doi:10.1093/brain/awq256 Brain 2010: 133; 3625–3634 | 3625

BRAIN
A JOURNAL OF NEUROLOGY

Mapping Go–No-Go performance within the subthalamic nucleus region

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The basal ganglia are thought to be important in the selection of wanted and the suppression of unwanted motor patterns according to explicit rules (i.e. response inhibition). The subthalamic nucleus has been hypothesized to play a particularly critical role in this function. Deep brain stimulation of the subthalamic nucleus in individuals with Parkinson's disease has been used to test this hypothesis, but results have been variable. Based on current knowledge of the anatomical organization of the subthalamic nucleus, we propose that the location of the contacts used in deep brain stimulation could explain variability in the effects of deep brain stimulation of the subthalamic nucleus on response inhibition tasks. We hypothesized that stimulation affecting the dorsal subthalamic nucleus (connected to the motor cortex) would be more likely to affect motor symptoms of Parkinson's disease, and stimulation affecting the ventral subthalamic nucleus (connected to higher order cortical regions) would be more likely to affect performance on a response inhibition task. We recruited 10 individuals with Parkinson's disease and bilateral deep brain stimulation of the subthalamic nucleus with one contact in the dorsal and another in the ventral subthalamic region on one side of the brain. Patients were tested with a Go–No-Go task and a motor rating scale in three conditions: stimulation off, unilateral dorsal stimulation and unilateral ventral stimulation. Both dorsal and ventral stimulation improved motor symptoms, but only ventral subthalamic stimulation affected Go–No-Go performance, decreasing hits and increasing false alarms, but not altering reaction times. These results suggest that the ventral subthalamic nucleus is involved in the balance between appropriate selection and inhibition of prepotent responses in cognitive paradigms, but that a wide area of the subthalamic nucleus region is involved in the motor symptoms of Parkinson's disease. This finding has implications for resolving inconsistencies in previous research, highlights the role of the ventral subthalamic nucleus region in response inhibition and suggests an approach for the clinical optimization of deep brain stimulation of the subthalamic nucleus for both motor and cognitive functions.

Keywords: subthalamic nucleus; deep brain stimulation; response inhibition; Parkinson's disease

Abbreviations: DBS = deep brain stimulation; STN = subthalamic nucleus; UPDRS = Unified Parkinson's Disease Rating Scale III

Received May 21, 2010. Revised July 13, 2010. Accepted July 30, 2010. Advance Access publication September 20, 2010

Introduction

A primary function of the basal ganglia may be to balance the selection of wanted and the suppression of unwanted motor patterns (Mink, 1996, 2003) and thoughts (Aron *et al.*, 2004; Aron and Poldrack, 2006). The subthalamic nucleus (STN) plays a critical role in the cognitive aspects of this function, notably the ability to select and inhibit prepotent or ongoing responses when appropriate (Aron and Poldrack, 2006; Frank *et al.*, 2007). The role of the STN in response inhibition has been supported by studies using functional neuroimaging in normal individuals, lesion studies of rodents and deep brain stimulation (DBS) of the STN in patients with Parkinson's disease. STN DBS can provide effective treatment for the motor symptoms associated with Parkinson's disease (Limousin *et al.*, 1995) while simultaneously impairing cognitive function, including the ability to withhold strong prepotent responses on tasks with strong response conflict, such as the Stroop Task's interference condition (Jahanshahi *et al.*, 2000; Schroeder *et al.*, 2002; Witt *et al.*, 2004), the stop signal task (Ray *et al.*, 2009), Go–No-Go tasks (Hershey *et al.*, 2004; Ballanger *et al.*, 2009) and decision-making tasks (Frank *et al.*, 2007). On the other hand, one study found improved stop signal task performance and no change in Go–No-Go performance with STN DBS (van den Wildenberg *et al.*, 2006). Similar to the majority of human work, rats with STN lesions show impaired ability to inhibit responses under conditions of strong conflict (Baunez *et al.*, 1995, 2001; Baunez and Robbins, 1997).

The (albeit limited) variability in overall effect of STN DBS on response inhibition across studies may, in part, reflect methodological differences, such as which type of response inhibition task was used. In addition, some studies used low levels of enforced response conflict (van den Wildenberg *et al.*, 2006; Ballanger *et al.*, 2009) or tested patients on dopaminergic medications (Schroeder *et al.*, 2002; van den Wildenberg *et al.*, 2006). Dopamine precursors (e.g. levodopa) and dopamine agonists have their own variable effects on cognition (Cools, 2006), making it difficult to isolate the specific effects of STN DBS.

Despite these differences, the general consensus is that there is a negative effect of STN DBS on response inhibition tasks, including Go–No-Go. Some studies have noted significant individual variability in the effects of STN DBS on Go–No-Go and other response inhibition tasks, and have leveraged this variability to ask questions about the neurophysiologic correlates of behavioural change (Schroeder *et al.*, 2002; Campbell *et al.*, 2008). This individual variability could be driven by several factors, including disease severity, pre-surgery cognitive function and, most importantly to the unique contribution of this study, the stimulation parameters and contact locations used to deliver DBS. Previously published work has examined responses to DBS using contacts and stimulation settings that had clinically been determined on a patient by patient basis. Thus, there has been substantial and uncontrolled within-group and across-study variability in the known (e.g. voltage, pulse width, frequency) and unknown (e.g. location of contact in STN) parameters of stimulation. Our study controls both types of parameters to address specifically how locations of active contacts modulate response inhibition performance.

