Stimulation of the Subthalamic Region Facilitates the Selection and Inhibition of Motor Responses in Parkinson's Disease

Wery P. M. van den Wildenberg[1], Geert J. M. van Boxtel[2], Maurits W. van der Molen[1], D. Andries Bosch[1], Johannes D. Speelman[1], and Cornelis H. M. Brunia[2]

Abstract

■ The aim of the present study was to specify the involvement of the basal ganglia in motor response selection and response inhibition. Two samples were studied. The first sample consisted of patients diagnosed with Parkinson's disease (PD) who received deep-brain stimulation (DBS) of the subthalamic nucleus (STN). The second sample consisted of patients who received DBS for the treatment of PD or essential tremor (ET) in the ventral intermediate nucleus of the thalamus (Vim). Stop-signal task and go/no-go task performances were studied in both groups. Both groups performed these tasks with (*on* stimulation) and without (*off* stimulation) DBS to address the question of whether stimulation is effective in improving choice reaction time (RT) and stop-signal RT. The results show that DBS of the STN was associated with significantly enhanced inhibitory control, as indicated by shorter stop-signal RTs. An additional finding is that DBS of the STN led to significantly shorter choice RT. The effects of DBS on responding and response inhibition were functionally independent. Although DBS of the Vim did not systematically affect task performance in patients with ET, a subgroup of Vim-stimulated PD patients showed enhanced stop-signal RTs in *on* stimulation versus *off* stimulation. This result suggests that the change in performance to stop signals may not be directly related to STN function, but rather results from a change in PD function due to DBS in general. The findings are discussed in terms of current functional and neurobiological models that relate basal ganglia function to the selection and inhibition of motor responses. ■

INTRODUCTION

Response inhibition, or the ability to stop ongoing actions, is an important characteristic of cognitive control and flexibility (Logan, 1994) that relies, in large part, on the prefrontal cortex (PFC) in interactions with other brain regions (Aron, Fletcher, Bullmore, Sahakian, & Robbins, 2003; Miller & Cohen, 2001). Functional imaging studies indicated the involvement of the PFC in response inhibition by comparing trials on which subjects executed a speeded response to ''go'' signals with trials on which subjects were required to withhold their response upon a ''no-go'' (Kelly et al., 2004; Garavan, Ross, & Stein, 1999) or a ''stop'' signal (Rubia, Brammer, & Taylor, 2003; Rubia et al., 2001). In the *stop-signal paradigm*, subjects are typically asked to perform a visual discrimination task that requires a fast button-press response with the right or the left index finger according to the identity of one of two choice signals (for a review, see Logan, 1994). On a small proportion of those trials, the onset of the choice signal is followed by a stop signal, generally a tone, instructing the subjects to refrain from responding (*stop trials*).

Stop-signal task provides a direct behavioral assessment of the ability to stop a planned or an ongoing motor response in a voluntary fashion. The stop task yields an estimate of the duration of the covert response-inhibition process (i.e., the stop-signal reaction time [RT]) (see Figure 1). This dependent measure of stop performance has also yielded evidence for the involvement of the PFC in response inhibition. A recent study of stop-signal RTs obtained from patients with lesions in the PFC indicated that the degree of damage within the right inferior frontal gyrus, more than other regions within the PFC, is critically related to impaired response inhibition (Aron, Fletcher, et al., 2003). Rieger, Gauggel, and Burmeister (2003) examined stop-task performance of patients with frontal lesions, patients with lesions outside the frontal cortex, patients with lesions in the basal ganglia, and orthopedic controls. Relative to controls, patients with right frontal or bilateral frontal lesions showed inhibitory deficits. Interestingly, patients with

[1]Universiteit van Amsterdam, [2]Tilburg University

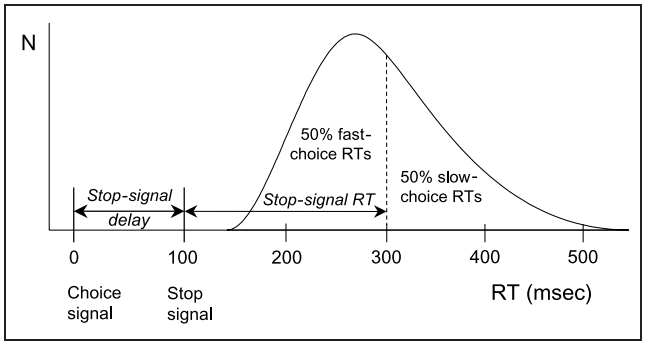

Figure 1. Estimation of stop-signal RT according to a race model (Logan, 1994; Logan & Cowan, 1984). The curve depicts the distribution of RTs on choice trials (trials without a stop signal) representing the finishing times of the response processes. Assuming independence of choice and stop processes, the finishing time of the stop process bisects the choice RT distribution. Given that the button-press response could be withheld in 50% of all stop trials, stop-signal RT (200 msec) is calculated by subtracting the mean stop-signal delay (100 msec) from the median choice RT (300 msec).

cerebrovascular lesions in the basal ganglia were also significantly slower in inhibiting their responses (Rieger et al., 2003) Finally, Gauggel, Rieger, and Feghoff (2004) examined stop-signal inhibition in patients with Parkinson's disease (PD; Dauer & Przedborski, 2003; Obeso et al., 2000) and in controls. They observed that patients with PD responded more slowly on *go trials* and inhibited more slowly to the stop signal. Interestingly, the slower inhibition to the stop signal was independent of the slowing on go trials, indicating that the slowing of stop-signal inhibition in Parkinson patients cannot be explained in terms of global slowing.

Recent studies that focused on patient groups suggest that the basal ganglia are implicated in varieties of inhibition (Seiss & Praamstra, 2004; Aron, Schlaghecken, et al., 2003; Praamstra & Plat, 2001). The findings of these studies converge on the notion that the basal ganglia play a critical role in the selection of required responses and in the suppression of responses that are incorrect or no longer relevant (see also review in Mink, 1996). The present experiment sought to further examine the role of the basal ganglia in stop-signal inhibition. The current approach differs from previous studies with similar aims in that we used a within-subject design instead of a between-subject design in which performance of clinical groups is compared with that of controls(e.g., Gauggel et al., 2004; Seiss & Praamstra 2004; Aron, Fletcher, et al., 2003; Aron, Schlaghecken, et al., 2003; Rieger et al., 2003). Participants in the current study consisted of a group of patients previously implanted with electrodes in the region of the subthalamic nucleus (STN) to treat symptoms of PD, such as bradykinesia and tremor (Benabid, 2003), by electrical deep-brain stimulation (DBS) (Lang, 2000; Limousin et al., 1995). DBS results in a dramatic and stable improvement of a patient's clinical condition (Krack et al., 2003). Metabolic and neurophysiological techniques typically indicate that DBS in the STN region improves cortical motor functions in several brain regions, including the PFC (Gerschlager et al., 1999), supplementary motor area (SMA; Ceballos-Baumann et al., 1999; Limousin et al., 1997), premotor cortex, and primary motor cortex (Däuper et al., 2002). It remains controversial whether these improved cortical motor functions are mediated by restoration of basal ganglia–cortex interactions (e.g., Williams et al., 2002; cf. Marsden & Obeso, 1994).

