

The impact of deep brain stimulation on executive function in Parkinson's disease

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Summary

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) or the internal segment of the globus pallidus (GPi) improves Parkinson's disease and increases frontal blood flow. We assessed the effects of bilateral DBS on executive function in Parkinson's disease patients, seven with electrodes implanted in the STN and six in the GPi. Patients were assessed off medication with stimulators off, on and off again. The groups showed differential change with stimulation on the Reitan Trail-Making test (TMT B) (STN more improved) and on some measures of random number generation and Wisconsin Card Sorting (STN improved, GPi worse with stimulation). Across the groups, stimulation speeded up responding (Stroop

control trial, TMT A) and improved performance on paced serial addition and missing digit tests. Conversely, conditional associative learning became more errorful with stimulation across the two groups. In general, change in performance with stimulation was significant for the STN but not the GPi group. These results support two opposite predictions. In support of current models of Parkinson's disease, 'releasing the brake' on frontal function with DBS improved aspects of executive function. Conversely, disruption of basal ganglia outflow during DBS impaired performance on tests requiring changing behaviour in novel contexts as predicted by Marsden and Obeso in 1994

Keywords: deep brain stimulation; Parkinson's disease; executive function; working memory; cognition

Abbreviations: DBS = deep brain stimulation; DLPFC = dorsolateral prefrontal cortex; DRS = Mattis Dementia Rating Scale; GPe = external segment of the globus pallidus; GPi = internal segment of the globus pallidus; PVSAT = Paced Visual Serial Addition Test; SMA = supplementary motor area; SNr = substantia nigra pars reticulata; STN = subthalamic nucleus; TMT = Reitan Trail-Making Test; UPDRS = United Parkinson's disease Rating Scale; VCLT = Visual–Visual Conditional Associative Learning test; WCST = Wisconsin Card Sorting Test

Introduction

Long-term experience of levodopa therapy for Parkinson's disease has highlighted a host of complications including end of dose deterioration, on–off fluctuations and dyskinesias. This has rekindled interest in other treatments for the disorder including a number of surgical interventions, which now offer effective ways of managing these problems and other symptoms of Parkinson's disease. Chronic high frequency electrical stimulation of the internal segment of the globus pallidus (GPi) or the subthalamic nucleus (STN) through

implanted electrodes has been shown to be clinically effective in improving the akinesia and rigidity and in reducing levodopa-induced dyskinesias (Siegfried *et al.*, 1994; Limousin *et al.*, 1995; Krack *et al.*, 1998a).

These surgical techniques have been driven by current models of frontostriatal circuitry and pathophysiology of Parkinson's disease (Albin *et al.*, 1989; Alexander and Crutcher, 1990; DeLong, 1990). In these models, the direct and indirect pathway from the striatum to the output nuclei

of the basal ganglia, i.e. to the GPi and the substantia nigra pars reticulata (SNr), are considered to produce opposing effects to facilitate or suppress cortically initiated activity, respectively. Activation of the direct pathway between the putamen and GPi/SNr results in disinhibition of thalamic nuclei which in turn facilitates cortically initiated activity. In contrast, the net effect of activity in the indirect pathway from the STN to the GPi/SNr via the external segment of the globus pallidus (GPe) and the STN is increased inhibition of thalamic targets and, consequently, reduced thalamic input to cortical areas. This model of frontostriatal functioning is supported by direct recordings of neuronal activity (Miller and DeLong, 1987; Bergman and Wichmann, 1990). In Parkinson's disease, degeneration of dopaminergic neurons in the pars compacta of the substantia nigra alters the balance of activity in the direct and indirect pathways, the net effect of which is increased inhibitory outflow from the GPi, and a resultant reduced activation of cortical projection sites via the thalamus (Miller and DeLong, 1987). In support of this model, increased firing rate of GPi neurons has been demonstrated in primate models (Bergman and Wichmann, 1990; Aziz *et al.*, 1991) and in patients with Parkinson's disease (Hutchinson *et al.*, 1994). Also, PET activation studies have shown that in Parkinson's disease, performance of willed actions such as random joystick movements or self-initiated finger extension is associated with underactivation of the putamen as well as the supplementary motor area (SMA), the dorsolateral prefrontal cortex (DLPFC) and the anterior cingulate (Playford *et al.*, 1992; Jahanshahi *et al.*, 1995). The activation of the same cortical areas is improved following deep brain stimulation (DBS) of the STN (Limousin *et al.*, 1997) or GPi (Davis *et al.*, 1997). The PET study by Limousin and colleagues showed that although both STN and GPi DBS improved the clinical symptoms of Parkinson's disease, only effective STN stimulation was associated with significantly greater activation of the SMA, anterior cingulate and DLPFC during random joystick movements (Limousin *et al.*, 1997). Effective STN and GPi stimulation differed significantly in terms of DLPFC activation, which was significantly higher in the former group.

