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Stimulation of contacts in ventral but not dorsal subthalamic nucleus normalizes response switching in Parkinson's disease

Ian Greenhouse^{a,b}, Sherrie Gould^c, Melissa Houser^c, and Adam R. Aron^{a,*}

^aDepartment of Psychology, University of California, 9500 Gilman Drive, La Jolla, CA USA

^bDepartment of Psychology, University of California, Berkeley, CA USA

^cDepartment of Neurology, Scripps Green Hospital, La Jolla, CA, USA

Abstract

Switching between responses is a key executive function known to rely on the frontal cortex and the basal ganglia. Here we aimed to establish with greater anatomical specificity whether such switching could be mediated via different possible frontal–basal-ganglia circuits. Accordingly, we stimulated dorsal vs. ventral contacts of electrodes in the subthalamic nucleus (STN) in Parkinson's patients during switching performance, and also studied matched controls. The patients underwent three sessions: once with bilateral dorsal contact stimulation, once with bilateral ventral contact stimulation, and once Off stimulation. Patients Off stimulation showed abnormal patterns of switching, and stimulation of the ventral contacts but not the dorsal contacts normalized the pattern of behavior relative to controls. This provides some of the first evidence in humans that stimulation of dorsal vs. ventral STN DBS contacts has differential effects on executive function. As response switching is an executive function known to rely on prefrontal cortex, these results suggest that ventral contact stimulation affected an executive/associative cortico-basal ganglia circuit.

Keywords

Cognitive control; Switching; Subthalamic nucleus; Deep brain stimulation; Parkinson's disease

1. Introduction

Switching is the ability to flexibly change between tasks or response sets (Monsell, 2003) and depends upon the frontal cortex and basal ganglia (Aron et al., 2003; Cools, van den Bercken, Horstink, van Spaendonck, & Berger, 1984; Cools, Ivry, & D'esposito, 2006; Isoda & Hikosaka, 2008; Mars et al. 2009; Neubert, Mars, Buch, Olivier, & Rushworth, 2010; Redgrave et al., 2010; Robbins, 2007; Yehene, Meiran, & Soroker, 2008). However, it is still unclear whether an anatomically specific frontal–basal ganglia circuit supports this type of executive function in humans. To address this, we used deep brain stimulation (DBS) to electrically modulate a part of the basal ganglia, the subthalamic nucleus (STN), while

measuring switching performance in patients with Parkinson's disease (PD). The patients' DBS electrodes were implanted in the STN of both hemispheres, and each electrode had multiple contacts through which stimulation could be delivered. Thus, we could target bilateral stimulation through either dorsal or ventral contacts, with the intention of affecting different putative STN subregions. Stimulation of this kind affects the STN itself, and also the connected basal ganglia and cortical circuitry (e.g. Cavanagh et al., 2011; Swann et al., 2011), possibly in a manner that is specific to the STN subregion being stimulated (Hershey et al., 2010). There is however some controversy about how many STN subregions there are and where they are located. While many tract-tracing studies in the rodent and monkey have identified up to three STN subregions whose different connectivity profiles suggest a dorso-lateral STN sensorimotor circuit, a ventral STN executive/associative circuit, and a ventro-medial limbic circuit (Alexander & Crutcher, 1990; Joel & Weiner, 1997; Karachi et al., 2005; Parent & Hazrati, 1995a, 1995b; Temel, Blokland, Steinbusch, & Visser-Vandewalle, 2005) (also see Brunenberg et al., 2012; Haynes, Lehman, Feeckes, & Haber, 2011), a recent review of structural imaging and tract-tracing studies by Keuken et al. (2012) indicates that a consensus has not been reached concerning the existence of separate STN subdivisions (with perhaps the greatest evidence for two subdivisions and much variability in anatomy). Here, we assumed that the STN has two or more subdivisions, one of which might be executive, and we opted for a neurostimulation approach to test for a functional dissociation. We hypothesized that ventral contact stimulation would affect switching as the ventral STN sector has been linked to the putative associative/executive circuit with prefrontal cortex.

