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Subthalamic nucleus stimulation influences expression and suppression of impulsive behaviour in Parkinson's disease

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Past studies show beneficial as well as detrimental effects of subthalamic nucleus deep-brain stimulation on impulsive behaviour. We address this paradox by investigating individuals with Parkinson's disease treated with subthalamic nucleus stimulation ($n = 17$) and healthy controls without Parkinson's disease ($n = 17$) on performance in a Simon task. In this reaction time task, conflict between premature response impulses and goal-directed action selection is manipulated. We applied distributional analytic methods to separate the strength of the initial response impulse from the proficiency of inhibitory control engaged subsequently to suppress the impulse. Patients with Parkinson's disease were tested when stimulation was either turned on or off. Mean conflict interference effects did not differ between controls and patients, or within patients when stimulation was on versus off. In contrast, distributional analyses revealed two dissociable effects of subthalamic nucleus stimulation. Fast response errors indicated that stimulation increased impulsive, premature responding in high conflict situations. Later in the reaction process, however, stimulation improved the proficiency with which inhibitory control was engaged to suppress these impulses selectively, thereby facilitating selection of the correct action. This temporal dissociation supports a conceptual framework for resolving past paradoxical findings and further highlights that dynamic aspects of impulse and inhibitory control underlying goal-directed behaviour rely in part on neural circuitry inclusive of the subthalamic nucleus.

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

Abbreviations: DBS = deep-brain stimulation; IFC = inferior frontal cortex; STN = subthalamic nucleus

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Introduction

Subthalamic nucleus (STN) deep-brain stimulation (DBS) has emerged as an important treatment option for individuals with Parkinson's disease, when medications are less effective at controlling their motor symptoms. In this treatment, electrodes are placed surgically in the STN of the basal ganglia and connected to a pulse generator that delivers high frequency current. With proper calibration, STN DBS ameliorates many of the debilitating motor deficits caused by the dopamine depletions in Parkinson's disease, including bradykinesia and rigidity (Limousin *et al*., 1995; Blandini *et al*., 2000). The STN is innervated by afferents from prefrontal cortical regions, suggesting that stimulating the STN may also modulate executive cognitive processes. Surgical procedures allow stimulation of the STN to be adjusted or completely turned off by a handheld control device, thus making it possible to study the role of the STN and the impact of STN DBS on cognitive performance (Parsons *et al*., 2006). In the current study, we used this strategy to investigate the effect of STN DBS on a fundamental aspect of executive cognitive control, the ability to suppress incorrect response impulses to facilitate the selection of goal-directed actions.

The STN is embedded in so-called indirect and hyperdirect frontal-basal ganglia pathways (Nambu *et al*., 2002). According to contemporary action selection models of the basal ganglia, activation of the STN via either pathway suppresses response outputs that interfere or compete with the selection of a desired response over the direct pathway of the basal ganglia (Mink, 1996; Kropotov and Etlinger, 1999; Redgrave *et al*., 1999). Recent empirical work in human and animal studies provides further support for a role by the STN in the neural circuitry that directs inhibitory action control (Aron and Poldrack, 2006; Frank, 2006; van den Wildenberg *et al*., 2006; Eagle and Baunez, 2010). Functional imaging studies of healthy adults performing the stop-signal task (Verbruggen and Logan, 2008) reveal an increase in STN activity when a subject must inhibit an action upon the occurrence of a salient stimulus (i.e. stop signal) in the environment (Aron and Poldrack, 2006). Key prefrontal structures, most notably the right inferior frontal cortex (IFC), the pre-supplementary motor area and the primary motor cortex, have been linked to patterns of activation during stop trials of the stop-signal task (Aron *et al*., 2003; Aron and Poldrack, 2006; van den Wildenberg *et al*., 2010). Each of these cortical areas sends monosynaptic, excitatory efferents to the STN, suggesting that this cortico-STN circuitry may play a prominent role in inhibitory action control (Nambu *et al*., 2002; Aron *et al*., 2007). The emerging role of the STN in inhibitory action control is also supported by studies of patients with Parkinson's disease and STN-lesioned rats performing the stop-signal task. Individuals with Parkinson's disease are slower than healthy controls at inhibiting their actions following presentation of a stop signal (Gauggel *et al*., 2004), a deficit that can be ameliorated by stimulation of the STN (van den Wildenberg *et al*., 2006). Rats with STN lesions also show an impaired ability to stop in an adapted version of the stop task (Eagle *et al*., 2008).

The need for inhibitory action control is instigated, however, not only by relevant external changes in an ever-changing environment (e.g. presentation of an external stop signal in the stop-signal paradigm), but also by irrelevant attributes or changes in the environment that activate conflicting response tendencies involuntarily. An experimental laboratory reaction time task, the Simon task (Simon, 1969), provides the context for an elegant demonstration of how irrelevant stimulus information can elicit a strong, pre-potent response impulse that interferes with goal-directed action (Fig. 1). The task requires speeded manual reactions to goal-relevant stimuli that are embedded in a goal-irrelevant stimulus dimension. For example, subjects may be asked to make left or right button presses mapped to red or green circles, respectively (i.e. colour is the relevant stimulus dimension) that are presented in the left or right visual half-field (i.e. spatial location is the irrelevant stimulus dimension). Information presented in the left visual field is consistently found to be responded to more quickly and accurately with the left than with the right

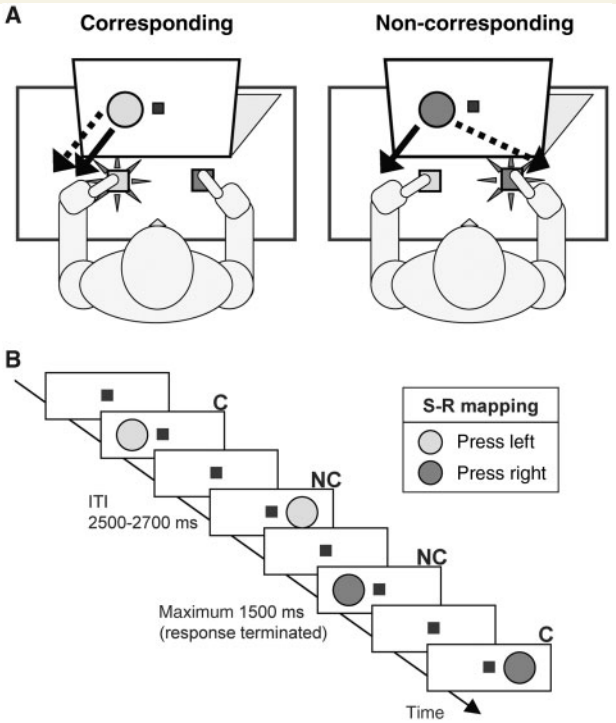

Figure 1 (**A**) Participants were instructed to press the left button in response to a blue circle and a right button in response to a green circle (dashed line). Responses are also driven by an irrelevant stimulus dimension, i.e. circle location, as indicated by the solid line. For corresponding trials, both relevant (i.e. colour) and irrelevant (i.e. location) stimulus dimensions activate the correct action. In non-corresponding trials, the irrelevant dimension activates an incorrect response, which interferes with selection of the correct response. (**B**) Depiction of the temporal and response elements of the task, as well as all possible stimulus configurations [corresponding (C) and non-corresponding (NC)] that were presented randomly and with equiprobability throughout each block of trials. ITI = inter-trial interval; S–R = stimulus–response.

hand, and vice versa. The irrelevant dimension, spatial location, is thought to engage an early, involuntary human impulse to activate a response by the hand on the side corresponding to the spatial location of the stimulus, the effect of which is to alter the timing and accuracy of the goal-directed response (Kornblum *et al*., 1990; Ridderinkhof *et al*., 2004). Specifically, when the irrelevant and relevant stimulus dimensions signal the same response, reaction time and response accuracy are facilitated (e.g. the colour of a stimulus presented in the left visual field calls for a left-hand response). However, when the responses signalled by the relevant and irrelevant stimulus dimensions conflict, reaction time is prolonged and error rates are increased (e.g. the colour of a stimulus presented in the left visual field calls for a right-hand response). This reduction in performance due to response conflict, coined the Simon effect, is presumed to represent the additional time needed to inhibit early response capture by the irrelevant stimulus dimension before the correct response can be activated and emitted. Thus, the Simon task is a powerful experimental framework for studying both the activation and suppression of impulsive responses that interfere with goal-directed action. More precisely, the magnitude of the Simon effect provides a sensitive quantitative metric of an individual's ability to resolve interference that arises from the tightly, temporally sequenced activation of conflicting responses.

