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The subthalamic nucleus and inhibitory control: impact of subthalamotomy in Parkinson's disease

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The aim of our study was to investigate two inter-related hypotheses about the role of the subthalamic nucleus. First that the subthalamic nucleus plays a role in adjusting response thresholds and speed-accuracy trade-offs and second that it is involved in reactive and proactive inhibition and conflict resolution. These were addressed by comparing the performance of 10 patients with Parkinson's disease treated with right subthalamotomy and 12 patients with left subthalamotomy, to 14 unoperated patients with Parkinson's disease and 23 age-matched healthy control participants on a conditional stop signal task and applying the drift diffusion model. Unilateral subthalamotomy significantly improved Parkinson's disease motor signs. Patients with right subthalamotomy had significantly faster Go reaction times with their contra-lesional hand than the unoperated patients and did not differ from the control participants, indicating their speed of response initiation was 'normalized'. However, operated patients made significantly more discrimination errors than unoperated patients and controls, suggesting that subthalamotomy influenced speed-accuracy trade-offs. This was confirmed by the drift diffusion model, revealing that while the unoperated patients had significantly lower drift rate and higher response thresholds than the control participants, the response thresholds for the operated groups did not differ from the controls and the patients with right subthalamotomy had a significantly higher drift rate than unoperated patients and similar to that of controls. The drift diffusion model further established that unlike the control participants, operated patients failed to show context-dependent strategic modulation of response thresholds. The patients with right subthalamotomy could not engage in late phase, fast inhibition of the response and showed minimal proactive inhibition when tested with the contra-lesional hand. These results provide strong evidence that the subthalamic nucleus is involved in response inhibition, in modulating the rate of information accumulation and the response threshold and

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influencing the balance between speed and accuracy of performance. Accordingly, the subthalamic nucleus can be considered a key component of the cerebral inhibitory network.

Keywords: Parkinson's disease; subthalamic nucleus; stop signal task; response inhibition; response thresholds

Abbreviations: SSRT = stop signal reaction time; STN = subthalamic nucleus

Introduction

The hyperdirect pathway connects the cortex with the subthalamic nucleus (STN) providing the quickest route for the cortex to influence the inhibitory output from the basal ganglia and to, in turn, regulate and fine-tune cortical activity (Nambu *et al.*, 2002). The direct and indirect striato-pallidal-frontal pathways have been proposed to constitute an ideal system for response selection and initiation under competition or conflict, with the indirect pathway through the STN inhibiting inappropriate responses to allow selection and initiation of the appropriate response through the direct pathway (Chevalier and Deniau, 1990; Redgrave *et al.*, 1999). More recently, this model has been further refined by Frank and colleagues (2006, 2007) who proposed that the STN is the source of a 'no go' or 'hold your horses' signal, which plays an important role in decision-making under conflict to prevent impulsive reactions and to allow time for reflection and evaluation of the available choices before a selection and response is made. It is further proposed that normally prevention of impulsive reactions in situations of conflict is achieved by increasing response thresholds to allow time for information accumulation (Frank, 2006; Frank *et al.*, 2007).

Inhibitory control over prepotent responses has been widely investigated with the Stop Signal Reaction Time (SSRT) task (Logan and Cowan, 1984) and imaging studies with this task in healthy participants have linked successful inhibition with activation of cortical areas such as the inferior frontal gyrus, presupplementary motor area, and subcortical areas such as the STN, caudate nucleus, and thalamus (Garavan *et al.*, 1999; Rubia *et al.*, 2003; Aron and Poldrack, 2006; Aron *et al.*, 2007; Li *et al.*, 2008; Xue *et al.*, 2008; Duann *et al.*, 2009; Hampshire *et al.*, 2010; Obeso *et al.*, 2013*a*). Interestingly, consistent right-lateralized activation in association with inhibition has been reported across studies, even when participants were using their right hand to respond (Aron and Poldrack, 2006; Aron *et al.*, 2007).

Investigation of the effect of focal brain lesions is a classic and arguably the most direct way to establish anatomo-functional correlations. The aim of the present study was to investigate the contribution of the STN to different volitional inhibitory processes that commonly occur in real life, specifically reactive inhibition (e.g. stopping the car at a red traffic light), proactive inhibition (e.g. slowing down walking when approaching a busy road or refraining from eating a piece of cake when dieting) and conflict resolution (e.g. should I spend my savings on a new car or have a holiday) by studying patients with Parkinson's disease who have had unilateral subthalamotomy. We compared the performance of patients with Parkinson's disease with unilateral subthalamotomy to unoperated patients and a healthy control group on a conditional stop signal task (De Jong *et al.*, 1995; Aron *et al.*, 2007; Obeso *et al.*, 2011*a*), which allows measurement of reactive and proactive inhibition and speed of conflict resolution. We also applied the drift diffusion model to the Go reaction times to quantify response thresholds. Based on the model of Frank and colleagues (2006, 2007), we predicted that (i) unilateral subthalamotomy would speed up reaction times, but increase discrimination errors relative to unoperated patients with Parkinson's disease; (ii) this alteration of speed-accuracy trade-offs would be associated with reduced response thresholds in patients with unilateral subthalamotomy relative to unoperated patients with Parkinson's disease, as evident in task performance and results of the drift diffusion model; (iii) patients with Parkinson's disease with unilateral subthalamotomy, particularly those with right subthalamotomies, would have greater problems with reactive inhibitory control relative to the unoperated Parkinson's disease group; and (iv) as a result of altered response thresholds with unilateral subthalamotomy, operated patients with Parkinson's disease would show significant differences on measures of proactive inhibition and conflict resolution relative to the unoperated Parkinson's disease group.

Materials and methods

Participants

We assessed 36 patients with Parkinson's disease and 23 healthy control participants (Table 1). All operated ($n = 22$, 10 with right and 12 with left subthalamotomy) and unoperated ($n = 14$) patients were evaluated and treated at the Centro Internacional de Restauración Neurológica (CIREN), Havana (Cuba). Patients exhibited bilateral but asymmetric motor features and subthalamotomy was performed contralateral to the most affected side. Patients with impulse control disorders and dopamine dysregulation syndrome were not included in the study. Further clinical information and surgical procedure are provided in the Supplementary material and in Table 1.