We used a response switching task that has been shown, in humans, to implicate the prefrontal cortex (Mars et al., 2009; Neubert et al., 2010) and, in monkeys, to specifically implicate the ventral STN (Isoda & Hikosaka, 2008). We studied PD patients On bilateral stimulation of the ventral STN, the dorsal STN, and Off stimulation at three separate visits. The comparison of dorsal and ventral stimulation was double-blind. We also compared the patients' switching performance with that of healthy matched controls. We targeted the stimulation at contacts within the ventral or dorsal STN using combined MRI and CT imaging and neurophysiological diagrams.

Based upon multiple studies of switching deficits in PD (Cameron, Watanabe, Pari, & Munoz, 2010; Cools et al., 1984; Cools, Barker, Sahakian, & Robbins, 2001; Gauggel, Rieger, & Feghoff, 2004; Kehagia, Cools, Barker, & Robbins, 2009), we predicted that patients tested with DBS Off would exhibit a greater switch cost (i.e. a significantly longer RT for switch than nonswitch trials) relative to controls. Furthermore, we hypothesized that ventral contact stimulation would change switching performance while dorsal contact stimulation would not. If so, this would provide evidence in humans that the ventral STN (and possibly the connected executive/associative frontal-basal-ganglia circuit) is important for response switching in humans.

2. Materials and methods

2.1. Participants

Eleven patients diagnosed with Parkinson's disease and treated with bilateral STN DBS were recruited from the Scripps Clinic in La Jolla, California. Ten age- and gender-matched

healthy controls were recruited from the La Jolla community. All participants provided informed consent and were tested at least six months following DBS surgery.

One patient's data was excluded from analysis because of an error rate greater than three standard deviations above the group mean. There were therefore ten patients and ten matched controls included in the analysis. The groups were matched on age, gender, handedness, MMSE, and NAART (Table 1, all p 's > 0.05). Controls were tested once, and each patient was tested at three separate visits. The time between the first and second visit was 14.0 ± 10.1 days, and the time between the second and third visit was 11.8 ± 11.8 days.

There were no significant differences in Unified Parkinson's Disease Rating Scale (UPDRS) III scores between Off, Dorsal, and Ventral stimulation conditions (Table 2). This is not surprising given that the experimental stimulation settings were not intended to be therapeutic for PD motor symptoms and, in all cases, were substantially different from the patients' typical treatment settings. Moreover, all patients who were taking dopaminergic medication remained on the same medication regimen throughout the entire study and were always tested in the on-medication state. Only the electrode contact and stimulation voltage changed across conditions. Stimulation was set as close to 3.2 V as was possible without producing any patient discomfort, corresponding to voltages used for treatment in this sample and in line with our previous study (Greenhouse et al., 2011). Patients were always stimulated at a frequency of 180 Hz with a 60 μ s pulse width, also corresponding to their treatment settings.

2.2. Neuroimaging and electrode contact selection

Before DBS surgery, MRI was acquired on a Siemens Symphony 1.5T scanner. This included scans with sagittal T1-weighting [TR = 2000 ms, TE = 2770 ms, flip angle = 15, 512 slices, $0.5 \times 0.5 \times 1$ mm], coronal T2-weighting [TR = 3630 ms, TE = 128 ms, flip angle = 180, 19 slices, $1 \times 1 \times 2$ mm], and axial T2-weighting [TR = 3400 ms, TE = 92 ms, flip angle = 180, 19 slices, $1 \times 1 \times 2$ mm]. The STN is hypointense in T2-weighted MRI due to higher iron content (Dormont et al., 2004). After DBS surgery, a coronal CT image ($0.5 \times 0.5 \times 0.625$ mm, 120 kV, 320 mAs) was acquired on a GE LightSpeed CT scanner. The quadripolar DBS lead (model 3389, Medtronic Activa System, Medtronic Inc.) is visible as an artifact within the CT image.

Electrode localization proceeded as follows: First, the T2-weighted and CT images were coregistered to the T1-weighted image using a mutual information function (Collignon et al., 1995; Wells, Viola, Atsumi, Nakajima, & Kikinis, 1996) in SPM 5 (Wellcome Department of Cognitive Neurology, London, UK). We used a conventional approach for direct visualization of the STN (e.g. Cho et al., 2010; Dormont et al., 2004; Forstmann et al., 2012; Hamani et al., 2005; Richter, Hoque, Halliday, Lozano, & Saint-Cyr, 2004; Starr, Vitek, DeLong, & Bakay, 1999). Two independent raters localized the STN in both the axial and coronal T2 images to capitalize on the better in-plane resolution of each of the different slice orientations. Localization was performed within each patient's native brain space because neuroanatomical atlases vary in terms of STN coordinates and the process of deforming patient images to atlas space can impose distortion on the STN (Richter et al., 2004; Ashkan et al., 2007). Each rater set the contrast values to maximize visibility of the STN.