Currently, the typical STN DBS behavioural study tends to assume that the STN is a homogeneous structure that acts and is acted upon as a single unit and that the electrode placement and contact location is relatively homogeneous across individuals. However, anatomical data have led to proposals that the STN, like other basal ganglia nuclei, is functionally heterogeneous, containing multiple segregated circuits subserving motor, cognitive and mood function through distinct connectivity to cortical regions. For example, the dorsal and lateral portion of the STN has connections with sensorimotor areas of the basal ganglia and thalamus, premotor and motor cortical areas, whereas the ventral portion of the STN has connections to higher order cortical regions closely associated with response inhibition such as the anterior cingulate and inferior frontal cortex (Parent and Hazrati, 1995*b*; Hamani *et al.*, 2004; Temel *et al.*, 2005; Florio *et al.*, 2007). On the basis of this anatomical information, the location of contacts used to deliver current within the STN region could have a significant impact on the kind of cognitive and behavioural responses invoked by STN DBS in the clinical or research setting. In addition, current spread from contacts probably affects fibres of passage and structures near the STN, and these effects could also differ depending on the location of contacts. For example, the dorsal STN is near the zona incerta and thalamus, and the ventral STN is near the substantia nigra pars reticulata (Parent and Hazrati, 1995*a*, *b*). We speculate that current spread from ventrally located contacts disrupts connections between the STN and anterior cingulate, inferior frontal or other relevant prefrontal regions, thus altering response inhibition skills. We directly test the hypothesis that the ventral STN region is critical for response inhibition performance by manipulating the location of DBS across the dorsolateral/ventromedial dimension in a within-subjects, double-blind and counterbalanced design. Using validated atlas registration of brain images (Videen *et al.*, 2008), we selected contacts that fell within the dorsal versus ventral areas of the STN for each patient and directly compared behavioural effects between the two stimulation conditions. We predicted that stimulation in the ventral STN region would impair response inhibition more than stimulation in the dorsal STN region. Results provide justification for considering a revision of the functional map of the STN region and the neural systems thought to underlie response inhibition skills.

Materials and methods

Participants

Ten participants with Parkinson's disease and bilateral STN DBS were recruited from the Washington University in St Louis Movement Disorders Centre. All patients signed informed consents in accordance with the Declaration of Helsinki and approved by the Washington University Human Research Protection Office. The patients met diagnostic criteria for clinically definite Parkinson's disease based on established criteria (Calne *et al.*, 1992; Hughes *et al.*, 1992; Racette *et al.*, 1999), including clear benefit from levodopa, and had no evidence of dementia on neuropsychological testing or additional neurologic diagnosis. The surgical technique for implantation of the DBS electrodes using microelectrode recordings and the programming paradigm was described elsewhere (Tabbal *et al.*, 2007). Soletra Model (Medtronic

Inc.) pulse generators were used in all patients. DBS therapy was optimized before recruitment into the study. In addition, selected participants had no other neurologic diagnosis or history (e.g. stroke, head injury).

We determined which side of the body had greater motor deficits by calculating motor scores with the Unified Parkinson's Disease Rating Scale III (UPDRS) (Lang and Fahn, 1989) at least 6 months post-surgery for DBS, while participants were off medication and off DBS. The contralateral side of the brain was then chosen for testing the selected unilateral DBS conditions in order to avoid issues related to asymmetrical electrode placements. This procedure allowed us to focus our data collection on unilateral conditions that are known to provoke the greatest motor and cognitive responses (Hershey *et al.*, 2008).

Neuroimaging

Pre-operative MRIs were acquired with a Siemens Vision 1.5 T scanner for clinical purposes and included two T_2-weighted turbo spin-echo sequences: one acquired in transverse planes covering the entire brain (time to repetition = 8904 ms, echo time = 90 ms, flip angle = 180, 53 planes, $1 \times 1 \times 2$ mm voxels) and one acquired in coronal planes spanning at least the STN, red nucleus and posterior commissure (time to repetition = 3700 ms, echo time = 96 ms, flip angle = 180, 19 slices, $1 \times 1 \times 2$ mm voxels). Head movement was prohibited during MRI by a Leksell stereotactic frame attached to the skull. Post-operative computed tomography images were acquired after removal of the frame with one of three Siemens Somatom scanners, definition 64 ($n = 6$), sensation 64 ($n = 2$) or plus 4 ($n = 2$), with 120 kV, 206–320 mA, and $0.5 \times 0.5 \times 1$ mm voxels (one subject had $0.5 \times 0.5 \times 2$ mm). Computed tomography images were examined for movement, recognizable by discontinuities along the skull in coronal and sagittal views. All scans analysed here had no noticeable movement.

Neuroimaging analyses

Image processing and atlas registration procedures were performed as described previously (Videen *et al.*, 2008). The rationale for this approach is based in part on the fact that intensity of the STN in T_2-weighted MRIs is known to vary throughout its extent, making definition of its borders impossible to discern even with higher resolution MRIs. We therefore rely on fiducials whose centres are easily and precisely identified in three dimensions. The atlas transformation based on these fiducials has been demonstrated to identify the centre of another easily defined structure (the red nucleus) within the same general area as the STN to within 1 mm in all three dimensions (Videen *et al.*, 2008). We excluded participants from our studies who had enlarged third ventricles or gross deformations along the midline, such that the localization of the atlas positions of the red nuclei differed by >2 mm (vector distance). The data analyses rely on paired measurements from two contacts whose centres are typically 4 mm apart. Given a precision of 1–2 mm in localization with respect to the STN, we are confident that the paired comparisons include relatively dorsal and ventral locations even though the exact locations vary from subject to subject.