Implanted brain electrodes allowed the examination of a patient's ability to activate and initiate motor responses, and to stop planned actions under *on* and *off* stimulation conditions. Within-subject comparisons employed in the current study, with each patient serving as one's own control, reveal the functional contribution of the stimulated brain region to task performance. If the behavior under investigation depends critically on the function of the basal ganglia, then modulating basal ganglia function by switching the STN electrodes on and off should systematically alter a patient's task performance.

Next to the STN-stimulated group, we also included a group of patients who have been treated with electrodes in a region outside the basal ganglia, namely, the ventral intermediate nucleus of the thalamus (Vim) (Benabid et al., 1996). Patients diagnosed with essential tremor (ET) benefit from Vim stimulation because it alleviates tremor symptoms, presumably via thalamic connections to the primary motor cortex (Jones, 1997). From a clinical point of view, both STN and thalamic DBS aim at improvement of motor functions, although the etiology and pathophysiology of Vim- and STN-stimulated groups are notably different. Nevertheless, contrasting the within-subject effects of Vim and STN stimulation is meaningful because DBS of the Vim neural circuitry primarily bypasses the basal ganglia.

The experiment comprised a stop-signal task designed to assess the ability to inhibit planned actions when instructed to do so and a version of the go/no-go task to investigate the selection and activation of motor responses. Based on previous reports that have related basal ganglia dysfunctions with impaired response inhibition (Gauggel et al., 2004; Seiss & Praamstra, 2004; Aron, Schlaghecken, et al., 2003; Rieger et al., 2003), we expected a modulation of basal ganglia function by means of DBS in the STN region to affect stopping latencies in the stimulation-on conditions, compared to stimulation-off conditions (see also Temel et al., 2005; Baunez et al., 2001). To our knowledge, this hypothesis has yet to be put to a direct test.

Besides response latencies to stop signals, responses on choice trials in the stop task (i.e., trials without a stop signal) also provide an informative index of voluntary motor control. Response latencies to choice signals

represent the total time of the processes involved in the motor response, including signal detection and discrimination, response selection, and response execution. Given the clinical reports of alleviated akinesia and rigidity (Limousin et al., 1995), and experimental evidence of enhanced response speed on various RT tasks (Hershey et al., 2004; Schroeder et al., 2002; Jahanshahi et al., 2000; Ceballos-Baumann et al., 1999), one would expect the DBS of the STN to improve choice RT. To test whether the anticipated beneficial effects of STN stimulation on responding extend to premovement processing rather than being confined to improved movement time (e.g., reversal of bradykinesia), we also probed the reaction process with a go/no-go task. In this task, subjects were required to respond exclusively with the same hand to a category of stimuli designated as *go signals*, and to withhold responding to *no-go signals*. Choice and go reaction tasks are identical, with the exception of the response selection stage, which is included in choice reactions, but not in go reactions (Gottsdanker & Schragg, 1985; Donders, 1868/1969). A choice response involves a selection between two overt motor response alternatives (i.e., choosing between moving the left index finger and moving the right index finger). A go response does not involve choosing between two overt response alternatives because the response set involves one hand only. Comparing choice reactions in the stop-signal task with go responses in the go/no-go task allows a within-subject assessment of the effects of brain stimulation on the efficiency of the response selection stage of the reaction process (Miller & Low, 2001).

METHODS

Patients and Surgery

Our study included 17 patients (10 men, 7 women; mean age, 58.4 ± 2.0 years) treated with DBS in the STN, and 15 patients (12 men, 3 women; mean age, 62.7 ± 2.1 years) with DBS in the Vim. The two patient groups did not differ significantly in terms of age, $F(1,30) = 2.16, p = .15, ns$. Summaries of relevant patient details can be found in Tables 1 and 2. All subjects gave their written informed consent prior to participation, in accordance with the Declaration of Helsinki, and the study was approved by the local research ethics committee. All patients remained on their normal medication throughout the study.

Table 1. STN Patient Information

					Years Since			UPDRS-3		Hoehn–Yahr		Choice RT		Go RT		Stop-signal RT	
No.	Age (Years)	Sex	MMSE	Diagnosis	Onset	Surgery	DBS	Off	On	Off	On	Off	On	Off	On	Off	On
1	53	M	28	PD	9	1	Bilateral	31	21	3	2	666	650	603	561	317	253
2	63	F	30	PD	12	1	Bilateral	53	27	5	4	960	911	453	482	237	216
3	56	M	30	PD	12	5	Right	20	7	2	1	619	495	406	392	298	231
4	62	F	25	PD	12	1	Bilateral	64	25	5	2.5	575	571	468	458	261	258
5	47	F	29	PD	11	1	Left	31	21	3	2.5	692	538	433	450	285	228
6	66	F	–	PD	13	1	Bilateral	–	–	–	–	704	607	535	481	264	257
7	68	F	–	PD	12	2	Bilateral	39	14	3	2.5	753	780	575	460	245	253
8	56	M	30	PD	12	2	Bilateral	–	–	–	–	859	730	706	576	372	262
9	63	M	–	PD	12	4	Bilateral	66	41	4	3	658	674	472	566	318	339
10	58	M	30	PD	13	1	Bilateral	26	12	3	2.5	671	578	498	551	319	260
11	56	F	29	PD	20	2	Bilateral	63	21	5	2.5	446	458	374	410	212	204
12	55	M	28	PD	20	1	Bilateral	30	12	3	2.5	458	525	424	403	240	222
13	62	M	29	PD	16	1	Bilateral	50	17	5	2.5	715	681	576	570	428	284
14	53	M	30	PD	14	2	Bilateral	48	14	3	2.5	679	517	479	421	239	219
15	59	M	27	PD	11	1	Bilateral	32	10	3	2.5	649	538	562	450	274	270
16	61	F	29	PD	14	4	Bilateral	34	38	4	3	692	745	572	608	282	227
17	54	M	29	PD	6	1	Bilateral	25	14	3	2.5	525	517	414	419	247	234

''On'' and ''off'' scores of the UPDRS-3 and the Hoehn–Yahr scales refer to presurgical on and off states in PD. On and off with respect to choice RT, go RT, and stop-signal RT refer to brain stimulation conditions. STN = subthalamic nucleus; MMSE = Mini Mental State Examination; DBS = deep-brain stimulation; UPDRS = Unified Parkinson's Disease Rating Scale; RT = reaction time; M = male; F = female; PD = Parkinson's disease.