These clinical and PET results constitute strong evidence for the role of the motor circuit in akinesia and bradykinesia and the current pathophysiological model of Parkinson's disease. Nevertheless, as noted by Marsden and Obeso (Marsden and Obeso, 1994), the very same results paradoxically cast doubt over the validity of current models of frontostriatal functioning. They argue that on the basis of these models, some deficit in voluntary movement, particularly in novel situations, would be expected in Parkinson's disease following pallidotomy or DBS of the GPi. However, they note that using standard clinical assessments, no such deficits are reported following surgery. To explain this apparent paradox, Marsden and Obeso suggest that 'the overall distributed system could continue to function without its basal ganglia component, except in those special contexts. Thus routine predictable and automatic movement

might continue without basal ganglia support. . . . However, they may be less able to respond to novel circumstances by changing their motor behaviour' (Marsden and Obeso, 1994). This latter situation is close to contemporary definitions of executive function (see below). Thus loss of basal ganglia output as a result of DBS might be expected to have its major impact on cognitive functions involving executive processes.

From the preceding accounts, two opposing predictions are possible. From the current model of akinesia in Parkinson's disease, one would predict that DBS would 'release the brake' on cortical activity in frontal areas including the DLPFC as demonstrated by PET results (Limousin *et al.*, 1997). Such reduction of the underactivation of the DLPFC would in turn be predicted to be associated with improved execution function and working memory with DBS. Conversely, based on the analysis of Marsden and Obeso (Marsden and Obeso, 1994), one would predict that although subcortical surgery such as DBS may not be associated with any noticeable change in routine behaviour, performance of non-routine novel tasks, such as those tapping executive function and working memory, would be disrupted further during DBS as this alters basal ganglia outflow to frontal cortex.

To date, three studies have reported the effects of DBS on cognitive function. Troster and colleagues and Vingerhoets and colleagues, respectively, assessed cognitive function in nine and 20 patients with Parkinson's disease, before surgery for *unilateral* DBS of the GPi and 3 months after surgery (Troster *et al.*, 1997; Vingerhoets *et al.*, 1999). On both occasions, patients were assessed on medication and, following surgery, the patients were assessed with the stimulators turned on. Ardouin and colleagues examined the impact of *bilateral* DBS of the STN or GPi on cognitive function in 62 patients (Ardouin *et al.*, 1999). These investigators also assessed patients before surgery and after 3–6 months of DBS with the stimulators turned on, some on and some off medication, on both assessment occasions. In all three studies, the majority of tests of cognitive function showed no significant change between the two assessments. The only exceptions were that semantic word fluency and visuoconstructive test scores were significantly worse after surgery with DBS in the study of Troster and colleagues, whereas first letter word fluency was worse and performance on the Trail-Making Tests versions A and B was faster and improved after surgery with DBS in the study by Ardouin and colleagues (Ardouin *et al.*, 1999).

All of the three studies described above compared pre-versus post-surgical changes in cognitive function, which does not distinguish between the effects of surgery and the effects of stimulation. Therefore, in the present study, we examined the effect of *stimulation* on cognition by assessing the patients after surgery and evaluating changes in cognitive function with stimulators turned on versus off. Furthermore, the clinically defined 'on' state may not be equivalent before and after surgery with DBS and, to avoid problems due to differential effects of medication on various aspects of

cognitive function (Girotti *et al.*, 1986; Gotham *et al.*, 1988; Lange *et al.*, 1992), we evaluated the impact of DBS on cognitive function after overnight withdrawal of medication.

Directly comparing the impact of DBS of the STN and GPi on cognitive function is of interest. Although with both types of DBS the target is to alter the balance of activity in the motor circuit, nevertheless, while DBS of the GPi only affects the GPi output pathways, DBS of the STN, which has connections to both the GPi and SNr, affects both of these output pathways from the basal ganglia. More importantly, as the DLPFC is a target of the thalamic projection from the SNr (Ilinsky *et al.*, 1985; Barbas *et al.*, 1991), the former cortical area may be influenced by DBS of the STN as suggested by the PET study of Limousin and colleagues (Limousin *et al.*, 1997). Studies of patients with focal lesions have shown that the DLPFC is involved in working memory and executive function (Milner, 1963, 1964; Owen *et al.*, 1990; Wiegersma *et al.*, 1990). Therefore, the aim of the present study was to assess the relative impact of bilateral DBS of the STN and GPi on cognitive function with a focus on executive function and working memory.