Localization of the dorsal and ventral STN borders was performed in the coronal plane (Richter et al., 2004; Hamani et al., 2005). The red nucleus, the lateral wall of the third ventricle, and the substantia nigra were used as landmarks in the coronal image for the selection of slices containing the STN. The slice approximately 2 mm posterior to the mid-commissural point generally provided best visualization. The axial image was used to define the posterior, medial, lateral, and anterior STN borders. In the axial plane, the slice in which the red nucleus diameter was greatest was located first, and this typically corresponded to the slice 4 mm inferior to the AC–PC plane. Second, the artifact caused by the DBS lead in the CT image was identified. Third, a model of the lead was scaled to match the voxel size of the artifact and overlaid on the image, see Fig. 1A–C. Fourth, for each patient, two raters independently chose the best ventral and dorsal contacts for the study, relative to the STN borders defined in the T2 image. Across the forty-four different electrode contacts (11 patients $\times$ 2 contacts $\times$ 2 hemispheres), there was strong inter-rater agreement (Spearman's $\rho = 0.95$, $p < 0.001$).

2.3. Neuroimaging correspondence with neurophysiology

We used intraoperative neurophysiological recordings as a way to verify/constrain our localization, as there is a proven good correspondence between these and T2 MRI at 1.5T (Hamani et al., 2005). Neurophysiological mapping was performed as described in Greenhouse et al. (2011) (and for more information, see Hutchison et al., 1998). In brief, this intraoperative recording procedure is used to detect a change in the pattern of cell firing that occurs when the ventral border of the STN is crossed, and this border is then used to define the target location for electrode implantation. A diagram of the approximate location of the electrode contacts relative to the ventral STN border was created using deformable plates from the Schaltenbrand–Wahren atlas (Fig. 1D). Contact selection was compared between the neuroimaging and neurophysiological diagrams. For the 22 contacts in the ventral STN and the 22 contacts in the dorsal STN there was strong agreement in the contact chosen by the two raters (averaged) and the neurophysiological diagrams (Spearman's $\rho = 0.91$, $p < 0.001$ and $\rho = 0.84$, $p < 0.001$, respectively). This correspondence between the neuroimaging and neurophysiological diagrams increased our confidence that our ventral contacts were in ventral STN.

2.4. Behavioral protocol

Patients were tested at three separate visits: with stimulation Off, with the Dorsal STN stimulated, and with the Ventral STN stimulated. The visit order was counterbalanced across patients, and the patients and experimenter were double-blind to the Ventral and Dorsal conditions. There was also an Off condition. Testing began at least thirty minutes after DBS adjustment. The UPDRS part III was administered to assess motor symptoms following DBS adjustment at each visit. For both tasks, stimuli were presented using the Psychtoolbox in Matlab R2009a (Mathworks, Natick, MA) running on a MacBook Pro laptop (Apple, Cupertino, CA), and responses were recorded with a USB-interfaced two-button keypad. Participants responded using the index and middle fingers of the right hand.

The response switching task was adapted from prior studies (Isoda & Hikosaka, 2007, 2008; Mars et al., 2009; Neubert et al., 2010; Neubert, Mars, Olivier, & Rushworth, 2011) (Fig. 2).