Table 2. Vim Patient Information

				Years Since			ET Rating Scale		Choice RT		Go RT		Stop-signal RT	
No.	*Age (Years)*	*Sex*	*Diagnosis*	*Onset*	*Surgery*	*DBS*	*Pre*	*Post*	*Off*	*On*	*Off*	*On*	*Off*	*On*
1	68	F	PD	8	3	Left	–	–	496	483	448	447	273	264
2	68	M	ET	16	1	Bilateral	–	–	836	838	472	455	234	269
3	73	F	ET	24	5	Bilateral	15	8	531	516	485	461	296	338
4	62	M	ET	19	4	Bilateral	61	50	580	637	405	427	296	283
5	56	M	ET	6	4	Bilateral	53	31	645	578	554	485	224	243
6	74	M	ET	9	4	Bilateral	72	42	683	708	501	465	234	203
7	68	M	ET	24	4	Right	23	13	564	641	449	481	309	274
8	53	F	ET	14	4	Right	79	50	644	658	509	641	298	275
9	32	M	ET	4	4	Bilateral	28	16	462	517	377	398	227	270
10	71	M	PD	18	2	Left	–	–	573	529	508	451	339	269
11	68	M	ET	7	1	Right	–	–	587	572	399	414	180	215
12	63	M	ET	12	1	Bilateral	–	–	652	619	417	402	253	229
13	59	M	PD	11	1	Right	–	–	577	565	537	527	248	225
14	69	M	PD	8	8	Bilateral	–	–	579	484	406	376	254	218
15	56	M	PD	12	6	Left	–	–	495	514	392	391	231	226

''On'' and ''off'' with respect to choice RT, go RT, and stop-signal RT refer to brain stimulation conditions. Vim = ventral intermediate nucleus of the thalamus; DBS = deep-brain stimulation; ET = essential tremor; Pre = presurgery; Post = 6 months postsurgery; RT = reaction time; M = male; F = female; PD = Parkinson's disease.

The STN macroelectrode used was model 3389 (Medtronic Ltd., Minneapolis, MN), with four platinum–iridium cylindrical surfaces (1.27 mm diameter, 1.5 mm length) and a center-to-center separation of 2 mm. Contact 0 was the most caudal, and contact 3 was the most rostral. Macroelectrodes were inserted after ventriculography and preoperative magnetic resonance imaging had identified the STN. Intended coordinates at the tip of contact 0 were 12 mm from the midline, 0–2 mm behind the midcommissural point, and 4–5 mm below the anterior–posterior commissure line (see also Williams et al., 2003). Because the electrical field of stimulation has a diameter of 4–5 mm, the immediate surrounding tissue (the STN region) is also implied when referring to stimulation of the STN. Intraoperative stimulation confirmed optimal placement of electrodes, similar to other published methods (Starr et al., 2002; Limousin et al., 1995). Stimulation parameters had been set individually for optimal clinical benefit.

In Vim patients, the position of the Vim relative to the intercommissural line was identified by positive contrast ventriculography, according to the stereotactic atlas of Schaltenbrand and Wahren (1977). Intraoperatively, macroelectrodes were applied to identify the optimal position for the electrode. The Vim site selected was the one in which the effect of the lowest-threshold high-frequency stimulation (130 Hz) was maximal, and in which neither high-frequency nor low-frequency stimulation (2 Hz) produced side effects. Once the site had been selected, a four-contact electrode (model 3387, Medtronic Ltd.) was implanted, with the second distal contact placed at the target site (see also Schuurman et al., 2000).

Procedure

Left- and right-hand responses were collected from response buttons that were positioned on a table in front of the patient, in such a manner that both forearms were comfortably supported. In the stop task, participants were required to respond quickly and accurately with the corresponding index finger to the direction of a right- or a left-pointing green arrow (choice trials). The arrow signal consisted of a rectangle (2 × 1 cm) and a triangle (1.5 cm height × 2 cm base). Arrows were presented pseudorandomly, with the constraint that they signaled left- and right-hand responses equally often. Arrow presentation was response-terminated. Intervals between subsequent choice signals varied randomly but equiprobably, from 1250 to 1750 msec in steps of 125 msec. During these interstimulus intervals, a white fixation point (3 × 3 mm) was presented. The green arrow changed to red on 30% of the trials, upon

which the choice response had to be aborted (stop trials). A staircase-tracking procedure dynamically adjusted the delay between the onset of the choice signal and the onset of the stop signal for each hand separately to control inhibition probability (Levitt, 1971). After a successfully inhibited stop trial, stop-signal delay in the next stop trial increased by 50 msec, whereas the stop-signal delay decreased by 50 msec in the next stop trial when the participant was unable to stop. This algorithm ensured that motor actions were successfully inhibited in about half of the stop trials, which yielded accurate estimates of stop-signal RT (Band, van der Molen, & Logan, 2003; see Figure 1). It compensated for differences in choice RT between participants, between stimulation conditions, and between the left and right hands. The stop task consisted of five blocks of 104 trials, the first of which served as a practice block to obtain stable performance.

In the go/no-go task, subjects responded with one index finger to go signals only. The size and probability of left- and right-pointing green arrows ($p = .50$), as well as intertrial intervals, were similar to the ones employed in the stop-signal task. In the left-hand version of the go/no-go task, participants responded quickly with the left index finger to arrows pointing to the left (go trials), but refrained from responding to arrows pointing to the right (no-go trials). Hands and instructions were reversed in the right-hand version of the no/no-go task. Both versions of the go/no-go task comprised three blocks of 100 trials, with each first block serving as a practice block.

Participants completed all tasks in two consecutive sessions, one with DBS (on condition) and one without DBS (off condition). A half-hour break between stimulation conditions ensured that tremors had subsided after inducing stimulation and that there was no rebound-exaggerated impairment after terminating stimulation. The order of tasks, go/no-go versions, and on and off stimulation conditions was counterbalanced across participants.

Data Analyses

Stop-signal RTs were estimated individually in each stimulation condition for each hand separately according to a race model (Logan, 1994; Logan & Cowan, 1984). According to the independence assumption of the race model, the stop and response processes operate independently. The start of the stop process is under experimental control by the stop-signal delay, but the finishing time of the stop process has to be inferred from the observed distribution of choice RTs (i.e., trials without a stop signal). The finishing time of the stop process bisects the choice RT distribution, with the left side of the distribution (representing fast responses) matching the distribution of RTs on stop trials that escape inhibition (see Figure 1). The right part represents slow choice RTs that would be inhibited because the stop process finished before. Because the dynamic tracking of the stop-signal delay assured successful response inhibition on half of the stop trials, the finishing time of the stop process was equal to median choice RT. Finally, mean stop-signal delay is subtracted from this finishing time to obtain an estimate of stop-signal RT (see Logan, 1994). Stop-signal tracking based on inhibition rates of approximately 50% provides stop latency estimates that are derived from the center of the choice RT distribution and are relatively insensitive to violations of the assumptions of the race model (e.g., Band et al., 2003; Logan, Schachar, & Tannock, 1997).