The atlas registration process included the following steps: after aligning the participant's MRI and computed tomography scans to each other using manual and automated tools, we identified a validated set of fiducials and used them to map images into Mai atlas space (Mai *et al.*, 2004). We chose the Mai atlas because it has coronal histological sections at regular 1.34 mm intervals that permit more precise three-dimensional localization of structures whose boundaries are indistinct in magnetic resonance images and is ideal for the midbrain area (see Videen *et al.*, 2008 for details). Next, the coordinates of each electrode tip were located on the original computed tomography image. Contacts were spaced along the electrode at 2.0 mm intervals with each exposed contact extending 1.5 mm (1.27 mm in diameter), separated from the next by a 0.5 mm gap (quadripolar electrode model 3389, Medtronic Activa System, Medtronic Inc.). The penetration of the electrode tip into the last plane in which it was visible was estimated by the ratio of its intensity in that plane to more dorsal planes in which the electrode fills the plane. The location of each contact was calculated by its distance (0, 2, 4 or 6 mm) along the line defined by the x, y, z coordinates of the centre of the tip and the x, y, z coordinates of the centre of the track three planes above it. Each effective lead coordinate was converted to atlas coordinates using the combined transformation matrix (computed tomography to atlas). The atlas location of each contact was visualized by plotting the contact coordinates on the appropriate Mai atlas images and superimposing this fused image onto the coronal MRI (resliced to match the Mai atlas). Based on other work and the electrode configuration and stimulator settings used in our study, it is probable that the current activates neurons and axons within a 2 mm radius from the centre of the contact (Butson and McIntyre, 2005, 2006). Thus, the best representation of the probable suprathreshold effect of monopolar stimulation at a given contact location is within a 2 mm radius sphere centred on the contact itself. While nearby structures and white matter tracts are thought to affect current spread (McIntyre *et al.*, 2004; Miocinovic *et al.*, 2006; Butson *et al.*, 2007), these complex effects cannot be measured here.

Contact selection

The current models of STN anatomical organization largely agree that the dorsolateral portion of the STN links to motor circuits, whereas the ventral aspect of the STN links to cognitive circuits (Parent and Hazrati, 1995*b*). We selected two contacts: one within 2 mm of the dorsolateral STN and the other within 2 mm of the ventral STN. Both contacts were located on the side of brain contralateral to the worst side of motor symptoms for each participant. When possible, we selected two contacts that were separated by at least one unused contact (e.g. contacts 1 and 3), to minimize any overlap in stimulated areas between the two conditions.

Stimulation parameters

The same DBS parameters were used for all ventral and dorsal STN contacts (monopolar configuration with 185 Hz frequency, 2.5 V amplitude and 60 μs pulse width). These settings were selected to produce a clear motor response while minimizing overlap of stimulation effects and untoward effects from excessive DBS such as dyskinesias, dystonia, dysaesthesias or eye movement abnormalities. Stimulation conditions were unilateral, e.g. if the worst side of the brain was determined to be the left, stimulation conditions were left dorsal and left ventral.

Behavioural protocol

Participants did not take Parkinson's disease medications overnight prior to the study and were in the 'practical-defined off state' (Moro *et al.*, 1999) at the time of testing. Motor and cognitive measurements were performed in three conditions: (i) both stimulators off (off); (ii) unilateral dorsal contact on (dorsal); and (iii) unilateral ventral

contact on (ventral). Condition order was counterbalanced across participants and both participants and experimenters collecting data were blind to condition. Participants were studied at least 42 min after changing stimulator conditions so that they were tested in near-steady-state motor status (Temperli *et al.*, 2003; Sturman *et al.*, 2008). Motor symptoms were measured using the motor subscale (part III) of the UPDRS by a blinded and validated rater. Lateralized UPDRS motor scores were summed for side of the body contralateral to stimulation (upper extremity: rest tremor, action or postural tremor, rigidity, finger taps, hand pronation/supination repetitive movements and hand opening/closing repetitive movements; lower extremity: foot tapping, rest tremor and rigidity; total possible = 36 points).

Response inhibition was measured with the Go–No–Go task. This task assessed the ability to select and inhibit a prepotent motor response appropriately under conditions of high prepotent response strength (Braver *et al.*, 2001). Participants monitored a visual display while single uppercase letters were presented one at a time, interspersed with the number '5' (250 ms duration, 1000 ms intertrial interval). Subjects were instructed to push a target response button at the occurrence of every letter (Go trial; response selection) but to withhold a response for a '5' (No-Go trial; response inhibition) and to be as accurate and rapid in their responses as possible. Following 15 practice trials, they performed 150 experimental trials. Target frequency was designed to place a high demand on response inhibition (83% letters, 17% '5's; 150 trials total). The proportion of correct Go trials, the proportion of correct No-Go trials, median reaction times for correct Go trials and median reaction times for false alarms (incorrect No-Go trials) were calculated. In addition, response indices were computed that took into account accuracy for both Go and No-Go trials and measured the ability to balance both the need to engage a motor response and the need to inhibit it appropriately.