Executive processes are involved in planning and allocation of attentional resources to ensure that goal-directed behaviour is initiated, maintained and monitored adequately to achieve goals. According to this definition, executive processes are also an integral part of tasks where appropriate response generation requires suppression of habitual responses. In light of this, and the current frontostriatal models suggesting that the direct and indirect pathways are concerned with facilitation or suppression of cortical activity, respectively (Alexander and Crutcher, 1990; DeLong, 1990), we selected tasks that allowed us to examine both these aspects of executive processing. Willing suppression of habitual responding is necessary for successful performance on the Stroop and random number generation. The Stroop requires suppression of the dominant response of reading the words in order to name the colour of ink in which the colour words are printed. During random number generation, the subject has to suppress habitual counting, a process which has been shown to involve the DLPFC (Jahanshahi *et al.*, 1998). In addition, in selecting our battery of tests of executive function, we were guided by two other principles. First, we selected tests for which there was evidence, either from studies of patients with frontal lesions, animal studies or investigations using functional imaging in normal subjects, that performance engaged the prefrontal cortex. Secondly, we included mainly tests which required self-generation of responses or some form of decision-making on each trial rather than routine generation of responses. These are the types of 'novel' tasks that Marsden and Obeso predicted might be most affected by subcortical surgery (Marsden and Obeso, 1994) and on which patients with Parkinson's disease perform poorly compared with age-matched normals (Gotham *et al.*, 1988).

Methods

Participants

Thirteen patients (10 male, three female) with a clinical diagnosis of Parkinson's disease based on the presence of two or three cardinal symptoms (tremor, bradykinesia and rigidity) and responsiveness to levodopa were assessed. All patients were right-handed. The mean age was 52.8 years (SD = 4.9, range 46–62), and the average duration of illness was 15.1 years (SD = 4.8, range 8–23). These included 10 of the 12 patients of Limousin and colleagues (Limousin *et al.*, 1997) with bilateral stimulators and three other patients with bilateral DBS of the STN or GPi from Italy and Spain, who were similar to the other 10 patients in all demographic and clinical features (Table 1). All patients had had quadripolar stimulating electrodes (Medtronic, Minn., USA) chronically implanted, according to the procedures previously described (Benabid *et al.*, 1994). Seven had electrodes implanted into the STN bilaterally, and six had electrodes implanted bilaterally in the posteroventral portion of the GPi; those with severe dyskinesias were allocated to the GPi group. Prior to surgery, all had severe and disabling Parkinson's disease as reflected by a mean Hoehn and Yahr (Hoehn and Yahr, 1967) rating of 4.5 when assessed off medication and 2.5 on medication. All patients were also rated on the United Parkinson's disease Rating Scale (UPDRS; Fahn *et al.*, 1987) both before and after surgery, with scores also indicating severe and disabling disease. The pre- and postoperative assessments of motor function were conducted by neurologists with considerable experience in assessment of patients with Parkinson's disease on the target rating scales. For all patients, the postoperative motor assessment was conducted by the same neurologist within a few days of the cognitive assessment. Time since surgery ranged from 2 to 26 months (Table 1). The average years of education for the sample was 11.8 (SD = 4.2). All patients were taking levodopa and were assessed after overnight withdrawal of medication, with the average time since the last dose being 13.7 h (SD = 1.8) at the start of testing.

For the STN group, the stimulation characteristics were as follows: mean pulse width 60 μ s (SD = 8.9), mean frequency 146.8 Hz (SD = 26.2) and mean voltage 2.8 V (SD = 0.65). For the GPi group, the stimulation parameters were: mean pulse width 82.5 μ s (SD = 12.5), mean frequency 135.8 Hz (SD = 11.0) and mean voltage 3.6 V (SD = 0.001).

Design

A within-subject repeated measures design was used. Each patient was assessed on the majority of the tests three times: with the stimulators off, then with the stimulators on and optimally set for control of motor symptoms, and with the stimulators off again. With this off-on-off design, comparison of the two assessments with the stimulators off permits an assessment of the potential effects of fatigue and practice. The Wisconsin Card Sorting and the word fluency tests were