Repeated measures analyses of variance (ANOVAs) were performed on median RT on correct trials, on stop-signal RT, and on square root error percentages with within-subject factor Stimulation (on vs. off) and between-subjects factor Region (STN vs. Vim stimulation). Additional analyses were performed on the subgroup of five Vim-stimulated patients diagnosed with PD (Vim PD).

None of the dependent measures differed between left and right responses, so the Results section reports analyses of data that were collapsed across hands. Because experimental tasks involved both hands, one could argue against the inclusion of unilateral DBS patients. Therefore, all analyses reported in Results were redone twice—first, including bilateral patients only (i.e., removing 2 of 17 in the STN group, and 7 of 15 in the Vim group), and second, including bilaterally and unilaterally stimulated patients; however, in the latter case, only the data from the response hand that corresponded to the side of DBS were included. The patterns of results obtained in these two analyses are similar to the ones reported in Results.

RESULTS

Stop-signal Task

Although the primary focus is on within-subject comparisons of task performance between stimulation conditions, we explored main group differences by means of an omnibus ANOVA. This analysis showed comparable choice RTs for the two patient groups, which were 642 ± 26 msec (median RT ± *SEM*) for STN-targeted patients and 592 ± 28 msec for Vim-targeted patients, $F(1,30) = 1.76$, $p = .19$. Similarly, overall stop-signal RTs did not differ between STN and Vim groups (266 ± 9 and 256 ± 10 msec, respectively; $F < 1$, *ns*). More important, the effects of brain stimulation differed between groups, as expressed by Region × Stimulation interactions for choice RT, $F(1,30) = 4.03$, $p = .05$, and for stop-signal RT, $F(1,30) = 4.75$, $p = .04$. Because our primary focus was on within-subject comparisons, the results are presented separately for STN- and Vim-targeted patients.

Choice Trials

Analyses of choice RT revealed that STN patients responded faster to choice signals in the on condition (619 ± 29 msec) than in the off condition (666 ± 31 msec), $F(1,16) = 7.05$, $p = .02$. Response accuracy on choice trials was 98% in both conditions ($F < 1$, *ns*). Although thalamic stimulation significantly reduced symptoms of ET ($p < .001$), as can be seen in Table 2, it did not affect response speed to choice signals (off stimulation, 593 ± 24 msec; on stimulation, 590 ± 25 msec; $F < 1$, *ns*). DBS of the Vim did not induce changes in the rates of choice errors either ($F < 1$, *ns*; see Table 3 for accuracy data). The Vim-stimulated group consisted of patients diagnosed with ET ($n = 10$) as well as patients with PD ($n = 5$). Follow-up analyses indicated that Vim stimulation did not significantly affect choice RT in the subgroups of Vim ET (10-msec slowing), $F(1,9) = 0.52$, $p = .49$, *ns*, or Vim PD patients (29-msec improvement), $F(1,4) = 2.28$, $p = .21$. A direct comparison of the DBS effects in Vim ET and Vim PD subgroups also failed to reach significance (−10 vs. 29 msec), $F(1,13) = 2.62$, $p = .13$, probably due to small sample sizes. Thus, DBS of the STN, but not of the Vim, markedly enhanced speed of responding, without decline in response accuracy (see Figure 2).

Stop-signal Trials

The tracking algorithm that dynamically adjusted the onset of the stop signal resulted in overall inhibition rates that were close to the anticipated 50% in both patient groups and in both stimulation conditions (STN: on stimulation, 52%; off stimulation, 53%; $F < 1$; Vim: on stimulation, 51%; off stimulation, 52%; $F < 1$). Within-subject comparisons between on and off conditions in the stop-signal task demonstrated that STN stimulation shortened stop-signal RT (see Figure 2). This was manifested in a main effect of Stimulation on stop latencies: off, 285 ± 13 msec; on, 248 ± 8 msec; $F(1,16) = 11.97$, $p = .003$. In contrast, stop performance of thalamic patients as a group did not change with brain stimulation (off stimulation, 260 ± 11 msec; on stimulation, 253 ± 9 msec; $F < 1$, *ns*). The effects of Vim stimulation on stop-signal RT tended to differ in the Vim PD subgroup (28-msec improvement) compared to Vim ET patients (5-msec slowing), as indicated by an interaction between Stimulation and Subgroup that just failed to reach conventional levels of significance, $F(1,13) = 3.83$, $p = .07$, *ns*. Although the subgroup of Vim PD is quite small, a direct comparison between the Vim PD subgroup and the STN group is potentially informative. These patients differ in terms of stimulated brain region, but share PD pathophysiology. For stop-signal RT, the interaction between Region and Stimulation is far from significant, $F(1,20) < 1$, *ns*, indicating that the DBS-related improvements in stop-signal RT in the Vim PD subgroup (28 msec), $F(1,4) = 5.88$; $p = .07$, and in the STN group (37 msec) are comparable.

Thus, stimulation of the STN improves inhibitory control in patients with PD. Additionally, Vim stimulation also seems to improve response inhibition in patients with PD but not in patients receiving thalamic DBS for ET treatment.

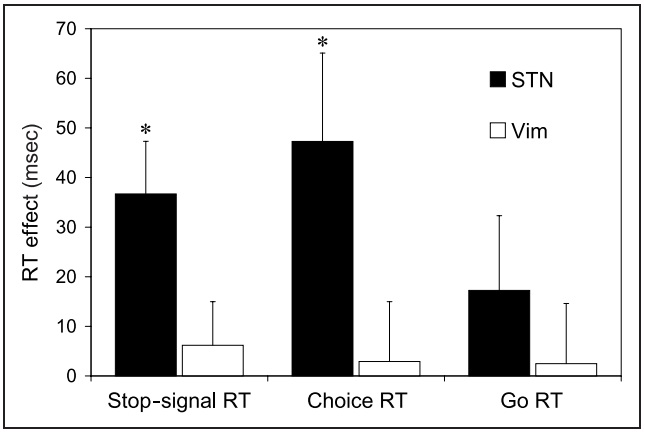

Figure 2. Effect sizes (off minus on DBS) on stopping (stop-signal RT) and responding (choice RT in the stop-signal task and go RT in the go/no-go task) in STN and Vim patients. Significant effects of DBS (*) were found for stop-signal RT and choice RT in STN-stimulated patients.