Importantly, the temporal dynamics of involuntary response capture by the irrelevant stimulus dimension and its subsequent inhibition on conflict trials can be dissociated, respectively, by distributional analyses that plot variations in response accuracy or in the Simon effect as a function of response speed (De Jong *et al*., 1994; Ridderinkhof, 2002). In conflict trials, fast responses are relatively more error prone, suggesting that early action selection processes are more often captured by involuntarily activated response impulses. Thus, inferences about the strength of response capture by incorrect response impulses can be drawn by focusing on accuracy rates associated with the fastest reactions in a conflict situation. According to the activation–suppression model, the rapid activation of an incorrect response impulse is followed temporally by the engagement and gradual build-up of online suppression of this response as an act of cognitive control (Ridderinkhof, 2002). Based on these temporal dynamics, the model predicts that slower reactions in conflict situations are less impacted by interference from incorrect response impulses because suppression has had more time to accrue and counteract them. Several studies now confirm that interference from incorrect response impulses in conflict tasks levels off or reverses at the slow end of reaction time distributions, consistent with top-down suppression of interference arising from activation of an incorrect response impulse. Moreover, the magnitude of the reduction in the interference effect at the slow end of the reaction time distribution is sensitive to demands placed on inhibitory control (Burle *et al*., 2002; Wijnen and Ridderinkhof, 2007), distinguishes individual and group differences in the proficiency of inhibitory control (Ridderinkhof *et al*., 2005; Bub *et al*., 2006; Wylie *et al*., 2007, 2009, 2010) and relates to individual differences in the engagement of prefrontal cortical regions associated with inhibitory control (Davelaar, 2008). Recent model-based functional magnetic resonance imaging studies indicate that response capture and response suppression in the Simon task are associated with dissociable neural activity (Forstmann *et al*., 2008*a*, *b*). Stronger capture by the incorrect response impulse is associated with increased blood oxygen level-dependent activity in the pre-supplementary motor area, whereas the steeper temporal reduction in the Simon effect (i.e. more proficient inhibition) is associated with increased blood oxygen level-dependent activity in the right IFC (Forstmann *et al*., 2008*a*, *b*).

Evidence supporting a role for the STN in inhibitory control over pre-potent response impulses is limited. The handful of studies in which comparisons have been made of the effect on inhibitory control (measured by Stroop, random number generation, or go/no-go tasks) of applying and removing stimulation to the STN in patients with Parkinson's disease has yielded paradoxical results. These studies have reported that, compared to withholding stimulation to the STN, applying STN DBS impairs, improves or has no impact on the ability to suppress pre-potent, impulsive response tendencies (Jahanshahi *et al*., 2000; Hershey *et al*., 2004; Witt *et al*., 2004; Thobois *et al*., 2007; Campbell *et al*., 2008; Ballanger *et al*., 2009). In contrast, STN lesions in animals have been found to induce a pattern of consistent premature selection of pre-potent response tendencies suggestive of deficits in response inhibition (Phillips and Brown, 2000; Winstanley *et al*., 2005; Eagle and Baunez, 2010). A contribution towards resolving these paradoxical results may be made by studying the effects of STN DBS on the well-characterized Simon effect. This effect has yet to be studied in patients with Parkinson's disease to elucidate the effects of stimulation to the STN on impulse and inhibitory control. However, the potential value of doing so is suggested in a recent study we completed of 52 medicated patients with Parkinson's disease. We used distributional analyses of performance on the Simon task to dissociate the effects of Parkinson's disease on the strength of involuntary capture by response impulses and the proficiency of suppressing these impulses (Wylie *et al*., 2010). These analyses demonstrated similar incorrect response capture (i.e. occurrence of fast errors) induced by the irrelevant stimulus dimension among patients and healthy control participants, but dramatically less proficient suppression of the interference among patients. Although the entire sample of patients displayed mild to moderate motor symptoms associated with Parkinson's disease, more severe ratings of motor dysfunction were strongly associated with poorer suppression of incorrect response impulses. Because of the hypothesized role of the STN in inhibitory action control, we speculated that the STN dysfunction in Parkinson's disease may contribute to difficulties suppressing involuntary response impulses.

In the current study, we extended this work by studying the effect of STN DBS on the expression and suppression of involuntary response impulses that conflict with goal-directed action in the Simon task. The performance of individuals with Parkinson's disease, both on and off STN DBS, and healthy controls was compared. Patients electing DBS surgery typically display more advanced motor dysfunction. Thus, we predicted that when DBS was not being delivered, patients would show poorer inhibitory control over incorrect response impulses, a pattern that would most closely resemble patients with Parkinson's disease with

more severe motor symptoms that we found in Wylie *et al*. (2010). Replication of this pattern would set the stage for our central prediction that inhibitory action control would be improved in patients with Parkinson's disease during STN DBS (cf. van den Wildenberg *et al*., 2006), and this improvement would result in a pronounced temporal reduction in the Simon effect for the slow segment of the reaction time distribution. However, recent evidence that STN DBS can produce impulsive behaviour (Frank *et al*., 2007; Smeding *et al*., 2007) suggested that this predisposition may manifest itself as stronger response capture by impulses (i.e. an increase in fast response errors for the fast segment of the reaction time distribution) when the STN is being stimulated. In combination, support for the last two predictions would reveal the paradoxical effects of STN DBS on cognitive processing.

Materials and methods

Participants

Seventeen individuals diagnosed with idiopathic Parkinson's disease, who were treated successfully with STN DBS and 17 healthy controls without Parkinson's disease participated in this study. Patients were recruited from the Movement Disorders clinic at the University of Virginia and the diagnosis of Parkinson's disease was confirmed by a neurologist specializing in movement disorders. Each patient had been treated with STN DBS for at least 3 months, exhibited a clinically effective and stable response to it, ambulated independently and was rated a Hoehn and Yahr Stage III (1967) or less when DBS was being delivered or turned off. With one exception, they were taking dopaminergic medications in conjunction with DBS and were tested during the ON state of their medication cycle. Eight of these patients were taking both a dopamine agonist and a dopamine precursor. All patients had chosen DBS surgery because their medications were no longer providing optimal control over their motor symptoms. However, all patients had demonstrated a positive response to dopamine pharmacotherapy in the early stages of their disease and prior to surgery.