At each visit, there were 30 practice trials and 180 test trials. Trials began with a white fixation square of 1 s at center screen. The square was then flanked on each side by colored squares (one yellow and one pink) for a variable cue-period (450–600 ms, uniform distribution). The center square then changed color to match one of the two flanking squares. Participants were instructed to respond with a button press corresponding to the matching side (i.e. index finger for a left response or middle finger for a right response). The response window was 1 s. The target stimulus was then replaced with the white fixation. A 400 ms 100 Hz tone sounded if there was an incorrect response or if a response was not completed within the response window. Importantly, the matching color (e.g. yellow) repeated for a series of 4 to 8 consecutive trials (uniform distribution). This increased response prepotency by encouraging participants to prepare a particular response during the cue-period based upon the matching color of the preceding trial. Trials for which the matching color remained the same as the previous trial are referred to as ‘nonswitch’ trials, and trials in which the matching color differed from the previous trial are referred to as ‘switch’ trials. Each trial was further categorized depending upon whether the response on that trial was the same (i.e. repeat) or different (i.e. alternate) from the previous trial. This resulted in four trial categories: switch-repeat, switch-alternate, nonswitch-repeat, and nonswitch-alternate (see Fig. 2). This was done based upon the classic finding that the switch cost differs for repeat and alternate responses (Cooper & Mari-Beffa, 2008; Kiesel et al., 2010; Rogers & Monsell, 1995). During the experiment proper, participants completed 180 trials; totaling thirty switch trials and 150 nonswitch trials.

3. Results

3.1. Controls vs. patients Off DBS

For correct response RT, ANOVA was performed with the factors trial type (switch vs. nonswitch), response type (repeat vs. alternate), and group (PD-Off vs. control). There was a main effect of trial type with switch trials slower than nonswitch ($F(1,18) = 6.09, p < 0.05$; Fig. 3A). There was a small but significant main effect of response type, with longer RT for repeat (529 ± 48 ms) than alternate (521 ± 53 ms) responses ($F(1,18) = 7.13, p < 0.05$). There was a significant interaction between trial type and response type ($F(1,18) = 7.67, p < 0.05$), replicating the well-established finding that there is a greater RT switch cost for repeat than alternate responses. The interaction between response type and group was also significant ($F(1,18) = 4.41, p = 0.050$), indicating that controls showed a larger difference between repeat (520 ± 49 ms) and alternate (506 ± 58 ms) response RT than did patients (551 ± 46 ms and 552 ± 53 ms, respectively). Most noteworthy was a highly significant three-way interaction of trial type, response type, and group for RT ($F(1,18) = 10.80, p < 0.01$), with controls exhibiting a larger difference between switch repeat (544 ± 52 ms) and switch alternate (501 ± 56 ms) response RT than did patients (551 ± 46 ms and 552 ± 53 ms, respectively). There were no other significant main effects or interactions.

To further examine the three-way interaction for RT, follow-up ANOVAs were run for the control and PD groups separately and included the factors trial type (switch vs. nonswitch) and response type (repeat vs. alternate). For controls there was a main effect of response type, i.e. longer RT for repeat (520 ± 49 ms) than alternate (506 ± 58 ms) responses ($F(1,9)$

= 14.32, $p < 0.01$) and a significant trial type by response type interaction for RT ($F(1,9) = 23.59$, $p < 0.001$), but no other significant main effects or interactions. Follow-up paired t -tests showed that the trial type by response type interaction was due to a significant switch cost for repeat response trials ($t(9) = 4.37$, $p < 0.01$) and no significant switch cost for alternate response trials ($t(9) = -0.72$, $p = 0.49$) (Fig. 3B). Alternate responses were in fact slightly faster for switch than nonswitch trials, albeit not significantly so. This pattern of behavior replicates previous studies of task switching in healthy populations that reported a switch cost for repeat and not for alternate responses (Aron et al., 2003; Rogers & Monsell, 1995).

For the PD group there was a trend toward slower RT for switch than nonswitch trials ($F(1,9) = 3.24$, $p = 0.11$), but no other significant main effects or interactions. In stark contrast to the control group, patients Off DBS did not exhibit a significantly greater switch cost for repeat than alternate responses (Fig. 3B). Thus, the control group showed a difference in the switch cost for repeat vs. alternate trials whereas the PD group did not, and this resulted in the significant three-way interaction observed in the overall ANOVA.

For errors, ANOVA was performed with the factors trial type (switch vs. nonswitch), response type (repeat vs. alternate), and group (PD-Off vs. control). There was a main effect of trial type, with more errors on switch vs. nonswitch trials ($F(1,18) = 12.98$, $p < 0.01$; Fig. 3C), but no other significant main effects or interactions.