Global versus Specific Effects on Choice RT and Stop-signal RT

With DBS of the STN, choice RT as well as stop-signal RT clearly decreased. Additional analyses were performed to assess whether improvement in the speed

Table 3. Means and Standard Errors of the Mean (in Parentheses) of Response Accuracy on Choice Trials in the Stop-signal Task, and on No-go Trials in the Go/No-go Task

	Accuracy on Choice Trials (%)		*Accuracy on No-go Trials (%)*	
Electrode Region	*On Stimulation*	*Off Stimulation*	*On Stimulation*	*Off Stimulation*
STN	98.1 (0.3)	98.0 (0.4)	96.6 (0.4)	97.0 (0.6)
Vim	98.5 (0.5)	98.3 (0.4)	96.0 (0.6)	95.3 (1.0)

STN = subthalamic nucleus; Vim = ventral intermediate nucleus of the thalamus.

of response inhibition was specific. An alternative would be that STN stimulation resulted in an overall improvement in processing speed, indiscriminately affecting the latency of the generation of responses and the time it takes to inhibit them. Analysis of covariance of stop-signal RT in the STN group with choice RT as covariate still yielded a significant stimulation effect on stop-signal RT, $F(1,16) = 5.14$, $p = .04$, and thus demonstrated that improvement in inhibitory control cannot be readily explained in terms of a stimulation-related gain in overall processing speed.

Go/No-go Task

First, an overall analysis of go RTs in the go/no-go task was performed. The impression that Vim patients responded faster to go signals (456 ± 17 msec) than did STN patients (494 ± 16 msec) was not confirmed statistically, $F(1,30) = 2.70$, $p = .11$, *ns*. Overall, operation of the electrodes did not affect the speed of go responses, $F(1,30) = 1.00$, $p = .33$, *ns*. The interaction between Stimulation condition and Region was not significant, $F < 1$, *ns*.

Subsequent examination of patient groups separately showed that STN stimulation did not affect performance in the go/no-go task. The speed of responding did not discriminate between the two stimulation conditions [off, 503 ± 21 msec; on, 486 ± 17 msec; $F(1,16) = 1.31$, $p = .27$, *ns*], nor did the rate of false alarms to no-go signals, $F(1,16) = 3.57$, $p = .08$. A similar pattern was obtained for the Vim group. Response speed (off, 457 ± 15 msec; on, 455 ± 17 msec; $F < 1$, *ns*) and false alarm rates did not differ significantly between thalamic stimulation conditions, $F(1,14) = 1.34$, $p = .27$, *ns*. Subsequent analyses of go/no-go task performance of VIM PD patients yielded comparable null findings.

DISCUSSION

DBS Improves Inhibitory Control in PD Patients

Previous research has shown that response inhibition relies on the integrity of PFC (for a review, see Aron, Robbins, & Poldrack, 2004). Recent indications that patients diagnosed with Huntington disease or PD show impaired suppression of primed responses support the view that the basal ganglia are also involved in inhibitory control (Seiss & Praamstra, 2004; Aron, Schlaghecken, et al., 2003). Additional evidence stems from behavioral investigations that applied the stop-signal task and reported prolonged stop-signal RTs in PD patients (Gauggel et al., 2004) as well as in patients with lesions within regions, including the basal ganglia (Rieger et al., 2003). Based on these previous results, we hypothesized that modulation of basal ganglia function would affect inhibitory motor control. This hypothesis was tested by means of a within-subject design that involved DBS in the region of the STN, an important nucleus within the basal ganglia, in patients diagnosed with PD. Performances in a stop-signal task and in a go/no-go task were compared between on and off stimulation.

The present results support the notion that the basal ganglia play a critical role in the ability to inhibit ongoing behavior. STN stimulation markedly improved stop performance, as indicated by an overall decrease in stop-signal RT of 37 msec. This improvement in inhibitory motor control cannot readily be interpreted in terms of a general speeding effect induced by DBS. Although choice responses were also faster with stimulation (by an average of 47 msec), analysis of shared variance indicated that the increase in the speed of stopping is independent of the facilitation of choice responses (see also Gauggel et al., 2004; Williams, Ponesse, Schachar, Logan, & Tannock, 1999). These findings suggest that the basal ganglia play a selective role in inhibitory control—a notion that is in line with the experimental literature discussed above and with current theories of basal ganglia function (Boraud, Bezard, Bioulac, & Gross, 2002; Middleton & Strick, 2000; Mink, 1996).

Comparisons between patient groups may be meaningful, although it should be acknowledged that Vim and STN patient groups differed in their pathophysiology and were ascertained postsurgery, rather than being randomly assigned. Predominance of disabling tremor that is poorly responsive to medication has been taken as an indication for targeting the thalamus (Benabid et al., 1996). Conversely, in patients showing classical symptoms of PD, such as rigidity, freezing, gait abnormalities, and levodopa-induced dyskinesia, the surgery of choice was DBS of the STN. Clinical measures of motor symptoms clearly showed that both groups benefited from treatment with DBS. Unfortunately, no clinical data were available for the Vim PD patients, which is a limitation of the current data set. Whereas the STN group showed improved responding and stopping during DBS, stimulation of Vim generally did not affect measures of voluntary motor control (see also Flament et al., 2002). However, the impact of Vim stimulation seemed to depend on psychopathology. The amelioration of stopping performance in Vim patients diagnosed with PD stands in contrast to the null effects observed in patients with ET. Although the small number of Vim PD patients included in the present study precludes strong conclusions, DBS of the Vim, like DBS of the STN, tended to alleviate inhibitory motor control in PD patients. This suggests that the change in performance in stop trials may not be directly related to STN function, but rather results from a change in PD function due to DBS in general.

Apparent Inconsistencies

The improved stop-signal RTs obtained in the present study stand in apparent contrast with previous literature

that linked STN stimulation with impaired response inhibition (e.g., Hershey et al., 2004; Witt et al., 2004). Most likely, the inconsistencies resulted from the use of different paradigms. That is, the current beneficial effect of STN stimulation on response inhibition was obtained using the stop-signal paradigm. In contrast, the conclusion that stimulation of the STN impairs response inhibition was based primarily on results obtained using the Stroop color word test. The Stroop task (Stroop, 1935) requires subjects to name the font color of color words (e.g., red) that are printed in an incongruent color ink (e.g., blue). This requirement induces a conflict between the tendency to read the color word and the actual task of naming the color of the font. The interference is indexed by the Stroop effect, which often reflects prolonged RTs compared with a control task (for a review, see MacLeod, 1991). Some studies showed an augmented Stroop effect with STN stimulation on the RT of vocal responses, but not on accuracy (Schroeder et al., 2002). Other studies reported no change in RT measures of interference, but instead found an increase in the number of wrong responses, but not in self-corrected errors (Witt et al., 2004; but see Jahanshahi et al., 2000, indicating augmented levels of self-corrected errors, but not of wrong responses). Finally, Pillon et al. (2000) failed to observe an effect of DBS of the STN on Stroop interference. Hence, the data that are currently available do not unanimously support the view that STN stimulation has a detrimental effect on interference control or response inhibition in the Stroop task.

Another discrepant view has been reported by Hershey et al. (2004), who observed that STN stimulation resulted in an increase in the frequency of commission errors on a go/no-go task. They interpreted this finding as reflecting impaired inhibitory control. It should be noted, however, that the reduction in response accuracy to no-go signals reported by Hershey et al. might be (partially) explained by faster responding to go signals, which suggests a trade-off between speed and accuracy rather than impaired inhibition. Evidently, a speed–accuracy trade-off could not have occurred in the current study because of the use of the tracking algorithm, which prevents delay of the response to the choice signal in order to increase the chances of inhibition to the stop signal (Logan et al., 1997).