Table 1 Demographic and clinical details of the patients

Patient	Sex	Age (years)	Disease duration (years)	Time since operation	Worse side	Preoperative				Postoperative (off medication)			
						H&Y off med.	H&Y on med.	UPDRS (III) off med.	UPDRS (III) on med.	H&Y off DBS	H&Y on DBS	UPDRS (III) off DBS	UPDRS (III) on DBS
STN													
1	M	51	16	7	L	5.0	3.0	79	31	4.0	2.5	68	13
2	M	49	10	15	L	5.0	2.0	65	12	5.0	2.5	63	31
3	M	56	23	26	L	4.0	2.0	52	7	3.0	2.0	30	10
4	M	50	15	12	R	4.0	2.0	51	19	4.0	2.5	67	26
5	F	52	14	4	R	5.0	2.5	73	25	4.0	2.5	48	26
6	F	62	14	13	R	5.0	3.0	68	22	5.0	2.5	67	30
7	M	62	15	5	L	5.0	2.5	51	24	5.0	2.5	63	40
Mean		54.4 (5.6)	15.3 (3.9)	11.7 (7.7)				62.7 (11.5)	20.0 (8.2)			58.0 (14.1)	25.1 (19.5)
GPi													
1	M	50	15	17	L	4.0	3.0	46	28	3.0	3.0	32	18
2	M	46	14	4	R	4.0	2.5	47	22	4.0	2.5	58	37
3	F	54	19	8	R	5.0	3.0	71	25	4.0	3.0	46	34
4	M	56	23	3	L	4.0	3.0	50	24	4.0	3.0	52	33
5	M	48	9	2	L	4.0	2.0	55	17	4.0	2.5	44	34
6	F	50	8	2	L	5.0	2.5	56	7	4.0	1.0	45	7
Mean		51.0 (3.7)	14.7 (5.8)	6.0 (5.8)				54.2 (9.2)	20.5 (7.6)			46.2 (8.7)	27.2 (11.9)

med. = medication; DBS = deep brain stimulation; H&Y = Hoehn and Yahr Rating Scale; UPDRS III = motor examination part of the United Parkinson's disease Rating Scale. Numbers in parentheses are SDs. Time since operation is given in months. L = left; R = right.

only administered twice, with the order of stimulators off versus on counterbalanced across the patients. Where appropriate and possible [word fluency, Reitan Trail-Making Test, missing digit, paced visual serial addition test, visual-visual conditional learning test (VCLT)], parallel forms of the tests were used for the repeated assessments, with the choice of the version used for each assessment balanced across subjects.

Tests used for screening

At the beginning of the testing session, patients were assessed with the stimulators on, on two tests that provide global measures of cognitive function. The Advanced Progressive Matrices (Raven, 1962), a non-verbal 'culture fair' test of abstract reasoning, which provides an IQ estimate, was administered to eight of the 13 patients. The Mattis Dementia Rating Scale (DRS, Schmidt *et al.*, 1994) assesses attention, verbal and non-verbal memory, motor initiation, construction and conceptual ability. The maximum score is 144, with a cut-off score of 130 or lower indicative of cognitive dysfunction. For eight of the patients, scores on the Mattis DRS were also available prior to surgery, which allows assessment of any impact of the surgery for implantation of the electrodes on cognitive function. The Beck Depression Inventory (Beck *et al.*, 1961) was also completed by 10 of the 13 patients. The range of scores on this is 0–63, with higher scores indicating higher depression.

Tests of executive function

Reitan Trail-Making Test (TMT; Reitan, 1958)

This test has two versions. TMT A requires the subject to connect up a sequence of numbers dispersed across a page as quickly as he/she can without lifting the pen from the paper, and is a simple measure of behavioural regulation and motor speed. In TMT B, the subject alternates between sequences of numbers and letters, which necessitates alternation of mental set. For each version, the time to complete the test is recorded. The difference score of the two versions has been used as an index of behavioural regulation and 'cognitive speed' independent of motor speed.

Paced Visual Serial Addition Test (PVSAT)

This is a visual version of the paced auditory serial addition test (Gronwall and Wrightson, 1981; Gotham *et al.*, 1988). Subjects were presented with a series of 33 random single digit numbers on the VDU. Each digit was presented for 1500 ms. The subject's task was to add the most recent number to the preceding one and say aloud the sum. Digits were presented at the rate of one every 4 s. The total number of errors (maximum 32) was noted.

Missing Digit Test

We used a modified version (Wiegersma *et al.*, 1990; Petrides *et al.*, 1993a) in which the subject was presented with a

pseudo-random sequence of nine of the 10 numbers between 1 and 10 and had to identify the missing digit. Numbers were presented on a VDU at the rate of one digit per 2 s, followed by a response prompt. Subjects were provided with feedback after each response. A minimum of 20 such sequences were completed, with a short break after 10 sequences. The percentage of sequences correct was calculated.

Stroop Colour Word Naming Test (Stroop, 1935; Perret, 1974)

Two versions were used, each consisting of 100 items. The first, so-called main or 'interference' version, required naming the colour of ink of colour words (green, blue, red) printed in incongruent ink. In the second 'control' version, subjects named the colour of rectangles. Subjects were instructed to perform each task as quickly as possible and to correct any errors. For each version, the total time and the number of errors were recorded. The difference score between the first and second versions takes motor speed into account and is a measure of the 'Stroop effect', the ability to maintain attention focused on one attribute of the colour words (ink) and ignore the other (meaning of colour words) while naming colours.