These measures are derived from signal detection theory, a common approach for the analysis of similar selection tasks that assumes that decision making takes place in a state of uncertainty and that uncertainty is measured through an analysis of correct (hit rate) and incorrect (false alarm rate) responses in a choice situation. In the Go–No-Go task, hit rate is the proportion of Go trials (letter trials) in which a correct press was recorded. False alarm rate is the proportion of No-Go trials ('5' trials) in which a subject incorrectly responded. The relationship between hits and false alarms allows calculation of a discriminability index, defined as the proportion of hits minus the proportion of false alarms, which is useful for estimating the individual's decision-making function (Macmillan and Creelman, 2005). The discriminability index used here, Pr, is an index of how well a person can discriminate between the two classes of trials, Go versus No-Go. For example, if individuals pressed the button for every trial, they would have a perfect hit rate and maximum false alarm rate, leading to a discriminability of 0. If they failed to press the button for every trial, they would have a hit rate of 0, but a perfect false alarm rate, again leading to a discriminability of 0. Bias is the probability of making one choice over the other in an uncertain state. The measure of bias used here, Br [(false alarm rate/1−Pr)−0.5], has a range from 0 to 1, with 0.5 indicating no bias, <0.5 indicating a liberal bias (tendency to choose Go over No-Go in an uncertain state) and >0.5 indicating a conservative bias (tendency to choose No-Go). Bias can be independent of discriminability (Snodgrass and Corwin, 1988).

Analyses

To compare behaviour across conditions, repeated measures general linear model analyses were performed with condition as the repeated variable (off, dorsal DBS, ventral DBS). Univariate analyses and *t*-tests were performed to follow up on significant omnibus main effects or interactions. The threshold for statistical significance for both omnibus and *a priori* determined follow-up tests was $P < 0.05$. For exploratory follow-up comparisons, a Bonferroni correction was applied. UPDRS scores, given their rank order nature, were analysed with non-parametric statistics only. When deriving change scores, only differences (e.g. dorsal–off) were used, not per cent change, due to the presence of '0's in some conditions.

Results

Participants

Participants were predominantly male, all right-handed, not demented and had moderately severe Parkinson's disease motor symptoms when off medications and off stimulation (Table 1). Five participants were stimulated on the left side of the brain and five were stimulated on the right side of the brain. One subject was stimulated at 2.0 V due to unpleasant DBS-induced side effects at 2.5 V. Seven participants used their right hand and three used their left hand to respond; the same hand was used for all three testing conditions for each individual.

For illustration purposes (Fig. 1), all contacts used in the study are shown on the right STN (i.e. images for the left STN flipped on the *x*-axis) and a 2 mm radius sphere was placed on the centre of each selected contact as a visual estimate of current spread. Using Mai atlas coordinates (centre coordinate on the anterior commissure), the *x* (absolute value) coordinate was not significantly different between the tested dorsal and ventral contacts (paired *t*-test, $t = -0.33$, $P = 0.75$). Since the entry point of the DBS electrode into the skull was purposefully chosen anterior to the coronal suture aiming posterior to the dorsolateral STN, the *y* coordinate was significantly more posterior (paired *t*-test, $t = 10.3$,

Table 1 Means and SDs for demographic and clinical characteristics of 10 patients with Parkinson's disease tested

	Mean (SD)
Age (years)	56.5 (5.6)
Age at onset (years)	42.4 (4.6)
Education (years)	16.4 (2.6)
MMSE (total score)	29.2 (0.8)
Months since DBS surgery	32.2 (15.9)
Off medication and DBS UPDRS motor subscale score (total)	36.9 (15.9)
Sex	9 males 1 female
Dorsal *x* (absolute value)	12.7 (1.0)
Dorsal *y*	−17.5 (1.7)
Dorsal *z*	−1.8 (1.0)
Ventral *x* (absolute value)	11.7 (1.0)
Ventral *y*	−19.5 (1.3)
Ventral *z*	−5.4 (0.4)

Average *x*, *y* and *z* position of the selected contacts are shown in Mai atlas coordinates. MMSE = Mini-Mental State Examination.

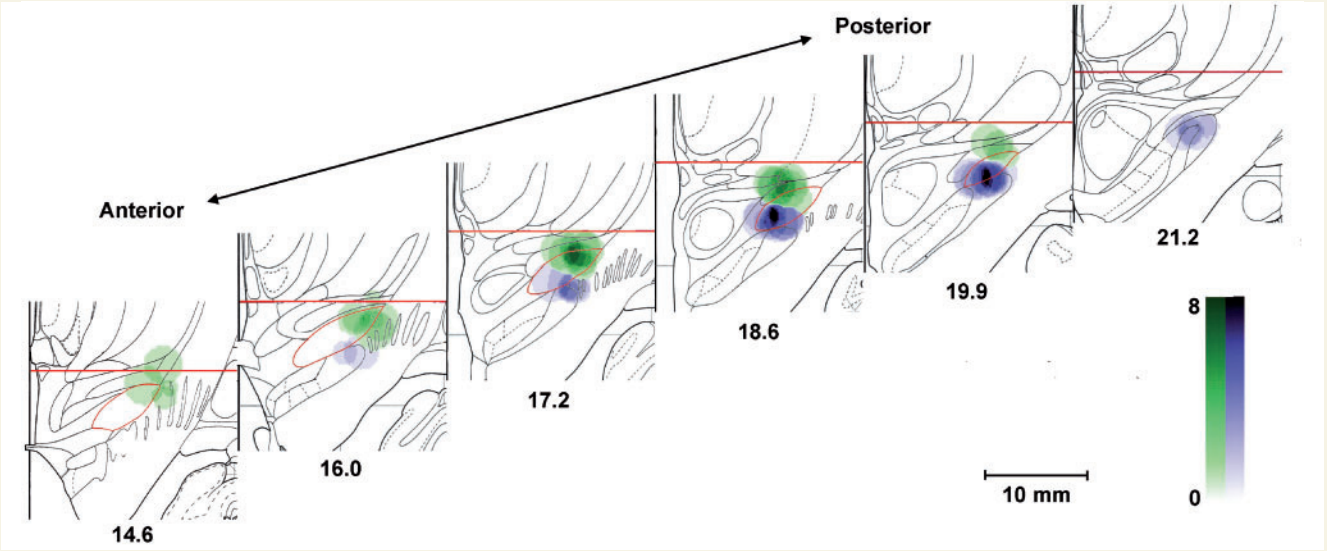

Figure 1 Location of selected dorsal (green) and ventral (purple) contacts for the sample. Contacts on the left side of the brain have been flipped along the *x*-axis for display purposes. The STN is outlined in red. A 2 mm radius sphere was placed on each contact used. Scale bar indicates number of points (participants) within 2 mm of the voxel.