DBS of the STN Improves Response Selection Processes

Consistent with other studies, the current findings indicate that STN stimulation yields faster generation of motor responses, but only in the choice task. The observation that the speed of go responses was not affected by DBS stands in marked contrast with the clear speeding up of choice responses. This dissociation can be interpreted to reflect the selectivity of STN stimulation on the reaction process. If DBS were to affect processing stages that are shared by the two types of responses, one would expect a significant reduction in both choice RT and go RT. However, the null effect on go RT suggests that improvement in responding is selective and most likely affects the efficiency of the response selection stages of the reaction process, rather than early stages in the processing chain (such as signal detection and signal discrimination) or late processes (such as motor execution related to movement time). This increase in efficiency seems to be characterized by a decrease in response latency rather than by a change in accuracy, rendering alternative interpretations in terms of a trade-off between speed and accuracy unlikely. Taken together, the current findings indicate that response selection processes benefit most from stimulation of the STN. These results fit well with studies that have indicated an important role of the basal ganglia in the neuronal network underlying the selection of alternative responses (Williams et al., 2005; Hocherman, Moont, & Schwartz, 2004; Seiss & Praamstra 2004; Boraud et al., 2002; Redgrave, Prescott, & Gurney, 1999; Mink, 1996).

Underlying Neural Circuits

The results of the present study provide support for a causal role of the basal ganglia in the ability to select and inhibit motor responses. The beneficial effects of STN stimulation on motor response control could be mediated by multiple neural pathways within the circuit connecting the cortex with the basal ganglia, and vice versa. First, DBS of the STN could affect the processing of information transmitted to the basal ganglia through its input structures. The striatum, the main source of input, receives projections from several cortical regions, including the motor cortex, premotor cortex, SMA, and PFC (for an overview, see Mink, 1996). A second interpretation of the present findings relates more directly to the function of the basal ganglia. It has been argued that the role of the basal ganglia is primarily one of *focused selection*—the interplay between the enhancement of motor mechanisms related to a desired movement and the inhibition of competing mechanisms at the cortical level (Mink, 1996). According to this hypothesis, the internal segment of the globus pallidus (GPi) is the site of focused selection. Accordingly, dopamine depletion associated with PD is thought to interfere with the balance between activation and inhibition in GPi, impairing the ability to disinhibit desired cortical motor programs and to completely inhibit competing motor programs. Third, brain stimulation within the basal ganglia could well have affected information processing that relies on efferent cortical projection areas, such as premotor and prefrontal regions. This conjecture seems plausible as several studies related DBS in

the basal ganglia with changes in activity in the premotor cortex, primary motor cortex (Däuper et al., 2002), SMA (Ceballos-Baumann et al., 1999; Limousin et al., 1997), and PFC (Gerschlager et al., 1999). Finally, neurophysiological recordings in monkeys indicated that the STN receives direct cortical projections, in particular from the frontal lobes, including Brodmann's areas 6, 8, and 9 (Hartmann-von Monakow, Akert, & Künzle, 1978). It has been hypothesized that PFC regions, such as frontal eye fields in the monkey, project to the STN without first projecting to the striatum, and that the inhibitory effects are mediated by this *hyperdirect pathway* (Nambu, Tokuno, & Takada, 2002; Hanes, Patterson, & Schall, 1998; Mink, 1996). If this is the case, it is quite possible that DBS of the STN affects processing of these prefrontal signals more directly.

Conclusions

DBS in the STN region improved the speed of generating and inhibiting motor responses. In particular, the beneficial effects on the reaction process could be limited to cognitive operations that are involved in response selection. Although the present data do not allow a further specification of the neurobiological pathways involved, DBS of the STN very likely caused improved control over voluntary movement through the modulation of activity within the functional loop between the cortex and the basal ganglia. The ability to inhibit ongoing motor responses, as studied with the stop-signal paradigm, thus seems to depend on the integrity of both the PFC and the basal ganglia. These findings are consistent with the current understanding of the functional role of the basal ganglia in motor behavior involving the selection and inhibition of motor mechanisms during the selection and execution of movements. It is not immediately clear how the improvement in inhibitory control associated with thalamic stimulation in PD patients should be interpreted. The beneficial effects of DBS in PD patients, irrespective of target site, might suggest that both STN and Vim stimulations affect the same neuronal circuit. On the other hand, the circuits that are affected in PD and ET seem to be distinct. Specification of underlying mechanisms is an interesting topic for further research. The present results indicate the efficacy of using well-defined neuropsychological paradigms, such as the stop-signal task, in patient groups to map specific impairments in cognitive control. Moreover, this experiment shows the value of within-subject comparisons of task performance collected while stimulators were on and off. Finally, the modulation of activity in specified nuclei by means of DBS may constitute a fruitful tool for further investigation of the neural basis of voluntary motor behavior, the pathology of PD, and symptom alleviation by brain stimulation.

Acknowledgments

Patients were recruited through the Academic Medical Center (Amsterdam, the Netherlands) and the St. Elisabeth Clinic (Tilburg, the Netherlands) with the help of Rianne Esselink and Peter Nijssen, respectively. We thank them both. We also thank Bert van Beek for programming the computer tasks, and Borís Burle, Eveline Crone, Thierry Hasbroucq, Sander Nieuwenhuis, and K. Richard Ridderinkhof for their helpful comments on previous drafts of this manuscript.

This work was supported by grants from the Royal Netherlands Academy of Arts and Sciences, the Netherlands Organization for Scientific Research (NWO), The Dutch Parkinson Disease Patients Association, and the Fyssen Foundation.

J.D.S. acts as an independent consultant for Medtronic Ltd., the manufacturer of implanted stimulators. The Movement Disorders Workgroup (Academic Medical Center) received an unrestricted research grant from Medtronic Ltd.

Reprint requests should be sent to C. H. M. Brunia, Department of Psychology and Health, Tilburg University, PO Box 90153, 5000 LE Tilburg, the Netherlands, or via e-mail: c.h.m.brunia@uvt.nl.

REFERENCES

Aron, A. R., Fletcher, P. C., Bullmore, E. T., Sahakian, B. J., & Robbins, T. W. (2003). Stop-signal inhibition disrupted by damage to right inferior frontal gyrus in humans. *Nature Neuroscience, 6,* 115–116.

Aron, A. R., Robbins, T. W., & Poldrack, R. A. (2004). Inhibition and the right inferior frontal cortex. *Trends in Cognitive Sciences, 8,* 170–177.