Electrodes were placed bilaterally in the STN of 14 patients and unilaterally in the left STN of three patients. The surgical procedure for STN DBS utilized standard stereotactic techniques with microelectrode recordings for electrophysiological localization and has been described previously (Elias *et al*., 2007). Briefly, macroelectrodes (Medtronic Model 3389) consisting of four platinum–iridium cylindrical surfaces, each with diameter 1.27 mm, length 1.5 mm, and edge-to-edge separation of 0.5 mm, were guided into the STN using MRI-guided stereotaxy and intraoperative microelectrode recordings. The planned coordinates for macroelectrode placement was based on direct visualization of the STN on T_2-weighted magnetic resonance images. Final electrode position was based on microelectrode recordings and confirmed intraoperatively with macrostimulation after implantation of the DBS electrode. Selection of final bipolar contacts and stimulation settings were determined on an individual basis to optimize control over clinically manifest motor symptoms.

Healthy elderly controls without Parkinson's disease were recruited from the local community via advertisement. Patients and healthy control candidates were excluded from the study if they had a history of a neurological condition (other than Parkinson's disease for the patient group), untreated or unstable mood disorder, bipolar affective disorder, schizophrenia or other psychiatric condition known to compromise executive cognitive functioning, or an untreated or unstable medical condition known to interfere with cognitive functioning (e.g. diabetes, pulmonary disease). All participants had normal or corrected-to-normal vision. Prior to participating in the study, they all provided informed consent that was fully compliant with standards of ethical conduct in human research as regulated by the University of Virginia human investigation committee.

Task and procedures

All participants completed their participation during a single session. Whereas healthy control participants completed the cognitive task just once, patients with Parkinson's disease completed two counterbalanced sessions of the task on the same day, once with DBS being delivered and once with it not. After turning stimulation on or off, patients waited 30 min before resuming the task. This ensured that motor symptoms had largely subsided after inducing stimulation and that the increase in motor symptoms had reasonably stabilized after terminating stimulation (Hristova *et al*., 2000; Lopiano *et al*., 2003). To verify the beneficial effects of STN DBS on basic motor control processes, patients performed measures of fine motor speed and dexterity (pegboard and finger tapping tasks) during the on and off stimulation conditions on the day of testing. These tasks were administered *in lieu* of the Unified Parkinson's Disease Rating Scale for time savings and because they correlate strongly with this scale (Muller *et al*., 2000; Haaxma *et al*., 2008).

The Simon task was implemented on an IBM-compatible computer with a 17-inch digital display monitor (Fig. 1). The computer screen, placed at a distance of 91 cm, was positioned so that stimuli appeared at eye level. Each block of trials was initiated by the appearance of a small square stimulus (0.8 cm in height and width with a subtended visual angle of 0.46°) in the centre of the computer screen. The square remained on the screen throughout the entire block and participants were instructed to fixate their gaze on this square as long as it remained on the screen. After a variable duration (randomly selected from the range 1750–2250 ms in intervals of 50 ms), a blue or green circle (shown against a white background) appeared to the left or to the right side of the fixation square and remained on the screen until either the participant issued a response or 1500 ms had elapsed. Each circle had a diameter of 2.1 cm that subtended a visual angle of 1.20°. The edge-to-edge separation between the circle and the fixation square (i.e. the distance the circle was displaced to the left or right of fixation) was 0.6 cm (i.e. a visual angle of 0.34°). Participants were instructed to make a button press, as quickly and as accurately as possible, on the basis of a pre-determined colour-response mapping (e.g. blue circle, right button press; green circle, left button press); the colour-response mapping was counterbalanced across subjects. Responses were made with the left or right thumb, each of which rested on a button positioned at the end of a grip held comfortably in each hand. After a response, the circle disappeared and the next trial began. Following completion of the 60th trial in a block, the fixation square was removed from the screen and participants received feedback on their reaction times and accuracy for that block of trials. A schematic of the trial structure is given in Fig. 1B.

Each trial was defined by one of two levels of correspondence (Fig. 1A). For 'corresponding' trials, the task-irrelevant spatial location of the circle matched the response side indicated by the task-relevant colour of the circle (e.g. a blue circle calling for a right-hand response was presented to the right of fixation). For 'non-corresponding' trials, the spatial location of the circle was opposite the response side

indicated by the circle colour (e.g. a blue circle calling for a right-hand response was presented to the left of fixation). Each trial type (corresponding or non-corresponding) appeared randomly and with equal probability within a block of trials. Following a block of 60 practice trials, each participant completed five experimental blocks of 60 trials for a total of 300 experimental trials (i.e. 150 trials for each level of correspondence).

Mean reaction times and transformed accuracy rates were used for statistical analyses. Since accuracy rates are not normally distributed, they were converted to square root values before being entered into an analysis of variance (ANOVA). Extreme reaction time values, defined as either anticipatory responses faster than 100 ms or as excessively delayed responses slower than 3 SD above the mean, were removed from analyses after visual inspection to verify each value as an extreme outlier. Less than 1% of the trials were eliminated per subject. Mean reaction time and accuracy rates were analysed using repeated-measures ANOVA.

To determine the strength of response capture and the proficiency of response suppression, we analysed characteristics of the reaction time distribution guided by the activation–suppression model (see also Forstmann *et al*., 2008; Wylie *et al*., 2009*a*, for identical analytic techniques and elaboration of conceptual rationale). Briefly, we assessed the strength of response capture by computing a conditional accuracy function for each level of correspondence. In this function, accuracy rates are plotted against reaction time for the entire reaction time distribution. All reaction times (accurate and inaccurate) were rank-ordered separately for each level of correspondence and separated into seven bins with equal numbers of trials. The number of bins was chosen empirically to provide a stable estimate of bin values (approximately 21 trials per bin). In previous work using the Simon task, we demonstrated that the pattern of results in Parkinson's disease and healthy control groups is consistent across different bin sizes (Wylie *et al*., 2010). Next, an accuracy rate was computed for each bin and plotted against the mean reaction time for that bin, producing seven separate accuracy values for corresponding and non-corresponding trial types alike. The strength of response capture for each level of correspondence was inferred from the pattern of fast errors evident for the fastest two reaction time bins. Stronger response capture is associated with a higher percentage of fast errors.

To measure how proficiently activation of the conflicting response was suppressed, we generated delta plots by plotting the Simon effect (i.e. mean reaction time for non-corresponding trials minus mean reaction time for corresponding trials) as a function of response speed (Ridderinkhof, 2002). In this procedure, unlike conditional accuracy functions, only correct trials are used. Delta plots, like conditional accuracy functions, involve procedures that rank-order reaction times at each level of correspondence for separation into seven bins with equal numbers of trials. Next, a Simon effect (i.e. delta value) was computed for each bin and plotted as a function of the average reaction time for that bin, producing seven delta plot values. The slopes between the delta values provide a measure of change in the Simon effect across the reaction time distribution that accounts for group differences in reaction time. The activation–suppression model asserts that the build-up of suppression should be maximal at the slow end of the reaction time distribution. Thus, our primary analysis of the proficiency of suppression focused on the slope connecting the slowest two reaction time bins (for discussions of the rationale for this choice, see Ridderinkhof, 2002; Forstmann, *et al*., 2008*a*, *b*; Wylie *et al*., 2010). A more negative slope indicates a greater reduction in the Simon effect and, inferentially, more proficient inhibitory control.

Results

This section is divided into three parts. Patient characteristics and related issues are described in the first part. Next, we describe the outcome of the analysis in which the performances of patients with their STN DBS turned off and healthy control participants on the Simon task were compared. As will be seen, the results of this analysis provided a replication of previous work that showed less proficient suppression of incorrect response impulses among medicated patients with Parkinson's disease compared to healthy controls (Wylie *et al*., 2010). Last, we examined the influence of DBS on basic motor processes and performance on the Simon task among patients. We describe the analytic output of a conventional within-subjects ANOVA on mean Simon effects that is followed by a description of the results yielded by the distributional analyses.