Procedure

The conditional stop signal reaction time task

The operated patients performed the conditional stop signal task twice, once with each hand. The hand contralateral to the lesion was assessed first. Unoperated patients with Parkinson's disease and controls also performed the task twice, once with each hand, starting with the dominant hand. For each hand, every participant performed three blocks of 128 trials of the conditional stop signal task.

The conditional stop signal task employed has been previously described in detail (Obeso *et al.*, 2011*a*, *b*). As shown in Fig. 1, this

Table 1 Demographic and clinical characteristics of the patients with Parkinson's disease with right or left subthalamotomy, unoperated patients with Parkinson's disease and healthy control participants

Group	Age (years)	Education (years)	MMSE	BDI	UPDRS-III PRE (OFF med)	UPDRS-III POST (OFF med)	Disease duration (years)	Time since surgery (months)	LEDD PRE (mg)	LEDD POST (mg)
Right subthalamotomy (n = 10)	52.70 (8.4)	10.90 (3.0)	27.78 (3.0)	8.10 (3.4)	55.80 (15.1)	22.82 (7.1)	11.70 (3.6)	5.00 (1.4)	1379.60 (266.0)	450.00 (243.9)
Left subthalamotomy (n = 12)	51.58 (8.7)	13.17 (3.4)	28.64 (1.3)	7.66 (5.7)	53.40 (17.6)	25.00 (5.5)	9.78 (4.6)	3.89 (1.4)	924.00 (277.1)	368.33 (208.4)
Unoperated PD patients (n = 14)	58.74 (5.1)	11.88 (2.7)	28.21 (1.4)	7.73 (3.5)	39.92 (9.9)		7.53 (3.7)		997.91 (333.1)	
Controls (n = 23)	55.00 (6.1)	15.48 (3.3)	29.61 (.6)	6.78 (4.2)						

Note: mean values are shown, the number in parentheses are standard deviations.
BDI = Beck Depression Inventory; MMSE = Mini-Mental Status Examination; PD = Parkinson's disease; UPDRS-III = Unified Parkinson's Disease Rating Scale – motor section III; LEDD = Levodopa equivalent daily dose; PRE = before surgery; POST = after surgery.

is a two-choice reaction time task requiring responses to left or right pointing arrows. The task consisted of a combination of Go and Stop trials. On Go trials, a left (or right) pointing green arrow was presented 500 ms after presentation of a black circular fixation point in the centre of a computer screen and participants had to respond as fast as possible by pressing a right or left key using the index or middle fingers of one hand. On Stop trials (25% of all trials), a stop signal (red cross) was presented after a variable stop signal delay following the green arrow. For each participant either the left or right pointing arrows were designated as the 'critical' direction. When a stop signal was presented following an arrow/go signal in the 'critical' direction, participants had to stop their response. In contrast, when a stop signal was presented following an arrow/go signal in the 'non-critical' direction, participants were instructed to ignore the stop signal and respond to the 'non-critical' go signal. Further details of the task are presented in the Supplementary material.

A variety of measures of interest were obtained, as shown in Table 2 and Supplementary Table 1. The key measures of interest were (i) speed of response initiation in both 'critical' and 'non-critical' Go reaction times; (ii) the SSRT, computed using the integration method, as a measure of how quickly a participant can inhibit a response on presentation of a stop signal (see Supplementary material for description of computation of SSRT); (iii) the time taken for conflict resolution on 'non-critical' stop signal trials or conflict-induced slowing obtained as the difference of 'non-critical' StopRespond reaction times and 'non-critical' Go reaction times; and (iv) the degree of proactive action restraint and adoption of a 'waiting strategy' on 'critical' Go trials in anticipation of the stop signal, reflected in the response delay effect, the difference between 'critical' and 'non-critical' Go reaction times.

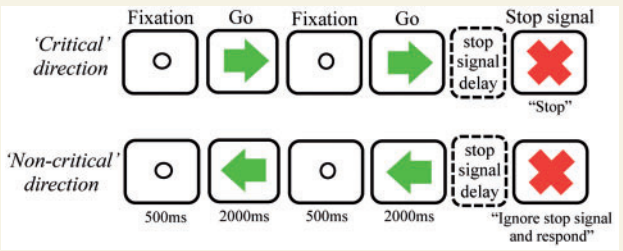

Figure 1 Diagram showing the 'critical' and 'non-critical' trials of the conditional stop signal task. On 'critical' direction trials, for example, arrows point to the right and participants must respond to the Go signal using their middle finger as fast as possible. For some trials, the stop signal is presented after a variable stop signal delay and the participant has to stop their response. For 'non-critical' direction trials, the stop signal is also presented after a variable stop signal delay in a proportion of trials, but participants are instructed to ignore the stop signal and respond to the go signal.

Drift diffusion model analysis

A drift-diffusion model (Ratcliff, 1978) was used to further investigate strategic effects on task performance. The drift-diffusion model assumes that responses are based on a noisy process of evidence accumulation and accounts for both the speed and accuracy of responses. The model contains three parameters of interest: boundary separation, drift rate, and non-decision time. Boundary separation refers to the distance between response thresholds for the two responses and allows participants to be more or less conservative. When boundary separation is high, more evidence is needed to make a decision, resulting in slower but more accurate responses. Drift rate refers to the speed at which evidence for the correct response accumulates; a high drift rate results in more accurate and speedier responses. Finally, non-decision time captures the time needed for other processes such as stimulus encoding and motor execution. The drift-diffusion model was estimated for each individual participant with Fast-DM (Voss and Voss, 2008), allowing the boundary separation (response threshold), drift rate, and non-decision time to differ between context ('critical' vs. 'non-critical'). Only the Go trials were analysed and Go trials immediately following StopRespond trials or incorrect Go trials were excluded to avoid any after-effects of response inhibition or post-error slowing (*cf.* Verbruggen and Logan, 2009*b*). Responses on the selected trials were coded as correct or incorrect, and the starting point of the

Table 2 Performance measures on the conditional stop signal reaction time task for contralesional hands of patients with Parkinson's disease with right or left subthalamotomy, and the dominant hands of unoperated patients and healthy controls participants