Table 2 Means ± SEM for Go–No-Go and UPDRS variables for each DBS condition

	Off DBS	Unilateral dorsal DBS	Unilateral ventral DBS
Go–No-Go Pr	0.81 (0.05)	0.80 (0.05)	0.73 (0.04)[a,b]
Go–No-Go Go trials, hit rate	0.98 (0.01)	0.98 (0.02)	0.96 (0.02)[a]
Go–No-Go No-Go trials, false alarm rate	0.84 (0.05)	0.82 (0.05)	0.78 (0.05)[b]
Go–No-Go bias	0.22 (0.13)	0.39 (0.08)	0.32 (0.07)
Reaction time (ms) for correct Go trials	460 (21)	451 (24)	441 (20)
Reaction time (ms) for incorrect No-Go trials	356 (23)	341 (19)	357 (30)
Lateralized UPDRS motor subscale score, contralateral to DBS	14.3 (1.6)	11.1 (1.6)[a]	10.6 (1.9)[a]
Ipsilateral to DBS	11.2 (1.9)	10.8 (1.7)	10.3 (1.9)

a Different from off, $P<0.05$.
b Different from dorsal, $P<0.05$.

$P<0.001$) and the *z* coordinate was significantly more inferior (paired *t*-test, $t=12.5$, $P<0.001$) for the ventral versus dorsal contact, as can be seen in Fig. 1. For the dorsal contacts, the spheres representing estimated current spread were most commonly found overlapping with the dorsolateral STN and zona incerta (third most anterior slice on Fig. 1); for the ventral contacts, the spheres representing estimated current spread were most commonly found overlapping with the ventral medial STN and the dorsal substantia nigra (third and second most posterior slices on Fig. 1). Out of 10 patients, the ventral and dorsal contacts were separated by one unused contact in eight patients and by two unused contacts in one patient. Only one patient had adjacent ventral and dorsal contacts. In this person, the presumed current spreads of the two contacts did overlap.

UPDRS

Motor scores contralateral to the side of brain stimulated differed across DBS conditions (Friedman's ANOVA by ranks, $P=0.01$). To determine which conditions were driving the main effect of condition on UPDRS scores, *post hoc* Wilcoxon signed rank test comparisons were performed and revealed significantly higher motor scores in the off DBS condition than in dorsal or ventral DBS conditions (dorsal: $P=0.01$; Cohen's $d=0.63$; ventral: $P=0.02$, Cohen's $d=0.67$), but no difference between dorsal and ventral DBS conditions (Table 2, Fig. 2A; $P=0.36$, Cohen's $d=0.10$). A similar pattern was found for individual symptom ratings such as tremor (Friedman's, $P=0.005$) and rigidity (Friedman's, $P=0.048$), but not bradykinesia (Friedman's, $P=0.36$).

Go–No-Go

Discriminability (Pr) differed across conditions [repeated measures model, effect of condition: $F(2,8)=13.3$, $P=0.003$]. The side of brain stimulated (left versus right) did not have an effect on Pr overall [$F(1,8)=1.3$, $P=0.29$] and did not interact with DBS condition [$F(2,7)=1.4$, $P=0.31$]. To determine whether our specific