Visual-Visual Conditional Associative Learning (VCLT, Petrides, 1985; Gotham et al., 1988)

The task requires the subject to learn by trial and error and remember arbitrary associations between pairs of visual stimuli. The arbitrary nature of the pairings reduces contextual discrimination. In the present version, six colours (red, black, yellow, green, blue and brown) were associated arbitrarily with six abstract geometric designs. The test material consisted of six cards bearing one of the six colours, and six cards bearing all of the six designs arranged in a different random order. For each block of trials, the subject was presented with the six colour stimuli in turn in a predetermined sequence. For each colour stimulus, the subject had to indicate a design which they thought to be associated with that colour. For each selection, the subject was told whether it was correct or not. If the selection was wrong, the subject continued to select other designs until the correct pairing was achieved. This procedure was repeated for a maximum of six blocks, with the colour stimuli presented in a new random sequence and using the six cards each bearing the designs in different random positions. The test ended after six blocks or when the subject had learned the six colour-pattern associations. The total number of trials, the total number of errors across all six blocks and the number of blocks to reach criterion were noted.

Wisconsin Card Sorting Test (WCST; Nelson, 1976)

The Nelson version consists of a pack of 48 cards on which are printed coloured geometrical figures that differ in one or

more dimensions: shape, colour or number. The subject is asked to discover the rule and sort each card by matching it to one of the four stimulus cards, with the rule changing after a number of correct sorts. The score is the number of categories correctly sorted (maximum six), the number and percentage of perseverative errors (two successive sorts on an incorrect dimension) and the number of non-perseverative errors.

Random Number Generation (RNG; Spatt and Goldenberg, 1993)

Subjects were instructed to generate a series of 100 numbers in a random fashion in synchrony with a visual pacing stimulus presented at 0.5 Hz. We obtained several measures of randomness calculated as described previously (Jahanshahi et al., 1998). The RNG index reflects any disproportion of digrams (adjacent items in a series) in the matrix adjusted for disproportions in the marginal cell frequencies. It varies between 0 and 1, and the higher the index the less random is the series. Chi-square (χ^2) measures the frequency with which each of the nine numbers in the set are selected relative to the expected frequency in a series of 100 numbers. Count scores are measures of seriation. Count score 1 measures the tendency to count in ascending or descending series in steps of 1. For example, 1-2-3 or 8-7-6-5-4. Count score 2 measures the tendency to count in ascending or descending series in steps of 2, for example 2-4-6-8 or 7-5-3-1. Individuals may have count scores that are lower than predicted from a random series if they are avoiding particular counting tendencies, or they may have a score which is too high if they are unable to suppress particular counting tendencies.

Word Fluency (Benton, 1968)

Two versions were completed, each for 60 s. In the phonemic version, subjects were asked to produce words beginning with a particular letter (V or R for the French patients, and S or A for the Spanish and Italian patients), excluding proper nouns and the same word with a different suffix. On the semantic version, subjects produced nouns belonging to a specific category (furniture or fruit, animals or boys names). The specific letters or categories used were counterbalanced for the stimulator 'on' versus 'off' assessments. On each test, the score was the number of words generated correctly.

Statistical analysis

The data were distributed normally. A series of two-way repeated measures ANOVA (analysis of variance) was used, with group (STN versus GPI) as the between-groups factor and stimulation condition (on versus off) as the repeated measures within-subjects factor.

Results

Characteristics of the STN and GPi groups

The patients with STN or GPi stimulation were matched in terms of age, sex and duration of illness ($P > 0.05$). Disease severity prior to surgery was also equivalent and the groups did not differ significantly in terms of mean Hoehn and Yahr ratings on or off levodopa medication (group $P > 0.05$), although, as expected, both groups had significantly lower Hoehn and Yahr ratings on than off medication [main effect of medication $F(1,11) = 201.0$, $P < 0.001$]. Similarly, prior to surgery, the two groups did not differ in terms of mean UPDRS part III ratings when assessed on or off medication (effects of group or group $\times$ medication, $P > 0.05$), and these ratings were significantly lower on than off medication [main effect of medication $F(1,11) = 156.5$, $P < 0.001$]. The time since surgery, i.e. the length of time for which they had had DBS at the time of the present study, was not significantly different for the STN and GPi groups [$t(11) = 1.5$, $P = 0.161$].