Trial description	Measure	Right subthalamotomy	Left subthalamotomy	Unoperated patients	Controls
'Critical' direction		*Contralesional hand*	*Contralesional hand*	*Dominant hand*	*Dominant hand*
Go	RT to go stimulus in 'critical' direction	514.11 (78.4)	541.97 (110.5)	622.58 (105.9)	508.02 (88.7)
StopInhibit	% correct inhibition	51%	50%	53%	53%
StopRespond	RT on failure to Stop trials	478.06 (90.7)	478.48 (83.9)	557.85 (111.5)	452.64 (59.7)
Go errors§	Number of omissions	1.90 (1.9)	1.91 (2.5)	5.72 (5.2)	0.56 (0.9)
Stop signal delay	Delay between Go and Stop signals	130.48 (79.3)	206.33 (118.5)	192.71 (78.6)	234.43 (88.1)
SSRT	RT	354.77 (77.9)	304.69 (68.9)	409.67 (106.7)	249.55 (49.4)
'Non-critical' direction					
Go	RT to Go stimulus in 'non-critical' direction	513.54 (100.4)	492.15 (105.8)	578.08 (88.7)	438.31 (44.3)
StopInhibit	% incorrect Inhibition	12.00 (6.3)	5.08 (5.0)	6.81 (6.8)	2.65 (3.8)
StopRespond	RT on trials with 'to be ignored' stop signal	634.00 (154.3)	604.01 (150.4)	782.19 (171.5)	556.21 (72.1)
Go errors§	Number of omissions	1.80 (2.25)	1.91 (2.5)	3.72 (2.6)	0.52 0(.7)
Conflict-induced slowing	'Non-critical' Stop Respond RT minus 'non-critical' Go RT	120.45 (87.5)	111.86 (66.2)	205.02 (104.0)	117.90 (56.1)
Other variables					
Go discrimination errors§	Number of errors	15.30 (11.7)	17.91 (16.0)	5.00 (5.0)	0.43 (0.6)
Response delay effect	'Critical' Go RT minus 'non-critical' Go RT	0.57 (38.4)	49.82 (52.3)	44.49 (79.6)	69.71 (64.7)

Standard deviations are given in brackets.
Stop signal delay (SSD) = the average stop-signal delay, computed from four staircases (see Supplementary material).
SSRT is computed for each patient by subtracting the mean SSD from the mean 'critical' Go reaction times.
Go omission errors = failure to respond on a Go trial.
Go discrimination errors = pressing the response key in the opposite direction indicated by the stimulus.
RT = reaction times.
§ = Mann-Whitney tests used.

diffusion process was fixed to lie halfway between the response thresholds.

Statistical analysis

Our main interest is the comparison of performance with the contralesional hand of the patients with right or left unilateral subthalamotomy to the dominant hand of the unoperated patients and control participants. For this, a series of one-way ANOVAs were completed on each reaction time measure obtained for the contralesional/dominant hands to compare participants' performance with Group (right subthalamotomy versus left subthalamotomy versus unoperated patients versus controls) as the between groups variable, with the Mini-Mental Score Examination and years of education on which the groups differed as covariates. Similar and separate analyses were completed to compare performance with the ipsi-lesional hand of the patients with right or left subthalamotomy and the non-dominant hand of the unoperated patients and healthy control participants again with Mini-Mental State Examination scores and years of education as covariates (Supplementary material). The results remained the same regardless of whether these covariates were included in the ANOVAs or not. *Post hoc* comparisons were type I error-corrected (Benjamini and Hochberg, 1995). Non-parametric tests were used to analyse the error data.

Results

The groups were well matched in age and clinical variables (Supplementary material). Unilateral right or left subthalamotomy significantly improved motor signs of patients as measured on the motor section (part III) of the Unified Parkinson's Disease Rating Scale ($P < 0.05$). As expected, this effect was mainly contralateral to the lesion side. Postoperatively, the operated patients had significantly lower Unified Parkinson's Disease Rating Scale-III scores and a reduction in medication relative to unoperated patients ($P < 0.05$; Supplementary material). No differences in Unified Parkinson's Disease Rating Scale-III were found between patients with right or left subthalamotomy after surgery (Supplementary material).

Effect of subthalamotomy on the conditional stop signal reaction time task

Table 2 shows the stop signal task results for the contralesional hand for the operated patients and the dominant hand of the unoperated patients and the healthy control participants the analysis of which is presented here. Supplementary Table 1 and Supplementary material 3 compare the ipsi-lesional hand of the operated patients and the non-dominant hand of the unoperated patients and controls.

'Critical' direction and reactive inhibition

As a result of the dynamic adjustment of the stop signal delay with the staircase procedure, all participants achieved probability of inhibition close to 50% (Table 2). Probability of correct inhibition was not significantly different across groups {Group [$F(3,59) = 0.27$, $P = 0.84$], Hand and Group × Hand interaction ($Fs < 1$)}. The mean stop signal delay showed a significant effect of Group [$F(3,59) = 2.98$, $P = 0.03$]. *Post hoc* comparisons showed that the patients with right subthalamotomy had significantly shorter stop signal delays than the controls [$t(31) = 2.79$, $P < 0.01$], but did not differ from the unoperated patients [$t(23) = 1.80$, $P = 0.08$]. None of the other comparisons were significant (Supplementary material).

For 'critical' Go trials, the main effect of Group was significant [$F(3,59) = 3.83$, $P = 0.01$] (Table 2 and Fig. 2). *Post hoc* comparisons revealed that patients with right subthalamotomy were significantly faster than the unoperated patients [$t(22) = 2.64$, $P = 0.01$], although not the case for patients with left subthalamotomy [$t(24) = -1.78$, $P = 0.08$]. The unoperated patients had significantly slower 'critical' Go reaction times than controls [$t(35) = -3.30$, $P = 0.002$]. None of the other comparisons were significant (Supplementary material).

The results of the 'critical' StopRespond reaction times (failed inhibition in Stop trials) are presented in the Supplementary material.