3.2. Effects of DBS

ANOVA was performed for the factors DBS condition (Off, Dorsal, Ventral), trial type (switch, no switch) and response type (repeat, alternate). Patients were significantly slower on switch than nonswitch trials ($F(1,9) = 5.02$, $p = 0.050$; Fig. 3A). There was also a significant trial type by response type interaction ($F(1,9) = 6.50$, $p < 0.05$) (i.e. a greater switch cost for repeat than alternate response trials). The three-way (trial type $\times$ response type $\times$ DBS condition) interaction for RT was also significant ($F(2,18) = 6.51$, $p < 0.01$, Fig. 3C). There were no main effects of DBS condition or response type.

To determine whether the Dorsal and Ventral DBS conditions differed, a follow-up ANOVA was run with the factors DBS condition (Ventral vs. Dorsal), trial type (switch vs. nonswitch), and response type (repeat vs. alternate). Again, patients were slower for switch than non-switch trials, ($F(1,9) = 5.59$, $p < 0.05$), and there was a significant trial type by response type interaction, ($F(1,9) = 9.42$, $p < 0.05$). Most importantly, there was a significant three-way interaction, ($F(1,9) = 10.28$, $p < 0.05$), and no other significant effects. To interpret this three-way interaction, additional follow-up ANOVAs were run separately for the Ventral and Dorsal DBS conditions and these included the factors trial type (switch vs. nonswitch) and response type (repeat vs. alternate). Results from the Off condition are reported above. For the Ventral DBS condition there was a significant interaction ($F(1,9) = 26.89$, $p < 0.001$) indicating a larger switch cost for repeat than alternate responses, but no significant main effects. For the Dorsal DBS condition switch RT was significantly slower than nonswitch RT ($F(1,9) = 8.07$, $p < 0.05$), but there was no significant main effect of response type and no interaction.

This pattern of results shows that patients in the Ventral DBS condition had a larger switch cost for repeat vs. alternate responses while this was not the case for the Dorsal or Off DBS conditions (Fig. 3B). Moreover, every patient in the Ventral DBS condition demonstrated a greater switch cost for repeat than for alternate responses, and this more closely resembled the pattern of the control group than the Dorsal or Off DBS conditions (see Fig. 4).

For errors, ANOVA was performed for the factors DBS condition (Off, Dorsal, Ventral) trial type (switch, no switch) and response type (repeat, alternate). There were more errors on switch than nonswitch trials ($F(1,9) = 11.62, p < 0.01$; Fig. 3C). However, there was no significant effect of DBS condition or response type, and there were no significant interactions.

4. Discussion

We used a double-blind and counterbalanced design to test response switching in a group of PD patients while DBS was targeted at either ventral or dorsal contacts in the STN. We also tested patients Off DBS as well as a matched group of controls. We found that patients Off DBS exhibited abnormal patterns of switching. Specifically, they showed an equivalent switch cost for repeat and alternate responses, whereas controls showed a typical pattern of a larger switch cost for repeat than alternate responses. The PD patients' abnormal pattern of performance became more like controls when stimulation was targeted at the ventral but not dorsal contact. Because switching is commonly attributed to the influence of prefrontal cortex over the motor system (Monsell, 2003; Robbins, 2007), and because we only observed differences on switch trials, we believe modulation of the associative/executive prefrontal–basal ganglia circuit to be the most parsimonious explanation for our results. Therefore, we attribute these findings to a role for the ventral STN in modulating executive functions via a specific frontal–basal ganglia circuit.

The controls exhibited the curious, but well-replicated, pattern of an RT switch cost for repeat, but not alternate responses (Cooper & Mari-Beffa, 2008; Kiesel et al., 2010; Rogers & Monsell, 1995). This pattern may result from: (i) a tendency to switch the rule and response simultaneously (i.e. a 'change all' signal), (ii) increased difficulty uncoupling recently established stimulus-response mappings, or (iii) the selective suppression of the last-executed (and possibly still active) response (Rogers & Monsell, 1995). Current behavioral evidence more strongly supports the latter, selective suppression, hypothesis (Cooper & Mari-Beffa, 2008; Hübner & Druey, 2006, 2008). We speculate that this difficulty in repeating the same response when a switch occurs might be a 'built in' basal ganglia design, consistent with the computational requirement for a clean switch to prevent dithering (Redgrave, Prescott, & Gurney, 1999). Interestingly, the PD patients Off stimulation deviated from this pattern by showing equivalent switch costs for repeat and alternate response trials on our task. While we cannot be sure of the mechanism underlying this difference between PD Off and controls, one possibility is that pathology of the basal ganglia in PD rendered these patients unable to selectively suppress particular responses; specifically, when they switch they may not suppress the response just made, but instead suppress more globally. Hence there is a switch cost regardless of whether there is a repeat or alternate response. Importantly, ventral but not dorsal contact stimulation restored the