From the scores of the patients on the Advanced Matrices, a mean IQ equivalent of 114.1 (SD = 12.5, range 90–126) was obtained, which is in the 'high average' range. The mean score on the Mattis DRS was 136.2 (SD = 5.5). Two of the patients scored below the cut-off score of 130. For the eight patients for whom Mattis DRS scores were available before and after surgery, the mean scores were not significantly different [$t(7) = 0.09$, $P = 0.93$], thus showing no impact of surgery for implantation of the electrodes on cognitive function. Self-reported depression on the BDI was very mild, with only two of the 10 patients assessed having scores indicative of moderate levels of depression. The patients with STN or GPi stimulators did not differ ($P > 0.05$) in years of education (GPi: mean = 12.8, SD = 4.0; STN: mean = 11.2, SD = 3.9), IQ estimates (GPi: mean = 110.4, SD = 14.5; STN: mean = 120.3, SD = 6.0), scores on the Mattis DRS (GPi: mean = 137.2, SD = 5.3; STN: mean = 135.2, SD = 6.2) or the Beck Depression Inventory (GPi: 5.6, SD = 4.9; STN: 10.0, SD = 5.0).

All patients had obtained a significant clinical benefit from DBS (Table 1), with stimulation leading to a significant decrease in UPDRS motor scores [main effect of stimulation $F(1,11) = 64.8$, $P < 0.001$]. There was a trend for this clinical improvement with stimulation to be greater for the patients with STN than GPi stimulators [group $\times$ stimulation $F(1,11) = 4.6$, $P = 0.055$]. The mean percentage improvement was 56.7 (SD = 14.5) for the STN group and 41.1 (SD = 22.3) for the GPi group. Also, as evident from Table 1, for both groups of patients, postoperative stimulation while off medication reduced UPDRS scores to a level similar to preoperative scores when patients were assessed on medication. In this respect, the extent of benefit obtained from stimulation approximates the preoperative benefits of levodopa. Postoperatively, when assessed off medication, Hoehn and Yahr ratings for the whole group was reduced from a mean of 4.0 with the stimulators off to a mean of 2.5

with stimulation, and there were no differences between the two groups (effects of group and group $\times$ stimulation $P > 0.05$).

The effect of STN or GPi stimulation on executive function

None of the differences between the two assessments when the stimulators were off were significant ($P > 0.05$). Therefore, the data from these were averaged and compared with data obtained when the stimulators were 'on'. The scores of the patients on the various tests of executive function, attention and behavioural regulation with stimulation on or off are presented in Table 2.

Across the STN and GPi groups, stimulation speeded up responding as indicated by significantly faster performance on TMT A [main effect of stimulation $F(1,18) = 18.1$, $P = 0.003$], and particularly the more demanding TMT B [main effect of stimulation $F(1,8) = 32.4$, $P = 0.001$], as a result of which the B – A difference score was significantly smaller [main effect of stimulation $F(1,8) = 13.9$, $P = 0.006$]. Performance on TMT A and B was faster for five of the six (83.3%) patients in the GPi group and all four of the patients in the STN group who had completed this test. The main effect of group was not significant for either TMT A or B or their difference score [respectively $F(1,8) = 0.06$, $P = 0.87$; $F(1,8) = 0.01$, $P = 0.93$; $F(1,8) = 0.01$, $P = 0.99$]. The group $\times$ stimulation interaction did not achieve significance for TMT A [$F(1,8) = 3.8$, $P = 0.088$], but was significant for TMT B [$F(1,8) = 13.0$, $P = 0.007$] and the difference score [$F(1,8) = 7.4$, $P = 0.026$]. From Fig. 1A and B it can be seen that these interactions were due to the fact that the speeding up of TMT B and the reduction of the difference score was differentially greater and significant for the STN [TMT B: $t(3) = 4.3$, $P = 0.022$; TMT difference score: $t(3) = 3.5$, $P = 0.04$] but not the GPi group [TMT B: $t(5) = 2.4$, $P = 0.059$; TMT difference score: $t(5) = 0.92$, $P = 0.401$].

Across the two groups, stimulation significantly improved performance on the PVSAT [main effect of stimulation $F(1,10) = 13.5$, $P = 0.004$], with six of the seven (85.7%) patients in the STN and five of the six (83.3%) in the GPi group showing improved performance. The main effect of group [$F(1,10) = 0.07$, $P = 0.79$] and the group $\times$ stimulation interaction [$F(1,10) = 0.07$, $P = 0.79$] were not significant. Stimulation produced a similar effect on the missing digit test. It resulted in significant improvement of performance on this test across the two groups (main effect of stimulation $F(1,10) = 7.3$, $P = 0.023$), but the main effect of group [$F(1,10) = 0.40$, $P = 0.54$] and the group $\times$ stimulation interaction [$F(1,10) = 0.06$, $P = 0.82$] were not significant. Performance was improved for equal proportions of patients (66.7%) in the two groups.