For SSRT, the main effect of Group was significant [$F(3,59) = 14.09$, $P < 0.001$] (Table 2 and Fig. 3). Patients with left subthalamotomy had significantly faster SSRTs compared to unoperated patients [$t(24) = 2.82$, $P = 0.01$]. Compared to controls, patients with right [$t(31) = 4.90$, $P < 0.001$] or left [$t(35) = 2.89$, $P < 0.01$] subthalamotomy as well as unoperated patients [$t(35) = 6.20$, $P < 0.001$] all had longer SSRTs. None of the other group differences were significant [$P > 0.05$].

Proactive action restraint

For the response delay effect difference score ('critical' Go – 'non-critical' Go reaction times) (Table 2 and Fig. 4), the main effect of Group was significant [$F(3,59) = 2.91$, $P = 0.04$]. *Post hoc* comparisons showed that patients with right subthalamotomy had significantly reduced response delay effect compared to controls [$t(22) = -3.12$, $P < 0.01$]. No other comparisons were significant (Supplementary material).

'Non-critical' direction and conflict-induced slowing

The results of the 'non-critical' Go and StopRespond reaction times (to be ignored stop signals) are presented in the Supplementary material.

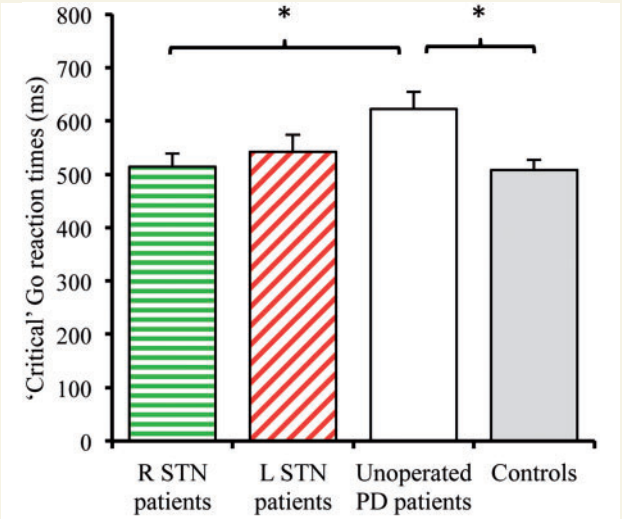

Figure 2 Mean 'critical' Go reaction times for operated patients with Parkinson's disease (PD) with right (R STN) or left (L STN) subthalamotomy, unoperated PD patients and control participants. The figure shows reaction times for the contralesional (operated patients) or dominant hands (unoperated patients and controls). Error bars indicate standard errors. Asterisks indicate $P < 0.05$.

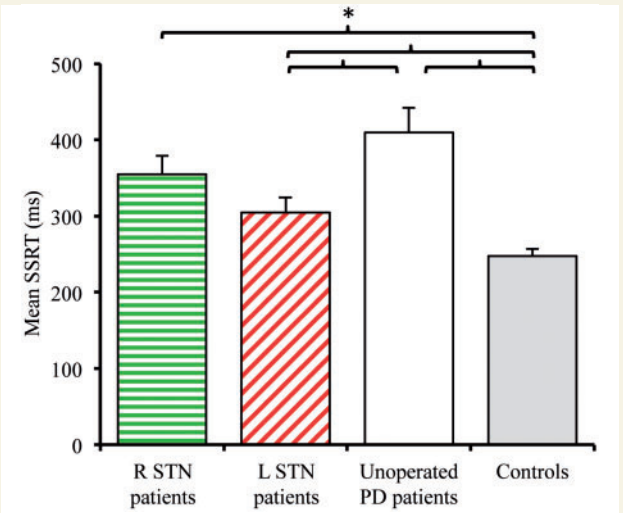

Figure 3 Stop signal reaction times (SSRT) for operated patients with Parkinson's disease (PD) with right (R STN) or left (L STN) subthalamotomy, unoperated PD patients and control participants. The figure shows results for the contralesional (operated patients) or dominant hands (unoperated patients and controls). Error bars indicate standard errors. Asterisks indicate $P < 0.05$.

For the measure of conflict-induced slowing (Table 2 and Fig. 5), the main effect of Group was significant [$F(3,59) = 3.57$, $P = 0.02$]. *Post hoc* comparisons showed that patients with right subthalamotomy had less conflict-induced slowing than the unoperated patients; the difference did not reach significance [$t(22) = 2.04$, $P = 0.06$] but it was significantly less for patients with left subthalamotomy compared to unoperated patients [$t(24) = 2.58$, $P = 0.01$]. The unoperated patients had significantly greater conflict-induced slowing than controls [$t(35) = 4.06$, $P < 0.01$], whereas for patients with right or left subthalamotomy conflict-induced slowing did not differ from controls [right: $t(31) = 0.10$, $P = 0.92$; left: $t(35) = -0.28$, $P = 0.77$].

Errors

For the discrimination errors between 'critical' and 'non-critical' directions (Table 2 and Fig. 6), a significant main effect of Group was found (Kruskal-Wallis, $\chi^2 = 36.36$, $P < 0.001$). *Post hoc* comparisons showed significantly more discrimination errors in patients with right ($U = 23.50$, $P = 0.02$) or left ($U = 29.00$, $P = 0.02$) subthalamotomy compared to unoperated patients. Furthermore, both right ($U = 1.00$, $P < 0.001$) and left ($U = 5.00$, $P < 0.001$) subthalamotomy groups had significantly higher discrimination errors than controls. Unoperated patients made significantly more discrimination errors compared with controls [$U = 41.00$, $P = 0.001$]. The two operated groups showed no significant differences from each other in terms of discrimination errors ($U = 57.50$, $P = 0.86$). The results for omission errors are presented in the Supplementary material.

Relative to the ipsilateral results, some of the effects of unilateral subthalamotomy were specific to the contralesional hand but others were observed for both hands. For the patients with right subthalamotomy, the significant group differences on the stop signal delay and the 'response delay effect', as well as their significantly faster 'critical' Go reaction times and significantly higher discrimination errors relative to unoperated patients were specific to the contralesional hand and not observed for the ipsi-lesional hand. In contrast, the effects of right or left unilateral subthalamotomy on SSRTs, 'non-critical' StopRespond reaction times, conflict-induced slowing, and omission errors were more global and observed for both the contralesional and ipsi-lesional hands.