switching pattern in the PD patients to that observed in controls: i.e. there was now the classic pattern of a switch cost for repeat, but not alternate, responses. Although the precise mechanism by which DBS restores function is unclear, our pattern of results is consistent with evidence that suggests STN DBS improves the quality of the signal passing between the basal ganglia and cortex rather than simulating a lesion of the stimulated target (Garcia-Munoz, Carrillo-Reid, & Arbuthnott, 2010; Li et al., 2012; Moran, Stein, Tischler, & Bar-Gad, 2012; Swann et al., 2011). Such an improvement in signal clarity may override pathological patterns of activity.

The selective suppression of a just-executed movement could be implemented via the so-called indirect pathway of the basal ganglia (Joel & Weiner, 1997; Mink, 1996; Nambu, Tokuno, & Takada, 2002; Shink, Bevan, Bolam, & Smith, 1996). This pathway is comprised of a projection from the striatum to the external pallidum and then to the STN and internal pallidum (striatum–GPe–STN–GPi, or alternatively, striatum–GPe–GPi) (Albin, Young, & Penney, 1989; Alexander & Crutcher, 1990). While healthy controls and ventrally stimulated PD patients might be able to use this pathway correctly to suppress the just-performed response on a switch trial, it is possible that PD patients Off stimulation, and those with dorsal stimulation, cannot. Instead these latter groups might fall back on a ‘global suppression’ of the motor system when a switch occurs, leading to increased RT for both repeat and alternate responses. Such global suppression may depend upon the hyper direct pathway through the STN. Further studies, at the neural/physiological level, are needed to validate this idea.

Whereas previous studies in PD have reported deficits in primary switch cost (i.e. independent of response type; repeat vs. alternate), here we did not detect such an effect. Instead, we observed an effect of DBS on the comparison of switch costs for repeat and alternate response trials. However, we note that most studies of switching in PD only looked at the overall switch cost and did not break it down by repeat/alternate responses (although see Cools et al., 2006; Helmich, Aarts, de Lange, Bloem, & Toni, 2009; Shook, Franz, Higginson, Wheelock, & Sigvardt, 2005). Further, previous studies typically used task set switching (or set shifting) rather than response switching paradigms. In any event, the current results clearly show, in humans, that ventral contact stimulation modifies at least one type of switching, thus extending the results from monkey neurophysiology (Isoda & Hikosaka, 2008) and pointing to the ventral STN and/or its influence on the associative frontal–basal ganglia circuit as being important for response switching.

Another study that used the dorsal/ventral stimulation methodology in humans observed impaired Go/NoGo task performance when DBS was delivered unilaterally to the ventral STN target Hershey et al. (2010). Our study extends this by showing that a separate measure of executive function is also sensitive to stimulation of the ventral STN, albeit with a different behavioral outcome. While that study reported impaired task performance resulting from stimulation only on the least affected side, possibly interfering with healthy function, we observed improved performance with bilateral stimulation, possibly remediating pathological activity responsible for abnormal task performance Off stimulation.

Importantly, there is no consensus on the existence of separate functional STN territories (Keuken et al., 2012). Our neurostimulation approach helps to address this question by providing functional information that cannot be attained using other neuroimaging methods (Mayberg & Lozano, 2002). We note that the precision of our approach may have been hindered by several factors. First, we lacked high-resolution anatomical imaging, which is superior to imaging at 1.5T (Brunenberg, Platel, Hofman, Ter Haar Romeny, & Visser-Vandewalle, 2011; Cho et al., 2010; Forstmann et al., 2012). Second, due to differences in anatomy, the trajectory of the electrode often varied across patients and sometimes between hemispheres. Third, the spread of DBS at the voltages used here is on the order of a couple millimeters, dropping in intensity as it extends outward from the stimulation contact (Maks, Butson, Walter, Vitek, & McIntyre, 2009). Although the focus of stimulation differed between our dorsal and ventral stimulation conditions, the distance between the dorsal and ventral contacts was an average of 3.2 ± 1.2 mm, meaning that the perimeters of the fields of stimulation overlapped between our dorsal and ventral stimulation conditions in many patients. Despite these limitations, we observed a behavioral dissociation between stimulation at dorsal and ventral contacts that we believe argues for a ventral ‘associative/executive’ fronto-basal ganglia circuit.