Across the two groups, stimulation was associated with significantly faster performance on the control condition

Table 2 Mean and standard deviations showing change on the various measures of executive function in the STN and GPi groups with stimulators on versus off

	STN			GPi		
	Off	On	Percentage change	Off	On	Percentage change
Reitan Trail-Making Test						
Version A – Total time (s)	64.8 (25.6)	40.5 (19.6)	36.7 (20.7)	54.1 (18.3)	45.1 (15.8)	16.0 (16.4)
Version B – Total time (s)	158.5 (64.5)	80.5 (30.1)	48.6 (5.8)	125.1 (49.6)	107.7 (55.0)	15.8 (11.4)
Difference Trail B – Trail A	93.75 (45.2)	40.0 (17.2)	55.9 (10.2)	70.9 (33.5)	62.6 (41.6)	14.4 (25.0)
Paced Visual Serial Addition						
Total errors	9.8 (7.5)	7.3 (7.1)	31.5 (48.0)	8.1 (6.0)	5.8 (6.3)	39.4 (46.0)
Missing Digit Test						
Percentage correct	46.7 (17.3)	53.6 (11.9)	6.9 (8.3)	53.3 (20.2)	59.2 (18.3)	5.8 (8.2)
Stroop						
Control condition (s)	88.0 (23.9)	78.3 (10.2)	8.3 (12.9)	77.4 (7.1)	70.7 (5.6)	8.3 (9.7)
Interference condition (s)	157.3 (28.3)	160.3 (19.0)	–3.8 (17.9)	142.75 (39.4)	136.3 (22.5)	1.7 (15.6)
Difference interference–control (s)	69.3 (20.6)	82.0 (22.4)	–22.2 (33.5)	65.3 (42.7)	65.7 (22.3)	–23.3 (52.3)
Visual–Visual Conditional Learning						
Total trials to criterion	54.9 (22.2)	67.7 (16.7)	–36.7 (44.6)	55.2 (16.1)	65.3 (9.2)	–25.4 (33.9)
Total errors	24.9 (14.3)	33.0 (15.7)	–49.2 (65.6)	24.4 (12.7)	29.3 (9.2)	–38.0 (59.0)
Number who reached criterion	4	2		4	1	
Number who did not reach criterion	3	5		2	5	
Random Number Generation						
Chi-square	3.5 (1.4)	2.1 (0.97)	35.7 (28.4)	2.1 (1.3)	4.1 (2.9)	–96.6 (102.6)
RNG index	0.41 (0.08)	0.37 (0.049)	9.2 (11.3)	0.38 (0.03)	0.39 (0.05)	–3.07 (11.9)
Count score 1	126.0 (117.9)	95.6 (62.2)	–8.2 (57.6)	79.6 (20.9)	98.6 (60.3)	–13.3 (51.2)
Count score 2	42.2 (14.9)	46.7 (22.6)	–25.8 (80.5)	69.0 (23.1)	56.2 (41.6)	25.7 (30.5)
Wisconsin Card Sorting Test						
Number of categories correctly sorted	3.0 (2.0)	5.2 (1.3)	125.0 (103.1)	4.8 (2.2)	5.0 (1.2)	68.7 (185.9)
Number of non-perseverative errors	8.4 (5.4)	4.6 (3.1)	43.7 (21.5)	6.2 (6.1)	5.4 (4.8)	–5.2 (89.5)
Number of perseverative errors	3.2 (2.2)	1.0 (1.4)	70.8 (34.4)	1.0 (0.7)	3.6 (3.2)	–275.0 (359.4)
Percentage of perseverative errors	21.9 (12.6)	9.9 (13.7)		16.1 (13.7)	42.7 (26.4)	
Word Fluency						
First letter – Total words generated	11.6 (7.3)	11.9 (6.3)	8.4 (22.5)	12.2 (2.4)	13.0 (4.4)	6.1 (21.6)
Category – Total words generated	10.1 (3.3)	12.0 (5.5)	20.2 (33.7)	12.4 (1.5)	14.8 (4.4)	23.6 (50.7)

For mean percentage change scores, positive scores indicate improvement and negative scores deterioration. Standard deviations are given in parentheses.

of the Stroop (naming the colour of coloured rectangles) [main effect of stimulation $F(1,10) = 5.4$, $P = 0.043$]. Five of the six patients (83.3%) in the GPi group and four of the six patients (66.7%) in the STN group who had completed this test were faster with DBS on than off. For this measure, the main effect of group [$F(1,10) = 1.6$, $P = 0.23$] and the group $\times$ stimulation interaction [$F(1,10) = 0.17$, $P = 0.68$] were not significant. For the Stroop main interference condition (naming the colour of colour words printed in colour incongruent ink) and the Stroop interference effect (difference between main and control tasks), none of the main or interaction effects were significant ($P > 0.05$). However, the patients made a greater number of self-corrected errors on the main interference condition of the Stroop with stimulation on compared with off, a difference which was significant for the STN [off: mean errors = 4.1 (SD = 3.5); on: mean errors = 6.7 (SD = 2.7); $P < 0.001$] but not the GPi

[off: mean errors = 4.7, (SD = 3.2); on: mean errors = 6.0 (SD = 4.2); $P = 0.114$] group.