Results of the drift diffusion model

The results of the three parameters derived from application of the diffusion model are presented in Fig. 7. The main parameter of interest is the boundary separation (response threshold), which showed a significant effect of Group [$F(3,59) = 3.35$, $P = 0.025$]. Unoperated patients had significantly higher response thresholds than controls ($P = 0.02$). In contrast, the response thresholds of the two operated groups did not differ from the controls ($P > 0.05$). There was also a trend towards the right subthalamotomy patients having a lower response threshold than the unoperated patients ($P = 0.09$). Response thresholds were higher in the 'critical' compared to the 'non-critical' context [$F(1,55) = 4.78$, $P = 0.033$]. The Group × Context interaction was also significant [$F(1,55) = 7.01$, $P < 0.001$], which was a result of the effect of context being significant for the controls [$t(22) = 5.03$, $P < 0.001$], but not for the unoperated or two operated patient groups (*P*-values > 0.05).

There was a significant Group effect on drift rate [$F(3,59) = 10.92$, $P < 0.001$]. *Post hoc* comparisons showed that controls had a significantly higher drift rate than unoperated patients ($P < 0.001$) and patients with left subthalamotomy

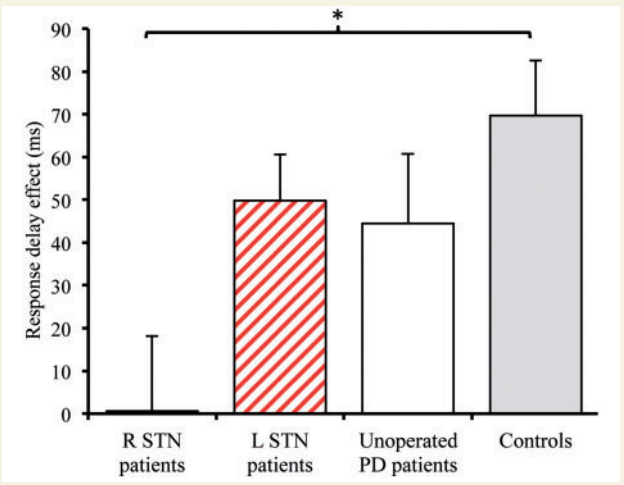

Figure 4 The 'response delay effect' for operated patients with Parkinson's disease (PD) with right (R STN) or left (L STN) subthalamotomy, unoperated PD patients and controls. The figure shows results for the contralesional (operated patients) or dominant hands (unoperated patients and controls). Error bars indicate standard errors. Asterisks indicate P < 0.05.

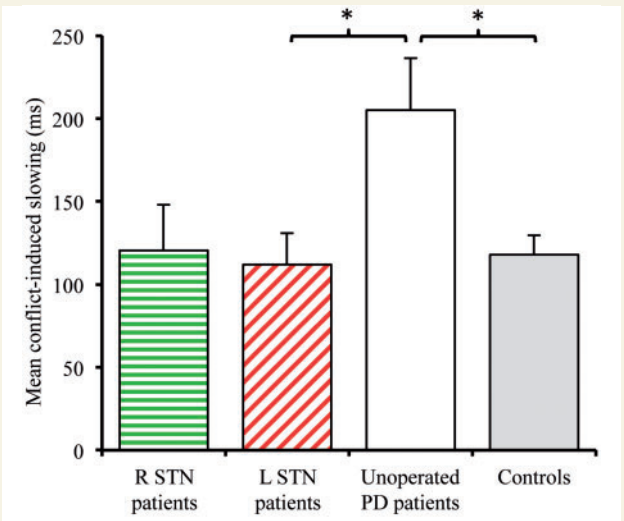

Figure 5 Mean conflict-induced slowing for operated patients with Parkinson's disease (PD) with right (R STN) or left (L STN) subthalamotomy, unoperated PD patients and control participants. The figure shows conflict-induced slowing for the contralesional (operated patients) or dominant hands (unoperated patients and controls). Error bars indicate standard errors. Asterisks indicate P < 0.05.

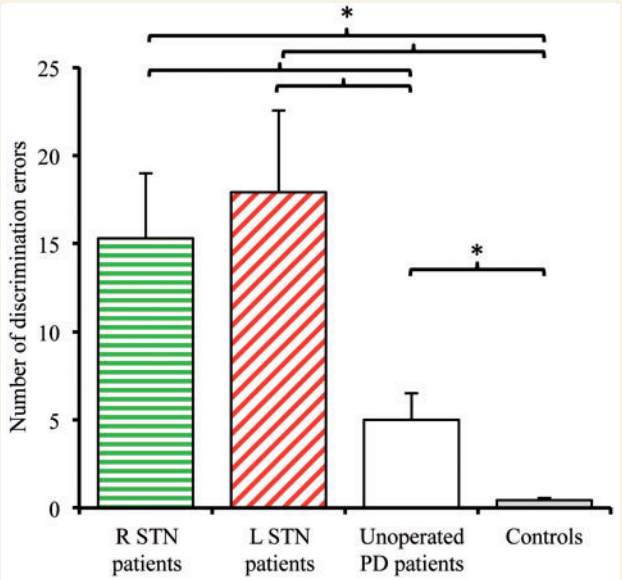

Figure 6 Mean discrimination errors for operated patients with Parkinson's disease (PD) with right (R STN) or left (L STN) subthalamotomy, unoperated PD patients and control participants. The figure shows discrimination errors for the contralesional (operated patients) or dominant hands (unoperated patients and controls). Error bars indicate standard errors. Asterisks indicate $P < 0.05$.

($P = 0.01$). The patients with right subthalamotomy had a significantly higher drift rate than the unoperated patients ($P = 0.01$), but did not differ from controls ($P = 0.46$). In addition, the drift rate was significantly higher in the 'non-critical' compared to the 'critical' context [$F(1,55) = 12.05$, $P < 0.001$]. The Group × Context interaction was not significant [$F(3,55) = 1.56$, $P = 0.21$].

