evoked neuronal activity

After DBS, NAc-evoked inhibitory responses were generally attenuated, with this suppression most prominent in neurons that were strongly inhibited during DBS, whereas evoked inhibition of putative interneurons was enhanced. In contrast, neurons receiving direct MD input were not significantly affected by DBS. MD-evoked inhibitory responses were unchanged after DBS, whereas excitatory responses (in putative interneurons and pyramidal neurons) were potentiated. These results suggest that DBS preferentially affects specific subpopulations of neurons, with a potentiation of evoked excitatory input to interneurons after DBS. This increased drive onto putative interneurons may reflect an LTP-like phenomenon produced by DBS, in which stimulation frequencies (i.e., 130 Hz) are consistent with those required for induction of LTP (Bliss and Collingridge, 1993).

Spontaneous LFP activity

LFP responses represent summed dendritic synaptic activity over a relatively large area and hence provide a measure of input to a region (Mitzdorf, 1985; Logothetis, 2003). Slow LFP oscillations (0.5–4 Hz) in neocortex occur during sleep and with certain anesthetics (Metherate and Ashe, 1993; Steriade et al., 1993; Cowan and Wilson, 1994; Amzica and Steriade, 1998) and reflect synchronous changes in membrane potential caused by recurrent cortical activity (Sanchez-Vives and McCormick, 2000; Shu et al., 2003). Analysis of the spectral density in this frequency band revealed an increase in power that developed during DBS. This increase in power may stem from sustained activation of corticostriatal axons by NAc DBS that would, in turn, drive recurrent activity in OFC. In contrast, 10 Hz DBS had no effect on slow LFP oscillations in OFC, arguing against anesthesia-related effects. Moreover, given the reported lack of efficacy of LF DBS on OCD symptoms, the enhancement of slow oscillations by HF DBS may be significant for therapeutic effects. Interestingly, DBS of the subthalamic nucleus in parkinsonian patients increases slow LFP oscillations within this region (Priori et al., 2006).

Evoked LFP responses

Single-pulse stimulation of either the NAc or MD resulted in robust short-latency LFP responses in OFC, presumably reflecting the synchronous activation of an afferent input. Given the lack of direct projections from NAc to OFC, the NAc-evoked response is likely attributable to antidromic activation of corticostriatal fibers. In contrast, the latency of the MD-evoked response is consistent with an orthodromic monosynaptic input, because conduction velocities of corticothalamic fibers are considerably longer than that of thalamocortical fibers (Pirot et al., 1994). The negative-going component of the LFP responses is glutamatergic, because LFP responses were greatly attenuated after local ionotropic glutamate receptor blockade. The positive-going component of the LFP response was eliminated after GABA_A receptor blockade and thus likely represents a GABAergic event produced by recurrent (with NAc stimulation) or orthodromic and recur-

Figure 8. Schematic of the proposed mechanism of action of NAc DBS on OFC neuron activity. NAc DBS produces antidromic activation of corticostriatal projections that activate a population of interneurons (circle) via recurrent collaterals. These interneurons in turn suppress firing in populations of pyramidal neurons (triangles). With maintained HF stimulation, this would induce an LTP in this recurrent inhibitory pathway (bold lines). Although certain pyramidal neurons would receive excitatory input from these same recurrent collaterals, inhibitory inputs are positioned [e.g., by targeting the soma or axon initial segment (Markram et al., 2004)] to potentially suppress the activity of these output neurons.

rent (with MD stimulation) activation of OFC interneurons. Blockade of GABA_A receptors eliminates both feedforward and recurrent inhibition, unmasking a robust secondary (recurrent) negative-going excitation. The amplitude of NAc-evoked LFP responses was potentiated after HF but not LF (10 Hz) DBS and remained elevated for at least 90 min. This DBS-induced potentiation was prevented by NMDA receptor blockade. The amplitude of MD-evoked LFPs did not change with any manipulation.

This evidence is consistent with tetanic stimulation-induced potentiation of excitatory drive mediated by recurrent collaterals. Thus, Phillips (1959) reported that subthreshold antidromic tetanic stimulation potentiated EPSPs mediated by recurrent collaterals. Moreover, potentiation of the NAc-evoked LFP response required HF stimulation and was dependent on NMDA receptor activation. Together, these data suggest an LTP-like potentiation of antidromically stimulated recurrent collaterals of pyramidal neuron axons and is consistent with the requirement for HF stimulation in the LTP range [i.e., >100 Hz (Bliss and Collingridge, 1993)] to produce therapeutic effects.

Implications

We propose that the effects of NAc DBS on OFC activity are mediated by antidromic activation of recurrent OFC collaterals, causing excitation of inhibitory interneurons and consequent suppression of principal cell output (in effect, “hijacking” the machinery mediating physiological recurrent inhibition) (Fig. 8). Indeed, antidromic activation of branched axons may mediate certain effects produced by DBS for movement disorders (Maurice et al., 2003; Grill et al., 2007). Furthermore, our model is

consistent with the therapeutic responses produced by DBS in OCD patients (i.e., normalization of OFC metabolic hyperactivity). Considering that sustained antidromic activation of corticostriatal fibers by NAc DBS will also suppress orthodromic impulses, OFC-striatal output may be reduced further still. DBS within this circuit has also been effective in the treatment of other disorders, including DBS of the subgenual cingulate gyrus for depression (Mayberg et al., 2005) and DBS of the NAc/internal capsule (Flaherty et al., 2005; Kuhn et al., 2007), thalamus (Visser-Vandewalle et al., 2003), and globus pallidus (Ackermans et al., 2006; Shahed et al., 2007) for Tourette's syndrome, which is often comorbid with OCD (Jankovic, 2001). Therefore, by altering the balance of excitation/inhibition within cortical efferent pathways, DBS may prove to have a more general effect of stabilizing disordered systems in a manner that may be generally applicable to patients exhibiting functional deficits within these circuits.

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