Aron, A. R., Schlaghecken, F., Fletcher, P. C., Bullmore, E. T., Eimer, M., Barker, R., Sahakian, B. J., & Robbins, T. W. (2003). Inhibition of subliminally primed responses is mediated by the caudate and thalamus: Evidence from functional MRI and Huntington's disease. *Brain, 126,* 713–723.

Band, G. P. H., van der Molen, M. W., & Logan, G. D. (2003). Horse-race model simulations of the stop-signal procedure. *Acta Psychologica, 112,* 105–142.

Baunez, C., Humby, T., Eagle, D. M., Ryan, L. J., Dunnett, S. B., & Robbins, T. W. (2001). Effects of STN lesions on simple vs. choice reaction time tasks in the rat: Preserved motor readiness, but impaired response selection. *European Journal of Neuroscience, 13,* 1609–1616.

Benabid, A. L. (2003). Deep brain stimulation for Parkinson's disease. *Current Opinion in Neurobiology, 13,* 696–706.

Benabid, A. L., Pollak, P., Gao D., Hoffmann, D., Limousin, P., Gay, E., Payen, I., & Benazzouz, A. (1996). Chronic electrical stimulation of the ventralis intermedius nucleus of the thalamus as a treatment of movement disorders. *Journal of Neurosurgery, 84,* 203–214.

Boraud, T., Bezard, E., Bioulac, B., & Gross, C. E. (2002). From single extracellular unit recording in experimental and human Parkinsonism to the development of a functional concept of the role played by the basal ganglia in motor control. *Progress in Neurobiology, 66,* 265–283.

Ceballos-Baumann, A. O., Boecker, H., Bartenstein, P., von Falkenhayn, I., Riescher, H., Conrad, B., Moringlane, J. R., & Alesch, F. (1999). A positron emission tomographic study of subthalamic nucleus stimulation in Parkinson Disease: Enhanced movement-related activity of motor-association cortex and decreased motor cortex resting activity. *Archives of Neurology, 56,* 997–1003.

Dauer, W., & Przedborski, S. (2003). Parkinson's disease: Mechanisms and models. *Neuron, 39,* 889–909.
Däuper, J., Peschel, T., Schrader, C., Kohlmetz, C., Joppich, G., Nager, W., Dengler, R., & Rollnik, J. D. (2002). Effects of subthalamic nucleus (STN) stimulation on motor cortex excitability. *Neurology, 59,* 700–706.
Donders, F. C. (1969). On the speed of mental processes. In W. G. Koster (Ed.), *Attention and performance II* (pp. 412–431). Amsterdam: North-Holland. (Original work published in 1868)
Flament, D., Shapiro, M. B., Pfann, K. D., Moore, C. G, Penn, R. D, & Corcos, D. M. (2002). Reaction time is not impaired by stimulation of the ventral-intermediate nucleus of the thalamus (Vim) in patients with tremor. *Movement Disorders, 17,* 488–492.
Garavan, H., Ross, T. J., & Stein, E. A. (1999). Right hemispheric dominance of inhibitory control: An event-related functional MRI study. *Proceedings of the National Academy of Sciences, U.S.A., 96,* 8301–8306.
Gauggel, S., Rieger, M., & Feghoff, T. A. (2004). Inhibition of ongoing responses in patients with Parkinson's disease. *Journal of Neurology, Neurosurgery and Psychiatry, 75,* 539–544.
Gerschlager, W., Alesch, F., Cunnington, R., Deecke, L., Dirnberger, G., Endl, W., Lindinger, G., & Lang, W. (1999). Bilateral subthalamic nucleus stimulation improves frontal cortex function in Parkinson's disease: An electrophysiologic study of the contingent negative variation. *Brain, 122,* 2365–2373.
Gottsdanker, R., & Shragg, G. P. (1985). Verification of Donders' subtraction method. *Journal of Experimental Psychology. Human Perception and Performance, 11,* 765–776.
Hanes, D. P., Patterson, W. F., & Schall, J. D. (1998). Role of frontal eye fields in countermanding saccades: Visual, movement, and fixation activity. *Journal of Neurophysiology, 79,* 817–834.
Hartmann-von Monakow, K., Akert, K., & Künzle, H. (1978). Projections of the precentral motor cortex and other cortical areas of the frontal lobe to the subthalamic nucleus in the monkey. *Experimental Brain Research, 33,* 395–403.
Hershey, T., Revilla, F. J., Wernle, A., Schneider Gibson P., Dowling, J. L., & Perlmutter, J. S. (2004). Stimulation of STN impairs aspects of cognitive control on PD. *Neurology, 62,* 1110–1114.
Hocherman, S., Moont, R., & Schwartz, M. (2004). Response selection and execution in patients with Parkinson's disease. *Cognitive Brain Research, 19,* 40–51.
Jahanshahi, M., Ardouin, C. M., Brown, R. G., Rothwell J. C, Obeso, J., Albanese, A., Rodriguez-Oroz, M. C., Moro, E., Benabid, A. L., Pollak, P., & Limousin-Dowsey, P. (2000). The impact of deep brain stimulation on executive function in Parkinson's disease. *Brain, 123,* 1142–1154.
Jones, E. G. (1997). A description of the human thalamus. In M. Steriade, E. G. Jones, & D. A. McCormick (Eds.), *Thalamus, Vol. II* (pp. 425–99). Amsterdam: Elsevier.
Kelly, A. M. C., Hester, R., Murphy, K., Javitt, D. C., Foxe, J. J., & Garavan, H. (2004). Prefrontal–subcortical dissociations underlying inhibitory control revealed by event-related fMRI. *European Journal of Neuroscience, 19,* 3105–3112.
Krack, P., Batir, A., Van Blercom, N., Chabardes, S., Fraix, V., Ardouin C., Koudsie, A., Limousin, P. D., Benazzouz, A., LeBas, J. F., Benabid, A. L., & Pollak, P. (2003). Five-year follow-up of bilateral stimulation of the subthalamic nucleus in advanced Parkinson's disease. *New England Journal of Medicine, 349,* 1925–1934.
Lang, A. E. (2000). Surgery for Parkinson disease. *Archives of Neurology, 57,* 1118–1125.
Levitt, H. J. (1971). Transformed up–down methods in psychoacoustics. *Journal of the Acoustical Society of America, 49,* 467–477.
Limousin, P., Greene, J., Pollak, P., Rothwell, J., Benabid, A. L., & Frackowiak, R. (1997). Changes in cerebral activity pattern due to subthalamic nucleus or internal pallidum stimulation in Parkinson's disease. *Annals of Neurology, 42,* 283–291.
Limousin, P., Pollak, P., Benazzouz, A., Hoffmann, D., Le Bas, J. F., Broussolle, E., Perret, J. E., & Benabid, A. L. (1995). Effect of parkinsonian signs and symptoms of bilateral subthalamic nucleus stimulation. *The Lancet, 345,* 91–95.
Logan, G. D. (1994). On the ability to inhibit thought and action: A users' guide to the stop signal paradigm. In D. Dagenbach & T. H. Carr (Eds.), *Inhibitory processes in attention, memory, and language* (pp. 189–239). San Diego, CA: Academic Press.
Logan, G. D., & Cowan, W. B. (1984). On the ability to inhibit thought and action: A theory of an act of control. *Psychological Review, 91,* 295–327.
Logan, G. D., Schachar, R. J., & Tannock, R. (1997). Impulsivity and inhibitory control. *Psychological Science, 8,* 60–64.
MacLeod, C. M. (1991). Half a century of research on the Stroop effect: An integrative review. *Psychological Bulletin, 109,* 163–203.
Marsden, C. D., & Obeso, J. A. (1994). The functions of the basal ganglia and the paradox of stereotaxic surgery in Parkinson's disease. *Brain, 117,* 877–897.
Middleton, F. A., & Strick, P. L. (2000). Basal ganglia and cerebellar loops: Motor and cognitive circuits. *Brain Research Reviews, 31,* 236–250.
Miller, E. K., & Cohen, J. D. (2001). An integrative theory of prefrontal cortex function. *Annual Review of Neuroscience, 24,* 167–202.
Miller, J. O., & Low, K. (2001). Motor processes in simple, go/no-go, and choice reaction time tasks: A psychophysiological analysis. *Journal of Experimental Psychology. Human Perception and Performance, 27,* 266–289.
Mink, J. W. (1996). The basal ganglia: Focused selection an inhibition of competing motor programs. *Progress in Neurobiology, 50,* 381–425.
Nambu, A., Tokuno, H., & Takada, M. (2002). Functional significance of the cortico-subthalamo-pallidal ''hyperdirect'' pathway. *Journal of Neurophysiology, 84,* 289–300.
Obeso, J. A., Rodríguez-Oroz, M. C., Rodríguez, M., Lanciego, J. L., Artieda, J., Gonzalo, N., & Olanow, C. W. (2000). Pathophysiology of the basal ganglia in Parkinson's disease. *Trends in Neurosciences, 23,* S8–S19.
Pillon, B., Ardouin, C., Damier, P., Krack, P., Houeto, J. L., Klinger, H., Bonnet, A. M., Pollak, P., Benabid, A. L., & Agid, Y. (2000). Neuropsychological changes between ''off'' and ''on'' STN or GPi stimulation in Parkinson's disease. *Neurology, 55,* 411–418.
Praamstra, P., & Plat, F. M. (2001). Failed suppression of direct visuomotor activation in Parkinson's disease. *Journal of Cognitive Neuroscience, 13,* 31–43.
Redgrave, P., Prescott, T. J., & Gurney, K. (1999). The basal ganglia: A vertebrate solution to the selection problem? *Neuroscience, 89,* 1009–1023.
Rieger, M., Gauggel, S., & Burmeister, K. (2003). Inhibition of ongoing responses following frontal, nonfrontal, and basal ganglia lesions. *Neuropsychology, 17,* 272–282.
Rubia, K., Russell, T., Overmeyer, S., Brammer, M. J., Bullmore, E. T., Sharma, T., Simmons, A., Williams, S. C., Giampietro, V., Andrew, C. M., & Taylor, E. (2001). Mapping motor inhibition: Conjunctive brain activations across