There was a significant effect of Group on non-decision time [$F(3,59) = 2.96$, $P = 0.04$]. Unoperated patients had significantly longer non-decision time than controls ($P = 0.023$), but the other group differences were not significant (P-values > 0.05). Non-decision time was significantly higher in the 'critical' compared to the 'non-critical' context [$F(1,55) = 7.67$, $P = 0.008$]. There was also a significant Group × Context interaction for non-decision time [$F(1,55) = 2.81$, $P = 0.048$]. *Post hoc* tests showed that unoperated patients had a significantly longer non-decision time in the 'critical' context [$t(13) = 2.69$, $P = 0.019$], whereas the remaining groups showed no such differences [$P > 0.05$].

The results of the diffusion model analysis suggest that although control participants were able to strategically adjust their decision process between the 'critical' and 'non-critical' context, the patients were not able to do so. Compared with the control participants, evidence accumulation was significantly slower for unoperated patients who also had higher response thresholds, resulting in overall slower reaction times. In contrast, for the patients with right subthalamotomy, the response thresholds and rate of evidence accumulation (drift rate) did not differ from those of controls. However, as the patients with right subthalamotomy did not increase their response threshold in the 'critical' context, their responses were as fast as those of controls, but also more erroneous. These results confirm that relative to unoperated patients, right subthalamotomy influenced speed-accuracy trade-offs by altering the drift rate such that response thresholds were reached faster.

Discussion

Unilateral subthalamotomy was associated with significant improvement of the motor signs of patients with Parkinson's disease and reduction of dopaminergic medication similar to previous studies (Alvarez *et al.*, 2001, 2005, 2009; Patel *et al.*, 2003). Patients with right subthalamotomy had significantly faster 'critical' Go reaction times with their contralesional hand than unoperated patients and did not differ from controls, suggesting that their speed of response initiation was 'normalized' to the level of controls. However, accuracy was compromised as patients with either right or left-sided subthalamotomy made significantly more discrimination errors than unoperated patients and controls. This profile of enhanced speed coupled with greater discrimination errors suggests subthalamotomy had an impact on speed-accuracy trade-offs. This was confirmed by the application of the drift diffusion model to the Go trials data, which showed that although drift rate was significantly lower and response thresholds were significantly higher for unoperated patients relative to control participants, response thresholds of patients with right and left subthalamotomy did not differ from controls. In addition, drift rate for patients with right subthalamotomy was similar to controls and significantly higher than unoperated patients. Furthermore, only controls showed strategic modulation of response thresholds according to context—'critical' versus 'non-critical'—while the patients with Parkinson's disease failed to show this context-specific adjustment of response thresholds. In relation to the ability to inhibit responses, similar to unoperated patients, SSRTs of the operated patients were also significantly prolonged compared to healthy control participants. Patients with right subthalamotomy showed minimal proactive action restraint (response delay effect) when responding with the contralesional hand, and had significantly shorter stop signal delays than the other groups, indicating they could not engage in fast, late phase reactive inhibition when tested with the contralesional hand. Patients with right and left subthalamotomy showed significantly less conflict-induced slowing than unoperated patients and at a level comparable to controls. Overall, the effects on reactive inhibition (stop signal delay) and proactive action restraint (response delay effect) and drift rate were more striking for the group with right subthalamotomy when responding with their contralesional hand, and can be considered specific to this group as they were not observed for the patients with left subthalamotomy.

Thus, patients with right subthalamotomy were unable to engage in late phase inhibition required only for instances of long stop signal delays when tested with the contralesional hand. Similarly, patients with right subthalamotomy failed to show any notable 'response delay effect', again only with the contralesional hand, indicating their failure to engage in proactive action restraint during 'critical' Go trials. These effects were not observed when the same patients were tested with the ipsi-

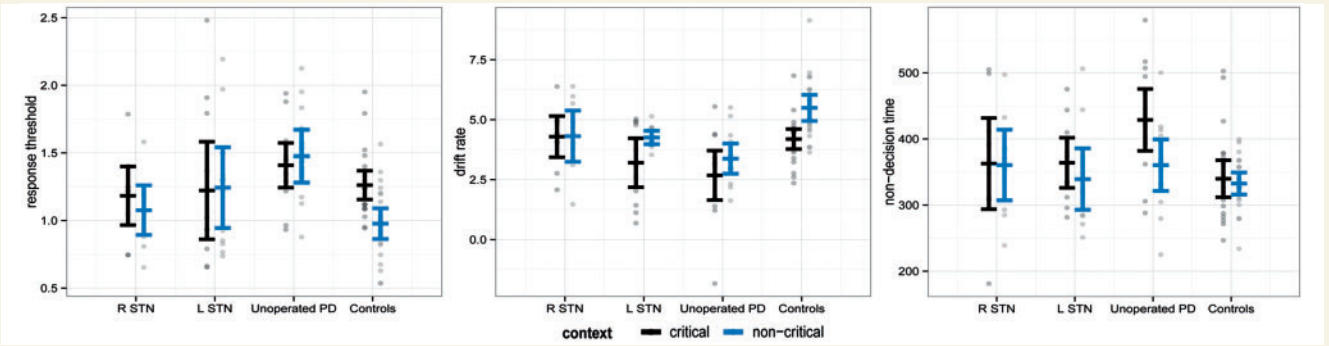

Figure 7 The response threshold (boundary separation), drift rate, and non-decision time parameters derived from application of the drift diffusion model for operated patients with Parkinson's disease (PD) with right (R STN) or left (L STN) subthalamotomy, unoperated PD patients and control participants. The figure shows the drift diffusion parameters for the contralesional (operated patients) or dominant hands (unoperated patients and controls). Error bars indicate 95% confidence intervals.

lesional hand. Furthermore, while there was a trend towards faster 'critical' Go reaction times and more discrimination errors for the ipsi-lesional hand, only observed when tested with the contralesional hand, the patients with right subthalamotomy had significantly faster 'critical' Go reaction times and made significantly more discrimination errors than unoperated patients, indicative of alteration of speed-accuracy trade-offs.