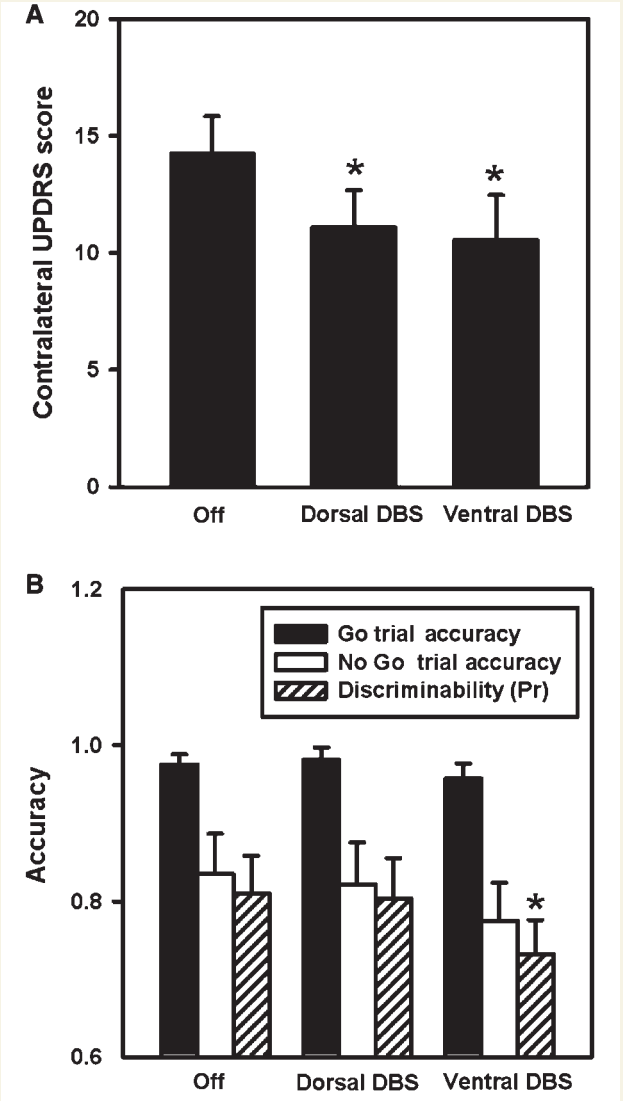

Figure 2 (**A**) Effects of dorsal and ventral DBS on mean ± SEM contralateral UPDRS motor scores across DBS conditions. Asterisk indicates that UPDRS scores were greater in the off DBS than in the dorsal DBS and ventral DBS conditions. (**B**) Effects of dorsal and ventral DBS on response inhibition discriminability, Go and No-Go trials and discriminability. Asterisk indicates that ventral DBS was associated with decreased discriminability compared with the off DBS and dorsal DBS conditions.

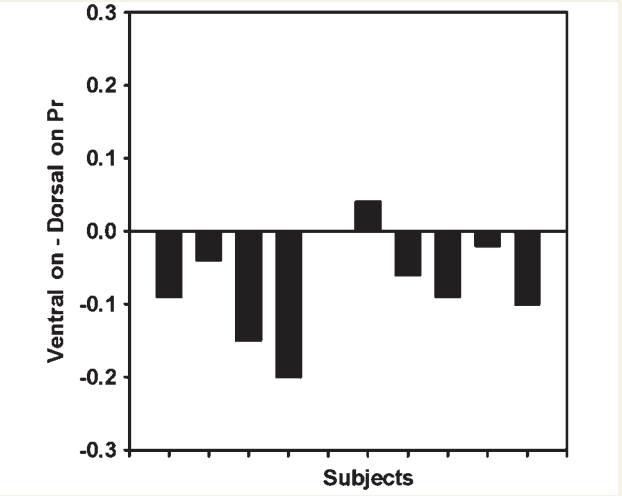

Figure 3 Individual subject's discriminability scores for the differential effect of stimulation for ventral and dorsal DBS conditions. Negative numbers indicate worse performance in ventral than in dorsal conditions.

hypothesis that ventral DBS effects were driving the main effect of condition on Pr, *post hoc* comparisons were performed and revealed that Pr was lower in the ventral DBS than in off DBS (paired *t*-test, $t = 2.4$, $P = 0.04$, Cohen's $d = 0.55$) and dorsal DBS conditions (paired *t*-test, $t = 3.2$, $P = 0.012$, Cohen's $d = 0.47$), but did not differ between off DBS and dorsal DBS conditions (paired *t*-test, $t = 0.89$, Cohen's $d = 0.06$) (Fig. 2B and Table 2). The pattern of lower Pr in ventral versus dorsal DBS conditions was apparent in 8 out of 10 individuals with only 1 subject showing the opposite pattern and 1 showing no difference (Fig. 3). Interestingly, this latter subject was the one with adjacent ventral and dorsal contacts and some overlap in the presumed current spreads of the two contacts. Response bias did not differ across condition [Table 2; $F(2,8) = 0.77$, $P = 0.49$].

To determine if the effect on Pr was driven more by errors on Go or No-Go trials, we performed similar repeated measures analyses with condition and trial type (Go versus No-Go) as repeated measures. This analysis revealed a significant main effect of trial type [$F(1,9) = 8.7$, $P = 0.016$; greater accuracy on Go versus No-Go trials overall] and of condition [$F(2,8) = 13.3$, $P = 0.003$; lower accuracy on the ventral DBS condition overall], but no interaction between trial type and condition ($P = 0.20$; Fig. 2B). To fully explore whether the effect of DBS condition was driven by decreases in accuracy in both Go and No-Go trials, we examined each trial type separately (Table 2). Within Go trials, the overall effect of DBS condition was not significant [Go trials; $F(2,8) = 3.1$, $P = 0.10$], but the ventral DBS condition did have significantly reduced accuracy compared with DBS off (paired *t*-test, $t = 2.6$, $P = 0.029$, Cohen's $d = 0.35$) and was marginally different from dorsal DBS (paired *t*-test, $t = 2.1$, $P = 0.06$, Cohen's $d = 0.43$). Within No-Go trials, there was a significant effect of condition [$F(2,8) = 11.1$, $P = 0.005$], and ventral DBS produced significantly lower accuracy than dorsal DBS (paired *t*-test, $t = 2.5$, $P = 0.03$, Cohen's $d = 0.29$), but not DBS off (paired *t*-test, $t = 1.7$, $P = 0.12$, Cohen's $d = 0.38$). Given Bonferroni correction for six comparisons ($0.05/6 = 0.008$), none of these more detailed paired comparisons was significant.

Subjects' median reaction times for correct Go trials, a typical measure of reaction time, did not differ across conditions [$F(2,8) = 1.1$, $P = 0.38$]. To explore whether false alarm reaction times were different from correct hits, we also analysed reaction times for incorrect No-Go trials. One subject had no false alarms in one condition and so was excluded from these analyses. Overall, reaction times for incorrect No-Go trials were faster than for correct Go trials [trial type, $F(1,8) = 44.9$, $P < 0.001$], but reaction times for incorrect No-Go trials and the difference between reaction times for correct Go and incorrect No-Go trials did

not differ across DBS conditions [effect of condition, $F(2,7) = 0.34$, $P = 0.72$; condition by trial type interaction, $F(2,7) = 0.82$, $P = 0.48$] (Table 2).