different versions of go/no-go and stop tasks. *Neuroimage, 13,* 250–261.
Rubia, K., Smith, A. B., Brammer, M. J., & Taylor, E. (2003). Right inferior prefrontal cortex mediates response inhibition while mesial prefrontal cortex is responsible for error detection. *Neuroimage, 20,* 351–358.
Schaltenbrand, G., & Wahren, W. (1977). *Atlas for stereotaxy of the human brain*. Stuttgart: Georg Thieme.
Schroeder, U., Kuehler, A., Haslinger, B., Erhard, P., Fogel, W., Tronnier, V. M., Lange, K. W., Boecker, H., & Ceballos-Baumann, A. O. (2002). Subthalamic nucleus stimulation affects striato-anterior cingulate cortex circuit in a response conflict task: A PET study. *Brain, 125,* 1995–2004.
Schuurman, P. R., Bosch, D. A., Bossuyt, P. M., Bonsel, G. J., van Someren, E. J., de Bie, R. M., Merkus, M. P., & Speelman, J. D. (2000). A comparison of continuous thalamic stimulation and thalamotomy for suppression of severe tremor. *New England Journal of Medicine, 342,* 461–468.
Seiss, E., & Praamstra, P. (2004). The basal ganglia and inhibitory mechanisms in response selection: Evidence from subliminal priming of motor responses in Parkinson's disease. *Brain, 127,* 330–339.
Starr, P. A., Christine, C. W., Theodosopoulos, P. V., Lindsey, N., Byrd, D., Mosley, A., & Marks, W. J. (2002). Implantation of deep brain stimulators into the subthalamic nucleus: Technical approach and magnetic resonance imaging-verified lead locations. *Journal of Neurosurgery, 97,* 370–387.
Stroop, J. R. (1935). Studies of interference in serial verbal reactions. *Journal of Experimental Psychology, 18,* 643–662.
Temel, Y., Visser-Vandewalle, V., Aendekerk, B., Rutten, B., Tan, S., Scholtissen, B., Schmitz, C., Blokland, A., & Steinbusch, H. W. (2005). Acute and separate modulation of motor and cognitive performance in parkinsonian rats by bilateral stimulation of the subthalamic nucleus. *Experimental Neurology, 193,* 43–52.
Williams, B. R., Ponesse, J. S., Schachar, R. J., Logan, G. D., & Tannock, R. (1999). Development of inhibitory control across the life span. *Developmental Psychology, 35,* 205–213.
Williams, D., Kühn, A., Kupsch, A., Tijssen, M., van Bruggen, G., Speelman, H., Hotton, G., Yarrow, K., & Brown, P. (2003). Behavioural cues are associated with modulations of synchronous oscillations in the human subthalamic nucleus. *Brain, 126,* 1975–1985.
Williams, D., Kühn, A., Kupsch, A., Tijssen, M., van Bruggen, G., Speelman H., Hotton, G., Loukas, C., & Brown, P. (2005). The relationship between oscillatory activity and motor reaction time in the parkinsonian subthalamic nucleus. *European Journal of Neuroscience, 21,* 249–258.
Williams, D., Tijssen, M., Van Bruggen, G., Bosch, A., Insola, A., Di Lazzaro, V., Mazzone, P., Oliviero, A., Quartarone, A., Speelman, H., & Brown, P. (2002). Dopamine-dependent changes in the functional connectivity between basal ganglia and cerebral cortex in humans. *Brain, 125,* 1558–1569.
Witt, K., Pulkowski, U., Herzog, J., Lorenz, D., Hamel, W., Deuschl, G., & Krack, P. (2004). Deep brain stimulation of the subthalamic nucleus improves cognitive flexibility but impairs response inhibition in Parkinson disease. *Archives of Neurology, 61,* 697–700.