Right subthalamotomy altered the drift rate, response thresholds and speed-accuracy trade-offs

In real life situations, both fast and slow responses can be more or less adaptive depending on the context and specific circumstances. For example, when faced with a threat to survival (sight of predator or fast approaching car when crossing the road), fast responses are biologically adaptive; whereas in a context of conflict, slow responses to allow for accumulation and consideration of more relevant information are more optimal. In fact, it has been proposed the mammalian brain has systems for fast and slow thinking (Kahneman *et al.*, 2011) and fast-but-inaccurate as well as slow-but-accurate decision-making (Trimmer *et al.*, 2008). In speeded reaction time tasks such as the one used in the current study, participants are instructed to respond fast but accurately. Speed-accuracy trade-offs can occur when fast responses compromise accuracy, whereas more accurate responding is associated with slower responses. The speed–accuracy trade-off is considered to be related to the setting of a response threshold (Bogacz *et al.*, 2010). Raising the response threshold allows time for accumulation, integration and consideration of all relevant information before initiating a response and is associated with accurate but slow responses. In contrast, fast responses and increased errors ensue with lowering of the response threshold.

The basal ganglia operations through the direct and indirect striato-pallidal pathways (Gurney *et al.*, 2004; Lo and Wang, 2006; Forstmann *et al.*, 2008; Bogacz *et al.*, 2010) and STN in particular (Frank, 2006) have been proposed to play a role in setting the response threshold and in speed-accuracy trade-offs. This proposal has some experimental support from studies using behavioural, EEG recording, imaging and mathematical modelling (Frank *et al.*, 2007; Forstmann *et al.*, 2008; Cavanagh *et al.*, 2011; Mansfield *et al.*, 2011). In healthy individuals, Fortsmann *et al*. (2008) have shown that when acting under time pressure to respond quickly, the presupplementary motor area and anterior striatum become more activated in participants with a large decrease in response caution. In a further imaging study, Mansfield *et al*. (2011) used a task switching paradigm and expanded these findings by demonstrating that variability in activation of the pre-supplementary motor area was negatively associated with the response threshold for both repeat and switch trials. In contrast, striatal activation was negatively related to response thresholds specifically for repeat trials, whereas right STN activation was positively related to response thresholds for switch trials only. Thus, the information value of the cues (repeat/switch) influences the setting of response thresholds, and while the presupplementary motor area biases the striatum to set an appropriate response threshold in more liberal situations with minimal response conflict, the right STN plays a significant role in setting more conservative thresholds under situations of conflict.

Our findings of significantly faster Go reaction times and increased discrimination errors coupled with the results of the drift diffusion model showing that although unoperated patients had significantly higher response thresholds than control participants, the response thresholds of patients with subthalamotomy did not differ from those of controls, support a role for the STN in adjusting response thresholds. Furthermore, patients with right subthalamotomy had significantly higher drift rates than unoperated patients and similar to the drift rate of controls, suggesting that right subthalamotomy had increased and normalized the rate of information accumulation in these operated patients with Parkinson's disease, probably explaining their overall faster Go reactions times. However, although healthy controls showed strategic modulation of response thresholds according to context, patients with subthalamotomy failed to show such context-specific adjustment to raise response thresholds in the 'critical' context as seen for controls and as a result, they made more errors.

As a result of the context-independent lowering of response thresholds by unilateral subthalamotomy, the response delay effect that reflects adoption of a 'waiting strategy' on 'critical' Go trials was significantly reduced for the contralesional hand in the group with right subthalamotomy relative to healthy controls and was less than unoperated patients. Similarly, as a consequence of lowered response thresholds, subthalamotomy provoked significantly less conflict-induced slowing in situations of conflict on 'non-critical' trials, when a stop signal was presented but had to be ignored, relative to unoperated patients, and at a level equivalent to healthy controls. In effect, on this task, subthalamotomy 'normalized' the excessive conflict-induced slowing observed for unoperated patients and reduced it to the level shown by healthy controls. As discussed below, this reduction and 'normalization' of conflict-induced slowing in the two operated patient groups is an example of 'adaptive' speeding on the conflict trials of our task, which directly resulted from a general lowering of the response threshold observed for subthalamotomy.

Patients with right subthalamotomy showed no proactive action restraint with the contralesional hand

As previously documented (Aron *et al.*, 2007; Chikazoe *et al.*, 2009; Verbruggen and Logan, 2009*a*, *b*; Jahfari *et al.*, 2010), when stop signals are expected, participants engage proactive response control strategies, as a result of which response thresholds are raised to slow down Go reaction times and increase the likelihood of stopping. In our study, based on the task instructions, when presented with an arrow in the 'non-critical' direction participants knew that they had to respond anyway even if a stop signal was subsequently presented and therefore, fast reaction times were appropriate on these trials. In contrast, on trials with an arrow presented in the 'critical' direction, there was a possibility that a stop signal would follow the go signal, in which case the response would need to be inhibited. Therefore, on 'critical' trials when participants were aware they might have to stop their response in a proportion of trials, they slowed down their Go reaction times. This 'anticipatory' or 'strategic' slowing of Go reaction times in the context of 'critical' Go trials where a proportion of the responses would have to be subsequently stopped, represents proactive action restraint.

Although contrary to instructions, this 'waiting strategy' on 'critical' Go trials adopted by controls as well as unoperated patients can be considered as an optimal approach in this task. This is because the common behavioural consequence of such proactive action restraint is that if a stop signal is presented, participants are more likely to stop. Patients with right subthalamotomy, when responding with their contralesional hand, showed a minimal response delay effect, indicative of poor proactive inhibitory control. This significantly reduced response delay effect relative to controls is a consequence of the general and context-independent lowering of the response threshold for patients with right subthalamotomy. This inability to adopt a 'waiting strategy' by patients with right subthalamotomy may reflect some degree of impulsivity, as delay aversion is a characteristic of impulsive individuals.

Right subthalamotomy interfered with fast and late inhibition of the motor response

Whereas 'critical' Go reaction times were significantly faster for patients with right subthalamotomy than unoperated patients, the SSRTs of these two patient groups did not differ from each other and were both significantly slower than the SSRTs of healthy control participants. Furthermore, patients with right subthalamotomy only achieved successful inhibition of their responses on 'critical' Stop trials with mean stop signal delays that were significantly shorter/easier than those of unoperated patients and healthy controls. Inhibition of the response is more difficult with longer stop signal delays as with a longer interval between go and stop signals, the Go response is more likely to be already initiated and closer to execution, and is therefore more difficult to stop. Patients with right subthalamotomy could only inhibit the response with significantly shorter mean stop signal delays when the Go response had not yet been triggered and was being planned rather than close to execution. Aron and Poldrack (2006) found that STN activation on successful Stop trials was greater with longer stop signal delays, indicating the STN was more engaged in successful inhibition in trials when the Go process was closer to execution. This suggests a greater role for the STN in the late phases of inhibition, when the Go response has already been triggered and is close to execution, which requires fast inhibition to prevent execution of the response.