Patient characteristics

The final sample included 17 patients with Parkinson's disease treated successfully with STN DBS and 17 healthy controls without Parkinson's disease. Two additional patients diagnosed with Parkinson's disease were recruited but not enrolled in the study. These two patients developed moderate amplitude tremor when DBS was turned off, which made it difficult for them to grasp and register responses comfortably using the handheld response devices for the Simon task. All other patients were able to use the response devices comfortably and effectively whether DBS was turned on or off. The two participant groups did not differ in age or education ($P > 0.05$), were free of dementia ($P > 0.05$; assessed by the Mini-Mental State Examination; Folstein *et al*., 1975) and did not meet criteria for major depression on the basis of clinical interview data obtained at the time of testing. Table 1 shows the relevant demographic information for the two groups, including the average DBS stimulation parameters and levodopa equivalents (Weintraub *et al*., 2006) for patients with Parkinson's disease at the time of testing.

Initially, nine of the recruited 19 participants with Parkinson's disease were scheduled to start participation in the DBS off condition, but two of these patients, as described earlier, presented with moderate amplitude tremor upon turning off DBS and were not enrolled in the study. Thus, in the final sample of 17 patients, 11 patients began the study with the DBS on condition and six patients began with the DBS off condition before switching to the alternate setting. To rule out order effects, we included test order as a between-subjects factor (i.e. DBS off first versus DBS on first) in a separate analysis. This analysis revealed no effects of test order on any of the key measures in the Simon task, thus in the following analyses, test order was not included as an experimental factor (see online Supplementary material for associated analyses). Moreover, we assessed the potential differential impact of unilateral stimulation on task performance by restricting the analysis to the 14 patients who were receiving bilateral STN DBS. The pattern of results was not altered by excluding the three unilateral patients. Thus the data for the two types of patients were combined in the final analyses [see Supplementary material for analyses of

Table 1 Demographic data for all groups and DBS settings for patients with Parkinson's disease (standard deviations shown in parentheses)

	Patients with Parkinson's disease	Healthy controls	Significance ($P < 0.05$)
Sample size	17	17	
Age (years)	61.8 (7.6)	62.6 (8.4)	NS
Education (years)	15.7 (3.2)	16.7 (3.1)	NS
Gender (male:female)	12:5	12:5	NS
MMSE (raw score)	29.2 (1.5)	29.4 (0.8)	NS
Years since disease onset	13.8 (5.9)	–	
Levodopa equivalent (mg)	633.1 (217.3)	–	
Bilateral:unilateral (left)	14:3	–	
DBS settings			
Left ($n = 17$)			
Voltage (V)	3.1 (0.9)	–	
Rate (Hz)	144.7 (18.2)	–	
Pulse width (ms)	75.0 (15.5)	–	
Right ($n = 14$)			
Voltage (V)	2.5 (1.5)	–	
Rate (Hz)	144.7 (18.2)	–	
Pulse width (ms)	78.8 (15.0)	–	

MMSE = Mini-Mental State Examination; NS = non-significant.

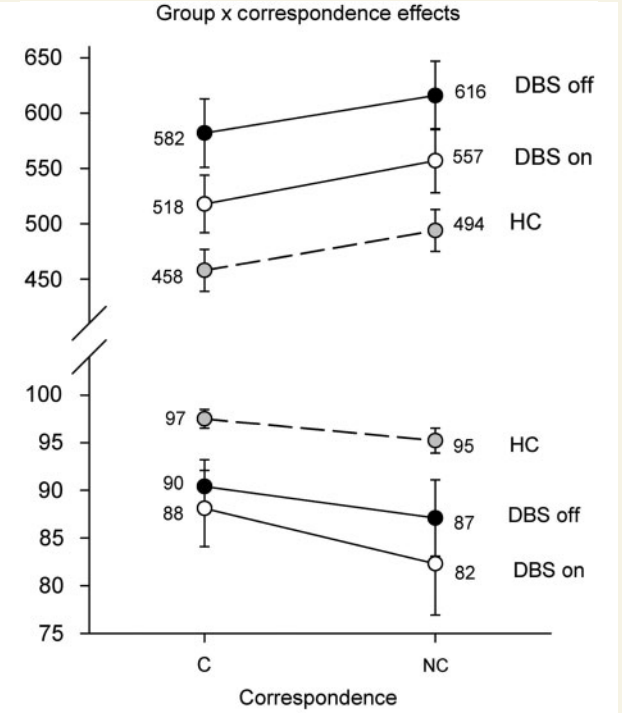

Figure 2 Mean reaction times for correct trials and overall accuracy rates for individuals with Parkinson's disease (DBS off, DBS on) and healthy controls (HC) as a function of Simon condition. Error bars indicate standard error of the mean. C = corresponding; NC = non-corresponding.

bilateral patients; cf. van den Wildenberg *et al*. (2006) for a similar strategy and discussion].

Comparison between healthy controls and patients with Parkinson's disease off stimulation

Group effects on mean reaction times and accuracy rates

Figures 2, 3 and 4 show the data for healthy controls and patients with Parkinson's disease both on and off STN stimulation. Here, attention is directed to comparisons of healthy controls and patients when stimulation was withheld. In Fig. 2, it can be seen that when DBS was not being delivered patients with Parkinson's disease were slower and less accurate than controls [Group: reaction time, $F(1,32) = 11.28$, $P = 0.002$; Accuracy, $F(1,32) = 4.55$, $P = 0.04$]. Figure 2 also shows that a classic Simon effect was produced in both groups, slower mean reaction times and lower mean accuracy rates for non-corresponding than for corresponding trials [Correspondence: reaction time, $F(1,32) = 178.93$, $P < 0.001$; Accuracy, $F(1,32) = 11.40$, $P = 0.002$]. Moreover, it can be seen that the magnitude of this effect did not differ between the two groups for either measure [Group × Correspondence: reaction time, $F(1,32) = 0.03$, $P = 0.87$; Accuracy, $F(1,32) = 0.68$, $P = 0.42$].

Group effects on the dynamics of response capture

The activation–suppression model asserts that susceptibility to response capture by activation of incorrect response impulses is manifest in the production of fast response errors on non-corresponding trials (i.e. trials in which there is conflict between the response signalled by the colour of the stimulus and by its spatial location, respectively). Thus, increases in the strength of response capture are hypothesized to be associated with increases in the production of fast errors for non-corresponding trials, an effect that, according to the model, is most visible for the fastest responses of the reaction time distribution. Accordingly, our analysis focused on accuracy rates for the two fastest reaction time bins (Bin factor). Together, these bins encompassed the fastest 30% of responses. The conditional accuracy functions for the entire reaction time distributions for corresponding and non-corresponding trials are shown, respectively, in Fig. 3A and B. As is apparent in this figure, fast errors were influenced strongly by the correspondence between the response activated by the spatial location of the stimulus and the response signalled by its colour [Correspondence, $F(1,32) = 24.83$, $P < 0.0001$]. That is, more fast errors occurred on non-corresponding than on corresponding trials. Moreover, the production of fast errors was greater for the fastest than for the second fastest reaction time bin [Bin, $F(1,32) = 9.28$, $P = 0.005$]. Fast errors were infrequent and did not vary across the two fastest bins for corresponding trials, but were most frequent for the fastest bin of non-corresponding trials and became less frequent for the second fastest bin of non-corresponding trials [Correspondence × Bin, $F(1,32) = 13.31$, $P = 0.001$]. Most importantly, when DBS was off, the pattern of fast errors (i.e. strength of response capture) did not differ between patients with Parkinson's