In summary, we show that stimulation of ventral but not dorsal STN contacts in Parkinson's patients remediated an abnormal pattern of response switching. The results affirm the importance of the basal ganglia for response switching, and specifically point to the idea that they might have a role in selectively suppressing the just-performed response when a switch occurs. The results also provide some of the first evidence that executive functions in humans may be sensitive to the modulation of specific subregions within the STN, supporting the existence of a putative ‘associative/executive’ frontal–basal ganglia circuit.

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Fig. 1.

Localization of deep brain stimulation electrode contacts in the subthalamic nucleus. (A) The subthalamic nucleus (outlined) was identified bilaterally in T2-weighted MRI scans. (B) The electrodes were visible as an artifact in a CT image (yellow) overlaid on the MRI. (C) A model of the electrode was scaled to the voxel size of the image. This allowed for the identification of those electrode contacts inside or overlapping with the dorsal and ventral borders of the subthalamic nucleus. (D) Neurophysiological diagrams were created from intraoperative single-unit recordings made during the implantation of the deep brain stimulation electrodes. The locations of the dorsal and ventral borders of the STN were determined based upon cell firing rates. A model of the electrode was then overlaid on a corresponding plate from the Schaltenbrand and Wahren Atlas for Stereotaxy of the Human Brain (in this example -12 mm lateral). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Fig. 2.

The response switching task (modified from Isoda & Hikosaka, 2008). Participants responded to the target box that matched the color of the central fixation box. White dashed circles indicate the correct response and did not appear to the subject. The target color stayed the same for a series of 4–8 trials and then switched to the other color for the next series of 4–8 trials. There were four categories of trials based upon the target color and response history: switch-repeat, nonswitch-repeat, switch-alternate, and nonswitch-alternate. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Fig. 3. Switching task results. (A) Reaction time (mean $\pm$ SEM), (B) switch cost (mean $\pm$ SEM) and (C) proportion of errors (% , mean $\pm$ SEM).

Fig. 4.

The switch cost (switch RT–nonswitch RT) for repeat and alternate responses for individual subjects. The dashed diagonal line represents unity. All of the patients in the Ventral STN DBS state and all of the controls show a smaller switch cost for alternate than repeat responses, while this is not the case for the Dorsal or Off STN DBS conditions.

Table 1

Participant characteristics for Parkinson's disease and control groups (mean ± std).

	Age (years)	Gender (F/M)	Handedness (L/R)	MMSE	NAART	UPDRS		
						Off	Ventral	Dorsal
PD	63.3 ± 7.3	2/8	1/9	28.2 ± 1.9	37.4 ± 8.6	8.7 ± 3.2	8.3 ± 3.6	10.2 ± 4.3
NC	61.8 ± 9.7	2/8	1/9	29.3 ± 0.8	42.5 ± 10.1			

Table 2

Patient characteristics and DBS parameters.

Subject ID	Age (yrs)	Gender	Handedness	Ventral contact		Dorsal contact		Ventral voltage		Dorsal voltage	
				Left	Right	Left	Right	Left	Right	Left	Right
PD01	76	F	R	0	4	2	6	2.2	3.2	2.5	3.2
PD02	54	M	R	0	5	1	6	3.2	3.2	3.2	3.2
PD04	70	M	R	0	4	1	5	1.5	1.7	2.8	2.6
PD05	64	M	R	0	4	2	5	3.2	3.2	3.2	3.2
PD06	56	M	R	0	4	1	5	3	2.2	3.2	3.2
PD07	70	M	R	0	6	3	7	3.2	3.2	3.2	3.2
PD08	63	F	L	0	4	3	7	2.2	3.2	3.2	3.2
PD09	55	M	R	2	4	3	5	3.2	3.2	3.2	3.2
PD10	65	M	R	1	4	3	5	2.9	3.2	3.2	3.2
PD11	60	M	R	0	4	2	7	2	2	2.8	2.8