Our results indicate right subthalamotomy specifically interfered with the late inhibition of the response when it was already close to execution, suggesting patients with right subthalamotomy could not engage in 'fast' inhibition of their responses when a stop signal was presented. We have previously reported a similar effect when patients were tested with STN stimulation on (Obeso *et al.*, 2013*b*), indicating that both right subthalamotomy and bilateral deep brain stimulation of the STN interfere with the ability to engage in fast and late inhibition of a motor response.

Subthalamotomy improved/reduced conflict-induced slowing

As expected, the 'non-critical' StopRespond reaction times were the slowest reaction times in this task for healthy controls, operated and unoperated Parkinson's disease groups, which suggests this conflict was operational for all participants. However, the magnitude of this conflict, as indexed by the conflict-induced slowing measure, was significantly greater for the unoperated patients as the two groups with subthalamotomy showed 'normalization' of conflict-induced slowing to a level similar to controls. This significant reduction of conflict-induced slowing in the two operated groups, in situations where unoperated patients experienced considerable slowing, is further evidence for the lowering of response thresholds with subthalamotomy as confirmed by the results of the drift diffusion model.

The precise nature of an experimental 'conflict' task determines the specific type of conflict faced by participants, which in turn determines the optimal strategies for conflict resolution for each task. For example, on the Stroop interference task, the optimal strategy for avoiding errors when naming the colour of ink of colour words printed in incongruent ink is to slow down. With deep brain stimulation of the STN, patients make significantly more errors on the Stroop interference task than with deep brain stimulation off (Jahanshahi *et al.*, 2000; Witt *et al.*, 2004). Similarly, on the probabilistic decision-making task used by Frank *et al*. (2007), the optimal conflict resolution strategy evident in the behaviour of the healthy control participants and patients with Parkinson's disease with deep brain stimulation off, was to slow down reaction times on 'win–win trials', to take time to reflect before responding. Patients with Parkinson's disease with deep brain stimulation did not show this optimal pattern, being more impulsive and had significantly faster reaction times on these trials (Frank *et al*., 2007). In our conditional stop signal task, a conflict between stopping and responding occurred on the 'non-critical' StopRespond trials, when a stop signal was presented but participants were instructed to ignore it and respond to the go signal. As evident from the unoperated patient group in the current study and past samples of unoperated patients assessed by us on the same task (Obeso *et al.*, 2011*a*, *b*, 2013*b*), these patients were more susceptible to and showed greater conflict-induced slowing than age-matched healthy controls. In contrast, for patients who had unilateral subthalamotomy, the magnitude of the conflict-induced slowing was significantly less than for the unoperated patients and equivalent to that seen in healthy controls, suggesting 'normalization' of conflict-induced slowing by unilateral therapeutic STN lesions. In our task, unilateral reduction of STN overactivity in patients with Parkinson's disease through surgery resulted in improvement and reduction of conflict-induced slowing. Thus, speeding up of responses in conflict situations was observed in patients with Parkinson's disease with unilateral subthalamotomy in the present task and in the probabilistic selection task in patients with STN stimulation on (Frank *et al.*, 2007; Cavanagh *et al.*, 2011). The difference was that these observed changes were 'adaptive' and 'maladaptive' effects of the STN 'manipulation' relative to the behaviour of healthy controls on these respective studies.

The subthalamic nucleus as a major node of the inhibitory network

Consistent with imaging results suggesting successful inhibition is achieved through activation of a right lateralized network of inferior frontal gyrus, pre-supplementary motor area, caudate and STN regardless of whether responding with the right or left hands (Garavan *et al.*, 1999; Rubia *et al.*, 2003; Aron and Poldrack, 2006; Aron *et al.*, 2007; Li *et al.*, 2008; Xue *et al.*, 2008; Duann *et al.*, 2009; Hampshire *et al.*, 2010; Obeso *et al.*, 2013*a*), our results show that in patients with Parkinson's disease, right subthalamotomy was associated with greater disruption of inhibitory processing, namely an inability to adopt proactive action restraint strategies and to engage in fast and late inhibition of the response, which were not seen in the group with left subthalamotomy.

All aspects of the current results indicate that therapeutic right-sided lesioning of the STN, in particular, produced effects on reactive and proactive inhibition and conflict-induced slowing that are all highly consistent with an increased drift rate and a lowering of response thresholds, as confirmed by the results of the drift diffusion model. As subthalamotomy disrupts the hyperdirect and indirect, but not the direct pathway (Obeso *et al.*, 2009), the effects observed here on alteration of response thresholds and speed-accuracy trade-offs should be mediated by the former two pathways. This effect appears to interfere with some higher order motor control processes that are mediated by the cortico-subthalamic inhibitory network. The reduced proactive inhibitory control, the performance marked by more errors, and the prolongation of SSRT and the inability to engage in fast and late inhibition observed here in patients with right subthalamotomy are examples of such adverse effects of interrupting the STN inhibitory network in Parkinson's disease.

Conclusion

The outcome of lesioning a specific brain area is arguably the most radical approach for investigating specific functions of that region and its connections in humans. Our results therefore, provide the strongest evidence to date that therapeutic unilateral lesioning of the STN altered the setting of response thresholds and speed-accuracy trade-offs in Parkinson's disease. The results also support a role of the right STN in inhibitory control and conflict resolution, achieved through resetting of response thresholds and adjustment of speed-accuracy trade-offs. This is in keeping with the idea that STN-cortical dysfunction is likely to play a critical role in the origin of impulse control disorders in Parkinson's disease induced by dopaminergic drugs (Rodriguez-Oroz *et al.*, 2011).

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Supplementary material

Supplementary material is available at *Brain* online.

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