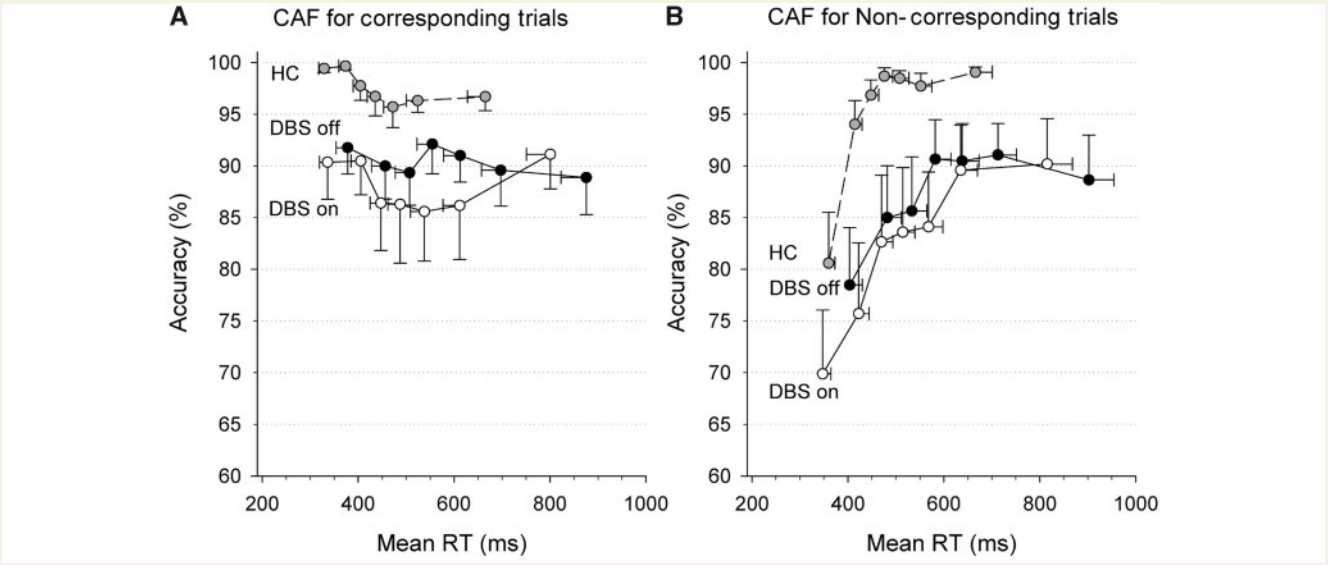

Figure 3 Conditional accuracy functions (CAF) for corresponding (**A**) and non-corresponding (**B**) trials for individuals with Parkinson's disease (DBS on, DBS off) and healthy controls (HC). Compared to no stimulation, STN stimulation induces more impulsive behaviour as evidenced by an increase in fast errors on non-corresponding trials. RT = reaction time; error bars indicate standard error of the mean.

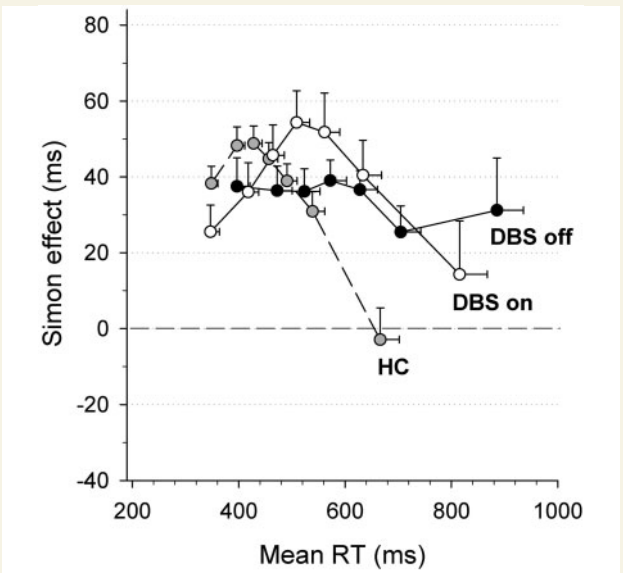

Figure 4 Delta plots depicting reduced Simon effect as a function of response speed for individuals with Parkinson's disease (DBS on, DBS off) and healthy controls (HC). Compared to no stimulation, STN DBS improves inhibitory control over conflicting response interference as evidenced by a sustained decrease of the Simon effect on slower correct trials. Error bars indicate standard error of the mean. RT = reaction time.

disease and healthy controls on either corresponding or non-corresponding trials, as is evident in Fig. 3A and B; all of the group comparisons had *P*-values > 0.10. To verify further, the absence of a group effect on fast incorrect response capture during conflict trials, an analysis restricted to Group effects on the entire conditional accuracy function for non-corresponding trials indicated that fast errors were restricted to the earliest bins [Bin, $F(1,27) = 3.79$, $P = 0.007$] among both patients and healthy controls [Bin × Group, $F(6,27) = 0.98$, $P = 0.46$].

Group effects on the dynamics of response inhibition

According to the activation–suppression model, the proficiency of response suppression is revealed by a reduction in the magnitude of the Simon effect at the slowest reaction times, as indexed in a delta plot by the slope of the segment connecting the two slowest reaction times bins (see 'Materials and methods'). It is evident in Fig. 4 that the slope of this segment of the delta plot is significantly less negative-going among patients not receiving DBS than among controls [$m = 0.01$ versus -0.29; $t(32) = -4.13$, $P < 0.001$]. Thus, in the absence of STN stimulation, patients were much less proficient than their healthy peers in suppressing an incorrect response impulse induced by conflicting, irrelevant response information.

Note that the patterns that emerged on the conditional accuracy functions and delta plots among patients when DBS was not being delivered resembled the patterns we reported earlier among medicated, non-DBS treated patients diagnosed with Parkinson's disease (Wylie *et al*., 2010), and in so doing provide further evidence supporting the conclusion that preserved response capture occurs in the context of impaired response suppression in these patients.

Comparisons between patients with Parkinson's disease on and off deep-brain stimulation

Basic motor control effects

The beneficial effect of DBS on basic motor control processes among patients, measured by the time taken to perform a nine-hole pegboard task and by the average number of index

finger taps completed on a tapping board across three 10 s trials, was assessed on the day of testing. A within-subjects ANOVA with Response Hand (left versus right) and DBS (off versus on) as the independent variables revealed that overall performance on the nine-hole pegboard task was comparable between the two hands (Right Hand: Mean = 32.6 s, SEM = 3.2 s; Left Hand: Mean = 33.9 s, SEM = 2.7 s), [Response Hand, $F(1,16) = 0.16$, $P = 0.69$)], and improved significantly (by 7 s) and equivalently in each response hand [DBS × Response Hand: $F(1,16) = 0.26$, $P = 0.62$] when stimulation was delivered to the STN (Mean = 30 s; SEM = 2.1 s) compared to when it was withheld (Mean = 37 s; SEM = 3.6 s) [DBS, $F(1,16) = 4.74$, $P < 0.05$]. Similarly, DBS benefited finger tapping control and speed (DBS On: Mean = 39.9, SEM = 2.0; DBS Off: Mean = 35.5, SEM = 2.1), [DBS, $F(1,16) = 7.94$, $P < 0.05$] equivalently across response hands [DBS × Response Hand, $F(1,16) = 0.35$, $P = 0.56$]. However, unlike the pegboard task, finger tapping was more proficient with the right (Mean = 39.6, SEM = 2.1) than with the left hand (Mean = 35.8, SEM = 2.0), [Response Hand, $F(1,16) = 5.39$, $P < 0.05$]. Since all of the patients were right-handers, this difference in finger tapping speed may simply reflect handedness.