Within the ventral DBS condition, per cent change in Pr did not correlate with per cent change in reaction time ($r = 0.19$, $P = 0.61$), difference in UPDRS motor score ($r_s = -0.50$, $P = 0.14$) or x, y or z coordinates of the ventral contact used (x: $r = -0.13$, $P = 0.72$; y: $r = 0.17$, $P = 0.64$; z: $r = -0.05$, $P = 0.88$). Within the dorsal DBS condition, per cent change in Pr did not correlate with per cent change in reaction time ($r = 0.46$, $P = 0.18$), difference in UPDRS motor score ($r_s = -0.19$, $P = 0.60$), or x, y or z coordinates of the ventral contact used (x: $r = -0.13$, $P = 0.73$; y: $r = 0.22$, $P = 0.55$; z: $r = -0.02$, $P = 0.99$).

In this sample, six participants used the hand ipsilateral and four used the hand contralateral to the side of brain being stimulated. However, change in Go–No-Go performance was not significantly different between these two groups for any condition (Mann–Whitney U-tests; dorsal DBS, discriminability, $P = 0.20$; ventral DBS, discriminability, $P = 0.29$; dorsal DBS, reaction time, $P = 0.29$; ventral DBS, reaction time, $P = 0.09$). Admittedly, our power to detect such differences is limited. However, the primary analysis in this article is a dorsal versus ventral DBS within-subjects comparison in which 8 out of 10 participants demonstrated the pattern of ventral worse than dorsal DBS for Go–No-Go discriminability. Interestingly, the two participants that did not show this pattern used the hand contralateral to the side of the brain stimulated. Furthermore, the lateralized UPDRS scores for the side of the body ipsilateral versus contralateral to the side of brain stimulated were not different within either the dorsal or ventral DBS conditions (Wilcoxon signed rank test; dorsal, $P = 0.77$; ventral, $P = 0.88$).

Discussion

This study directly manipulates stimulation across the dorsolateral/ventromedial dimension of the STN region in a controlled, double-blind and within-subjects design. Results indicate that stimulation of the ventral, but not dorsal, STN region impairs cue-driven behaviour of a prepotent motor response, while stimulation of both STN regions improves Parkinson's disease motor sign ratings. The dissociation between location of stimulation and responses across two functional domains (motor and cognitive) may reflect a difference in the dispersion of motor versus cognitive circuits through the STN region. Whereas motor function may be widely dispersed across the dorsolateral/ventromedial dimension of the STN, cognitive functions underlying performance on tasks such as Go–No-Go may be more restricted to the ventral STN region. These findings are consistent with clinical reports suggesting that STN DBS has robust effects on the motor signs of Parkinson's disease but that cognitive responses to STN DBS are more variable.

As we and others have found, DBS STN affects task conditions with higher cognitive control demands, including but not limited to Go–No-Go. These tasks include noun/verb generation (Castner *et al.*, 2007), declarative recall (Halbig *et al.*, 2004) and verbal associative fluency (Rothlind *et al.*, 2007). In contrast, STN DBS can improve performance on extinction (Funkiewiez *et al.*, 2004) and non-declarative memory tasks (Halbig *et al.*, 2004). This pattern suggests that tasks with greater cognitive control demands are most susceptible to the negative effects of STN DBS. In this context, our data do not necessarily support task specificity of the effects of DBS STN; rather these data strongly suggest location specificity of the effects of STN DBS on Go–No-Go performance, which could be a sign of a more fundamental change in higher order attentional control. Finally, this study may have clinical implications for the consideration of contact location within the STN region for optimal non-motor outcome.

This study has a number of important and unique strengths. We performed within-subject comparisons using fixed stimulation variables, altering only location of the contact used to deliver current. In contrast, previous STN DBS studies have tended to use clinically determined stimulation settings, which can vary substantially in the current applied, location of active contact within the STN and even the contact configuration used (e.g. monopolar versus bipolar). The experimental design in our study reduces between-subject variability in clinical characteristics or stimulation parameters. In addition, participants were tested in the 'practically defined off' medication state, reducing variability across individuals and potential interactions between medication and stimulation effects on response inhibition. Given the reported direct effects of dopaminergic medication on response inhibition (Cools *et al.*, 2003; Frank *et al.*, 2007), reducing this potential confound when testing the effects of DBS is important. Although changes in overall motor function and speed/accuracy trade-offs across stimulation conditions could explain changes in cognitive task performance, our results are not consistent with such explanations. Indeed, in our study, motor and cognitive responses were dissociated across stimulation conditions: both stimulation conditions improved motor performance, neither condition changed Go–No-Go reaction time and only ventral stimulation impaired Go–No-Go accuracy. Finally, we used a validated and reliable method for identifying the location of contacts within the STN region. We did not rely on surgical targeting data, which may not precisely correlate with the final position of the contacts, or on visual inspection of post-surgical MRIs that might contain artefacts induced by the DBS lead and that poorly define the boundaries of the STN (Dormont *et al.*, 2004). Instead, we used a validated atlas registration method tailored to derive an objective and quantifiable fit in the STN region.

Limitations of this study include the relatively small sample size and unilateral stimulation conditions, which make strong tests of any hemispheric asymmetry of response inhibition mediation difficult. Although the role of the right STN and right inferior frontal gyrus in response inhibition has been emphasized (Aron *et al.*, 2004), the literature does not consistently support this idea (Ray *et al.*, 2009). Further, previous work on a large sample comparing left and right unilateral STN DBS on Go–No-Go performance found that stimulation on the more affected side of brain had the greatest impact on performance, not hemisphere of the brain (Hershey *et al.*, 2008). On a related note, we had to vary which hand was used to respond in the Go–No-Go task across participants. However, after thoroughly exploring this potential

confound, we conclude that it is highly unlikely that any differences in hand used explain our primary results.