There were no significant correlations between performance or change in performance on the pegboard/finger tapping tasks and any of the key Simon task measures (e.g. overall mean reaction time, mean Simon effects, final delta slope, proportion of fast errors; all P-values > 0.10). Additionally, none of these measures on the Simon task or changes in them correlated with levodopa equivalent or DBS voltage values (all P-values > 0.10).

Mean reaction times and accuracy effects on the Simon task

As illustrated in Fig. 2, mean response latencies were faster among patients when DBS was being delivered than when it was not, but mean accuracy rates only tended to be reduced [DBS: reaction time, $F(1,16) = 6.76$, $P = 0.01$; Accuracy, $F(1,16) = 3.24$, $P = 0.09$]. It can also be seen that a robust Simon effect was produced in these patients during stimulation; reaction times were slower and accuracy rates were lower for non-corresponding than for corresponding trials [Correspondence: reaction time, $F(1,16) = 28.88$, $P < 0.001$; Accuracy, $F(1,16) = 9.15$, $P = 0.008$]. However, as is also evident, the magnitudes of these mean interference effects were not altered on either measure by whether or not DBS was being delivered to the STN [Correspondence × DBS: reaction time, $F(1,16) = 0.24$, $P = 0.63$; Accuracy, $F(1,16) = 2.79$, $P = 0.11$].

Effects of deep-brain stimulation on the dynamics of response capture

As is apparent in the conditional accuracy functions shown in Fig. 3A and B, fast errors were influenced strongly by the correspondence between the response activated by the spatial location of the stimulus and the response signalled by its colour whether or not stimulation was delivered to the STN. Specifically, more fast errors occurred when non-corresponding as opposed to corresponding responses were activated [Correspondence, $F(1,16) = 14.10$, $P = 0.002$]. Consistent with the hypothesized temporal dynamics of response capture, error rates were higher for the fastest compared to the second fastest reaction time bin [Bin, $F(1,16) = 6.07$, $P = 0.02$]. However, as expected, this pattern depended on stimulus–response correspondence [Bin × Correspondence, $F(1,16) = 7.86$, $P = 0.01$]. In Fig. 3A it can be seen that accuracy rates were quite high and stable across the two fastest reaction time bins for corresponding (i.e. non-conflict) trials, irrespective of stimulation status. In contrast, a pronounced reduction in accuracy rates on non-corresponding (i.e. conflict) trials is clearly evident in Fig. 3B, a reduction that is strongly suggestive of incorrect response capture early in processing.

Overall, patients with Parkinson's disease made more fast errors when DBS was delivered than when it was withheld [DBS, $F(1,16) = 6.08$, $P = 0.02$]. However, production of these fast errors was bound very closely to stimulus–response correspondence [DBS × Correspondence, $F(1,16) = 7.96$, $P = 0.01$]. Specifically, as can be seen in Fig. 3A, the presence or absence of DBS did not influence fast errors on corresponding trials. In contrast, as illustrated in Fig. 3B, when DBS was being delivered, the production of fast errors was larger on non-corresponding than on corresponding trials, once again strongly suggestive of an increase in the strength of early incorrect response capture in the face of conflict. Moreover, this increase in fast errors induced by DBS on non-corresponding trials was consistent across the two fastest reaction time bins [DBS × Correspondence × Bin, $F(1,16) = 0.13$, $P = 0.72$]. We analysed the effect of DBS across the entire conditional accuracy function for non-corresponding trials to provide further verification of the specificity of this effect on fast incorrect response capture during conflict trials. This analysis, consistent with the analysis on the two fastest bins described above, indicated that accuracy rates were lowest in the earliest response bin when stimulation was being delivered [Bin × DBS, $F(6,96) = 2.57$, $P < 0.05$]. This pattern of results indicates that response capture was greatest among patients when response conflict occurred and STN DBS was being delivered, and suggests that patients with Parkinson's disease made more impulsive errors when stimulation was delivered than when it was withheld.

Effects of deep-brain stimulation on the dynamics of response inhibition

The effect of STN DBS on the final delta plot segment is clear in Fig. 4. When DBS was withheld, patients showed no clear reduction of Simon interference between the two slowest reaction time bins. However, a decidedly negative delta slope for the slowest segment is evident when stimulation was being delivered. To verify these visual impressions, we first completed a repeated-measures ANOVA that included within-subject factors of slope with six levels (slopes for bins 1–2, 2–3, ... 6–7 of the delta plot) and DBS with two levels (off, on). The activation–suppression model predicts that the slope of the delta plot will be more negative late in processing when suppression of the interference effect is maximal. Support for this prediction would be expressed in the ANOVA by a significant Slope × DBS interaction. This is precisely what the analysis yielded [$F(5,12) = 5.14$, $P = 0.009$]. The presence of this interaction provides analytic

justification of our *a priori* rationale for doing a simple paired one-way *t*-test on the final delta slope. The paired comparison provided statistical confirmation of the visual impression; namely, a more negative-going slope with DBS on ($m = -0.17$) than off ($m = 0.01$), [$t(16) = -2.38$, $P = 0.01$]. According to the model, this finding suggests that patients diagnosed with Parkinson's disease were more effective at suppressing incorrect response activation during STN stimulation.

Examination of Fig. 4 also reveals a strikingly different overall pattern of interference effects when stimulation was being delivered to rather than withheld from the STN. In addition to more effective suppression of interference at the slowest segments of the distribution, STN DBS produced a steeper initial rise in interference across the early portions of the delta plot. Although we made no *a priori* predictions about the initial portions of the delta slope, we suspected that the DBS-induced increase in initial interference would be related to the pattern of stronger response capture (i.e. fast errors from the conditional accuracy function analysis) that was also induced by stimulation. Thus, we calculated a slope encompassing the change in interference over the four fastest bins, what we call the 'activation–interference slope'. For comparison purposes, we also computed a more broadly defined suppression slope that encompassed the change in interference over the slowest four bins, even though previous studies have demonstrated that the final delta slope is the most sensitive measure of the proficiency of suppression. Repeated-measures ANOVA with DBS (on versus off) and slope (activation versus suppression) as within-subject factors showed a significant slope effect [$F(1,16) = 14.98$, $P < 0.01$]; the early positive-going slope ($m = 0.09$) associated with activation of the incorrect response impulse contrasted with the late negative-going slope ($m = -0.09$) reflecting suppression of this activation. Although the presence or absence of DBS did not produce an overall change in the slopes of the delta plots between the two conditions [DBS, $F(1,16) = 0.20$, $P = 0.66$], the slopes associated with early activation and late suppression did vary with DBS [DBS × Slope, $F(1,16) = 9.10$, $P < 0.01$]. Compared to no stimulation, stimulating the STN produced a steeper positive interference slope across the early portion of the distribution [$F(1,16) = 5.69$, $P < 0.05$], as well as a steeper negative slope across the late portion of the distribution [$F(1,16) = 4.47$, $P < 0.05$].

As expected, the early activation slope correlated negatively with the accuracy rate on conflict trials for the fastest reaction time bin when the STN was being stimulated ($r = -0.54$, $P < 0.05$), but not when the STN was not being stimulated ($r = -0.37$, $P = 0.15$). This provides further support for the conclusion that stimulating the STN induces stronger response capture by conflicting response impulses that leads to fast impulsive errors and greater initial interference with goal-directed action. Notably, the suppression slope corresponding to the late portion of the reaction time distribution correlated neither with the early positive-going activation slope (DBS On, $r = 0.29$, $P = 0.25$; DBS Off, $r = 0.10$, $P = 0.70$) nor with the percentage of fast errors on conflict trials (DBS On, $r = -0.15$, $P = 0.56$; DBS Off, $r = 0.00$, $P = 0.99$) with or without STN stimulation. This finding provides additional support for the conclusion that an early response capture process and a later evolvement of top-down suppression of interference are dissociated.

Discussion

The aim of this study was to determine the effect of STN DBS on cognitive control processes in patients diagnosed with Parkinson's disease when they experience conflict from the activation of an incorrect response impulse. We summarize and discuss the main findings first, before evaluating the implications for the controversy that characterizes the effects of STN DBS on impulse and inhibitory control.

Subthalamic nucleus deep-brain stimulation and the expression and suppression of impulsive behaviour

The Simon task successfully produced conflict from response impulses in patients with Parkinson's disease and healthy controls. Responses were faster and more accurate when relevant (i.e. colour) and irrelevant (i.e. spatial location) features of an imperative stimulus corresponded to the same response, but slower and less accurate when these features signalled conflicting responses. More importantly, in support of the activation–suppression model, incorrect response capture was demonstrated by a dramatic increase in fast errors on conflict trials. Top-down suppression of this capture, which gradually builds up to counter activation of incorrect response impulses, was evidenced by a clear reduction in the Simon effect for the slowest subset of reaction times when suppression was predicted to be maximal. These patterns replicate previous findings (Burle *et al*., 2002; Forstmann *et al*., 2008*a*, *b*; Wylie *et al*., 2009*a*, *b*, 2010) and establish the importance of studying the dissociative effects of STN DBS on action control in Parkinson's disease. First, we discuss the effects of DBS on mean performance before turning to the temporal dynamics of response capture and inhibition revealed by distributional analyses.

STN DBS had differential effects on mean task performance. Patients were 61 ms faster in reacting and overall accuracy tended to decrease with DBS turned on. These results fit with clinical observations of improved motor function (Krack *et al*., 2003) and replicate experimental studies reporting the beneficial effects of STN DBS on voluntary action selection using a variety of reaction time tasks (Hershey *et al*., 2004; Williams *et al*., 2005; van den Wildenberg *et al*., 2006). Comparisons of DBS in the on and off states showed similar mean Simon effects for both reaction time and accuracy that did not differ from healthy controls, although there was a tendency for STN stimulation to reduce error rates in conflict trials. Interestingly, previous studies comparing patients with Parkinson's disease and healthy controls have reported equivocal findings for mean Simon effects (cf. Cope *et al*., 1996; Praamstra and Plat, 2001; Fielding *et al*., 2005; Schmiedt-Fehr *et al*., 2007; Wylie *et al*., 2010).

However, these past findings relied on mean values that masked critical temporal effects of DBS on interference processing that were revealed by distributional analyses (Wylie *et al*., 2010).

More specifically, STN DBS increased the tendency to make fast impulsive errors on conflict trials, while at the same time improving the capacity to suppress interference effects as time passed. Here, processing of irrelevant information captured the motor system to such an extent that an overt response error could not be prevented in ~30% of the fast responses on non-corresponding trials. Notably, the proportion of fast errors in the fastest reaction time bin was higher for patients with Parkinson's disease with their DBS turned on than for healthy controls, despite both groups showing similar reaction time values for this fastest bin (patients with Parkinson's disease with DBS on = 347 ms; healthy controls = 349 ms). Hence, patients receiving STN stimulation responded as quickly as healthy controls in conflict trials, but were more susceptible to capture by incorrect response impulses. The emergent distributional patterns revealed that DBS reduced the accuracy of fast responses on conflict trials without altering non-conflict accuracy. This 'selective' effect argues against the interpretation that DBS induces a global shift in the speed-accuracy trade-off. Although the effect of DBS on impulsivity does not result from a general trade-off between speed and accuracy, the enhanced involuntary stimulus-driven response capture might be related to the effect of DBS on speed *per se*. DBS produced a shift in speed for the entire non-corresponding conditional accuracy function distribution compared to when DBS is turned on. This shift in speed induced by STN DBS may produce more fast errors (i.e. increased impulsivity), but we cannot dissociate the speed increase from the accuracy decrease.

Although patients with Parkinson's disease issued most responses on conflict trials correctly, processing of the incorrect impulse clearly interfered with goal-directed responding as reflected by the persistent Simon effect on reaction time. In fact, even when a response error was not made, STN stimulation enhanced the magnitude of early interference by an incorrect response impulse. However, STN stimulation also influenced a temporally dissociable process; it markedly reduced the magnitude of interference as response speed slowed. For relatively long reaction times, interference from the activation of incorrect response impulses was more effectively counteracted when the STN was being stimulated. This dynamic pattern of reduced interference over time may reflect improved top-down inhibitory control over involuntary response tendencies in order to actively reduce interference with processing of voluntary goal-directed actions. Although largely absent when DBS was off, stimulation of the STN resulted in a dynamic pattern of interference control that closely matched that of healthy controls.

Does subthalamic nucleus deep-brain stimulation improve or impair impulse control?

How can apparently contradictory effects of DBS, production of both poor impulse control and improved interference control, be reconciled? Based on the current results, we propose that STN DBS influences two temporally dissociable aspects of processing in conflict situations: (i) an early aspect that mediates one's initial susceptibility to response capture by pre-potent action impulses; and (ii) a later process engaged by cognitive control mechanisms to 'selectively' suppress incorrect responses that interfere with goal-directed action selection.

An effect of STN DBS on initial response capture by pre-potent action impulses is compatible with several previous findings and interpretations. For example, in an extensive review of animal studies, Eagle and Baunez (2010) described a pattern of increased impulsive action following lesions of the STN, which led them to conclude that the STN is critically involved in premature response control. Similarly, Frank *et al*. (2006, 2007) have argued that the STN plays a key role in holding responses in check. They reported that STN stimulation in patients diagnosed with Parkinson's disease led to faster, impulsive reactions in high conflict situations, suggesting a diminished ability to hold initial response tendencies in check. In a recent study of the effects of STN stimulation on performance in the go/no-go task, Ballanger *et al*. (2009) reported an increased susceptibility to error commission in patients with Parkinson's disease who were receiving STN stimulation. The authors interpreted this effect as evidence of increased impulsivity and proposed that STN stimulation may modulate the gating of response initiation mechanisms. A role for the STN in behavioural activation has been proposed by several investigators who have postulated that abnormal STN activity in Parkinson's disease contributes to difficulties initiating movement (Albin *et al*., 1989; DeLong, 1990; Mink, 1996). It has been proposed that one mechanism by which stimulation of the STN may exert its beneficial effects on clinical symptoms of Parkinson's disease is by slackening excessive braking of action, thus allowing patients with Parkinson's disease to initiate movement more spontaneously and responsively (for a review, see Montgomery and Gale, 2008).

Consistent with these data patterns and views, patients in our study were faster at making choice reactions with DBS, but this benefit came at a cost. When the STN was stimulated, patients were less able to prevent fast errors that were driven by incorrect, stimulus-driven response impulses (Frank *et al*., 2007; Ballanger *et al*., 2009). Stronger capture by the incorrect response in the Simon task has been linked to increased activation of the pre-supplementary motor area that sends direct, monosynaptic projections to the STN and has been implicated in response selection processes (Forstmann *et al*., 2008*b*). The pre-supplementary motor area is also activated when individuals press for response speed in choice reaction tasks, which has the effect of lowering response thresholds and increasing susceptibility to premature responding (Forstmann *et al*., 2008*c*). These findings raise the intriguing hypothesis that STN DBS alters pathways linking pre-supplementary motor area to the STN, which in turn alters the setting of response initiation thresholds that control premature, impulsive responding.