In terms of clinical relevance, our study does not imply that the motor benefit from dorsal and ventral STN DBS is equal or that there is no 'sweet spot' with respect to optimal DBS-induced motor benefit. We purposefully used a low DBS voltage (2.5 V) in our study, based on clinical observation that a higher DBS voltage applied close to the internal capsule or substantia nigra is likely to cause adverse effects. However, a higher voltage could reveal that dorsal DBS provides a more substantial motor benefit than ventral DBS or that our motor effects are underestimates of what is present in the clinical setting. Finally, we recognize that DBS current spread probably affects fibres of passage and structures near the dorsal STN, such as the zona incerta and structures near the ventral STN, such as the substantia nigra pars reticulata. We cannot exclude the contributions of these regions or pathways to the behavioural effects seen with STN DBS in clinical settings, other STN DBS studies or in our study. Nevertheless, we clearly distinguished effects from stimulation in the region of dorsal STN from stimulation of the region of ventral STN; estimated current spread between these two regions was clearly spatially different and is probably more constrained in our study than with typical clinical settings.

Our findings have a number of important implications for models of neural systems underlying response selection and inhibition. Aron *et al.* (Aron *et al.*, 2004; Aron and Poldrack, 2006) have posited that the STN is involved only when there is an ongoing response that has to be stopped mid-stream (as in the stop signal task) but not when inhibition of a prepotent (but not yet initiated) response is needed (as in Go–No-Go). They base this distinction in part on a study that did not find an effect of STN DBS on a Go–No-Go task (van den Wildenberg *et al.*, 2006). However, that study was conducted while patients were on dopaminergic medications and used clinically chosen DBS contacts and stimulation settings. More recent papers and the current study suggest that this distinction between tasks should be softened and support a more general role of the STN in response discriminability in high conflict situations (Aron *et al.*, 2007). For example, a recent study showed that STN DBS induced faster and less accurate responses in high conflict win-win decision trials on a probabilistic selection task (Frank *et al.*, 2007). The authors hypothesize that the STN sends a 'No-Go' signal to the internal segment of the globus pallidus, which ultimately raises decision thresholds in the face of conflict. Stimulation may disrupt this signal, leading to inappropriately unchanged or even lowered thresholds in conflict situations. Our results here indicate that the ventral STN but not the dorsal STN region plays a role in this process and may be involved in both aspects of cue-driven behaviour, engaging and inhibiting the correct motor response in conflict situations.

These findings have broader implications for the proposed functional map of the STN. Previous proposals have emphasized the distinct regions of the STN based on anatomical work: motor circuits in the dorsal and lateral STN, cognitive circuits in the ventral and medial STN. However, our data suggest that motor function can be positively influenced by stimulation along the dorsolateral/ventromedial axis of the STN. This finding is consistent with evidence that in optimally treated patients there is significant variability of the location of the clinically chosen contact (Saint-Cyr *et al.*, 2002; Starr *et al.*, 2002; Mallet *et al.*, 2007; McClelland, III *et al.*, 2007, 2009). In summary, our study highlights the need to be cautious in treating DBS as an anatomically and functionally uniform challenge to the STN. Our findings are also consistent with the idea that different functional pathways involving the STN (e.g. motor and cognitive) may not be tightly segregated, but rather interspersed to some degree at the level of the STN (Mallet *et al.*, 2007) or downstream (Haber *et al.*, 2000; McFarland and Haber, 2000).

In addition, previous maps of the STN have been two-dimensional, focusing on the dorsal–ventral dimension through the anterior–posterior centre of the STN, where it is largest. However, the shape of the STN tapers dramatically anterior and posterior to this central portion, and it is unclear how functions are mapped throughout this dimension. It is important to note that in our data, due to the trajectory of the implanted electrode, the position of the dorsal and ventral contacts differs as expected in the dorsal–ventral dimension (z), but also the anterior–posterior dimension (y). To build a three-dimensional map of the STN, greater sampling of contact locations across all dimensions of the STN with concurrent measurements of all behavioural domains (motor, cognitive and mood) would be necessary.

Finally, understanding the stimulation variables, such as contact location, that influence cognitive function in patients with STN DBS may help to devise better programming strategies. We could then minimize the risk for cognitive impairment while maximizing the benefit for motor function depending on the stimulation settings chosen. In the future, it may be possible to assay the cognitive skills that are most sensitive to STN DBS during programming, guiding the programmer to choose the contact that provides the least adverse cognitive effects while still providing acceptable motor benefit.

Funding

The Greater St Louis Chapter of the American Parkinson's Disease Association (APDA); National Institutes of Health (grant numbers NS41509 and NS58797); NCRR (grant number UL1 RR024992); Neuroscience Blueprint Grant at Washington University (grant number P30 NS057105); APDA Advanced Centre for Parkinson's Disease Research at Washington University; McDonnell Centre for Higher Brain Function; the National Alliance for Research on Schizophrenia and Depression and the Barnes-Jewish Hospital Foundation (Elliot Stein Family Fund, the Handelman Fund and Jack Buck Fund for Parkinson's Disease Research).

Conflict of interest: Dr Karimi previously received partial fellowship funding from Medtronic Inc., the manufacturer of the implanted stimulators; no other authors have any conflicts of interest to disclose.

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