While STN stimulation increased the expression of impulsive response errors, it also produced benefit to cognitive control processes that selectively suppressed interference from incorrect response capture and produced correct responses on conflict trials. The build-up of selective suppression evolves over the course of a correct trial, which maximally benefits slower trials and further distinguishes this process from early response capture. This benefit of STN DBS on top-down inhibitory control over pre-potent action impulses extends previous studies that used

the stop-signal paradigm to demonstrate critical involvement of the STN in the suppression of actions that are initiated *voluntarily* but later determined to be inappropriate. These studies point to the so-called hyperdirect pathway, linking the right IFC directly to STN, as a strong candidate for implementing online stopping control over motor responses to facilitate adaptive behaviour. For example, stop-signal inhibition has been associated with activation in both the right IFC and right STN in healthy individuals (Aron and Poldrack, 2006). Similarly, right IFC lesions impair stopping (Aron *et al*., 2003). Compared to healthy controls, patients diagnosed with Parkinson's disease take longer to inhibit ongoing responses in the stop-signal task (Gauggel *et al*., 2004), a deficit that is ameliorated by STN DBS (van den Wildenberg *et al*., 2006). The beneficial effect of DBS stimulation on stopping proficiency was not replicated in a recent study by Ray and colleagues (2009). This discrepancy might be related to the fact that their sample consisted of 10 patients with Parkinson's disease with unilateral DBS, whereas van den Wildenberg and colleagues (2006) included a sample of patients with Parkinson's disease with predominantly bilateral DBS.

The current results suggest that the circuitry connecting the right IFC and STN may also be important when pre-potent response impulses must be inhibited selectively. Individual differences in right IFC activity have already been linked to inhibitory control over pre-potent response impulses in the Simon task (Forstmann *et al*., 2008*b*), with diffusion tensor imaging revealing that individual differences in inhibition are associated with differences in the density of coherent white-matter tracts in the right IFC region (Forstmann *et al*., 2008*a*). Thus, this growing body of evidence suggests that the cortical component of the network associated with stopping a voluntarily initiated response, the right IFC, may be involved critically in inhibiting *involuntary*, pre-potent response impulses in the Simon task. In light of these findings and the current results, improvements in selective suppression induced by stimulating the STN may reflect alterations to pathways connecting the right IFC and STN. Taken altogether, it is interesting to speculate that with stimulation, the STN is more responsive (i) to pre-supplementary motor area inputs, which would increase susceptibility to early response capture; and (ii) to right IFC inputs, which would improve selective suppression. This speculation is in line with suggestions that STN stimulation improves the fidelity of information flow through the STN, rather than simply preventing it as in a lesion effect (cf. Liu *et al*., 2008; Montgomery and Gale, 2008). Although in need of further empirical support, this could explain the apparent contradiction between poor impulse control and improved selective suppression with STN DBS.

The theoretical and neurological framework presented here suggests that STN DBS affects at least two distinct and temporally dissociable processes involved in conflict situations. This dissociation may help reconcile some of the mixed findings concerning the effect of STN DBS on impulse and inhibitory control. Studies that point to *impaired* inhibitory control may have detected increased vulnerability to the production of fast impulsive errors, whereas those that report improved inhibitory control may have detected enhanced proficiency of the more slowly developing top-down selective suppression mechanism. For example, mean Stroop interference effects on reaction time are not altered among patients with Parkinson's disease taking (Jahanshahi *et al*., 2000) or not taking (Witt *et al*., 2004) dopamine medication, although both groups of patients produced more impulsive errors when the STN was being stimulated. Conversely, STN stimulation has been observed to improve the ability to suppress habitual counting responses on a random number generation task, and this improvement was correlated with increased impulsive errors on the Stroop task (Witt *et al*., 2004). This contradiction bears an intriguing resemblance to our findings. Interestingly, a follow-up study of random number generation that required patients to generate numbers at a faster rate reported the opposite effect when speed of responding was emphasized (Thobois *et al*., 2007); that is, patients with DBS turned on made more errors in habitual counting. This might be explained by the effect of time pressure on the pre-potency of habitual responding; when speed is stressed patients may have more difficulty overcoming the automatic pre-potent response. Other investigations of DBS effects also highlight the need to distinguish between impulsive behaviour as reflected in accuracy rates and the subsequent engagement of inhibitory control. Hershey *et al*. (2004) studied go/no-go task performance in medication-withdrawn patients with Parkinson's disease and found that STN DBS produced higher commission errors to 'no-go' stimuli when pre-potency was high for 'go' responses. Moreover, reduced accuracy correlated with faster reaction times, suggesting that STN DBS may speed reactions at the cost of greater vulnerability to impulsive errors. Campbell *et al*. (2008) and Ballanger *et al*. (2009) reported a similar pattern of increased commission errors to 'no-go' stimuli coupled with faster reaction times with STN DBS. In sum, the seemingly paradoxical DBS findings pertaining to inhibitory control may be resolved when the capture by an incorrect response impulse is temporally dissociated from its suppression.

It is important to acknowledge some limitations and extant issues associated with the current study results. First, as with most studies of the effect of STN DBS on inhibitory control and other cognitive processes, it remains unclear how variations in stimulation parameters, electrode location and contact selection influence cognitive processes (Voon *et al*., 2006). In animal work, variations in STN stimulation parameters have been shown to influence the expression of premature responding in a reaction time task (Desbonnet *et al*., 2004). Even though we did not observe a relationship between primary stimulation settings and cognitive effects, there is a need for parametric investigation of stimulation settings on specific cognitive processes measured in conflict and stopping tasks. Additionally, all of our patients were taking their usual dopamine medication at the time of testing. Dopamine neuropharmacokinetics have been linked to certain expressions of impulsive behaviour (Pattij and Vanderschuren, 2008). The interaction between medication status (ON versus OFF) and DBS status (on versus off) has not been investigated rigorously in many studies. This design is quite demanding on patients, but would certainly allow for better specification of DBS versus medication effects and their interactive influences. Taking into consideration the results from other studies of STN DBS described above, there is a general pattern of increased impulsive action when the STN is being stimulated that is present independent of medication

status. There are also studies showing improved top-down inhibition due to STN stimulation in patients with Parkinson's disease after overnight withdrawal and while taking their dopamine medication. In the present study, there were no relationships between dopamine dosage and any of the key cognitive measures. Thus, while it appears that medication status is unable to account for the patterns of impulse and inhibitory control, future studies that systematically account for both medication status and DBS status are needed.

Conclusion

Methods that expose the temporal dynamics of information processing show dissociable effects of STN DBS on the expression and suppression of impulsive behaviour. STN stimulation increases fast impulsive response errors, yet improves inhibitory control over interference from response impulses on correct trials. This distinction provides a theoretical framework that helps interpret seemingly contradictory findings in the DBS literature on inhibitory control. It also provides a background against which to interpret problems with impulse control following STN DBS that are observed clinically (Ceravolo *et al.*, 2009). Specifically, patients with Parkinson's disease receiving STN DBS are more susceptible to reacting impulsively in situations requiring a speeded decision among highly conflicting response alternatives. It is important for future studies to investigate the link between impulse control on experimental cognitive tasks and the type of real world impulse control difficulties observed clinically. Finally, our observations fit with the notion that inhibitory control over both voluntary and involuntary actions may involve the same neural circuitry in which the right IFC and STN are critical.

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Supplementary material

Supplementary material is available at *Brain* online.

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