Effective stimulation also resulted in significant deterioration of performance on the VCLT. Across the two groups, the total trials to criterion [main effect of stimulation: $F(1,11) = 6.0$, $P = 0.032$] and the number of blocks of trials to reach criterion [stimulation on versus off, $\chi^2(12) = 20.8$, $P = 0.05$] were significantly higher with stimulation. The main effect of group [$F(1,11) = 0.02$, $P = 0.89$] and the group $\times$ stimulation interaction [$F(1,11) = 0.08$, $P = 0.785$] was not significant for the total trials to criterion. With the stimulators off, eight of the 13 patients (62%) reached the criterion of correctly associating the six designs with the six colours in six or fewer blocks. In contrast, with the stimulators on, only three of the 13 patients (23%) achieved criterion. The total number of errors showed a similar pattern of deterioration with stimulation, but none of the main or interaction effects were statistically significant ($P > 0.05$).

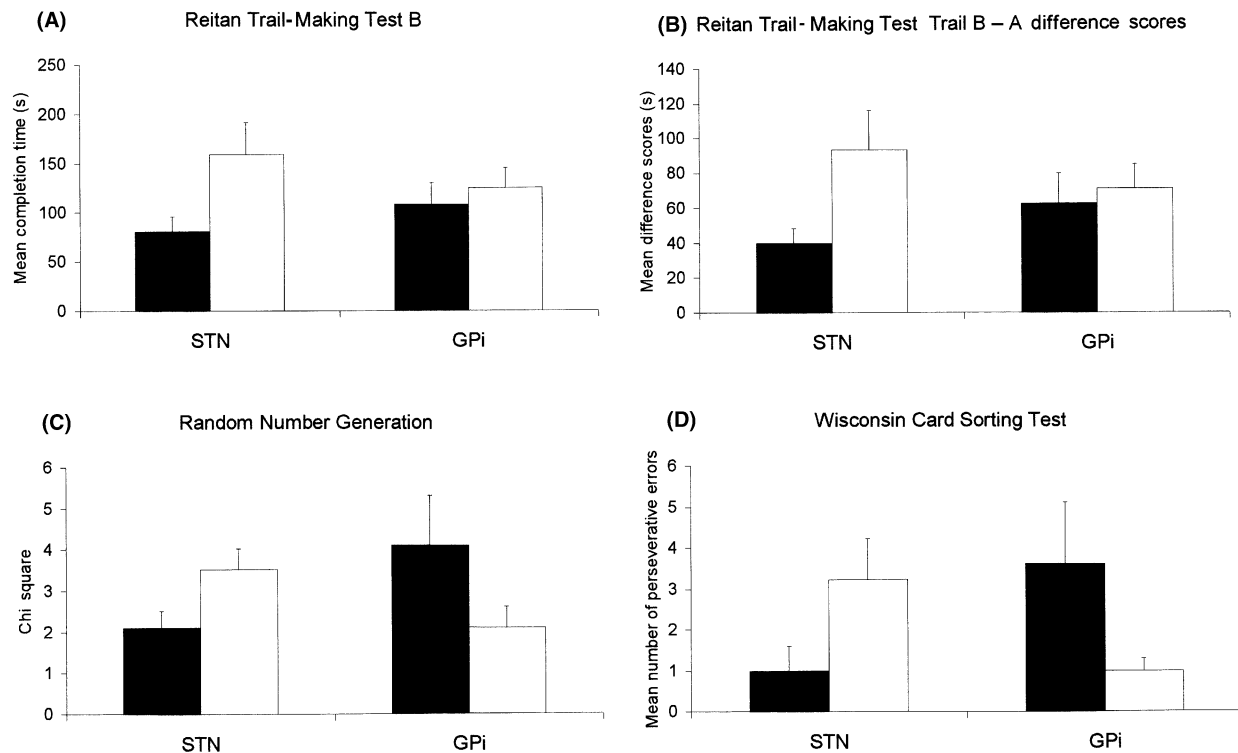


Fig. 1 Simulation resulted in (A) a significantly greater improvement on TMT B and (B) a significantly greater reduction of the TMT B–A difference score on this test for the STN than the GPi group. (C) Change in the χ^2 measure of RNG indicative of greater randomness of responses for the STN but not the GPi group. (D) Significant differential change of perseverative errors on the WCST, which were reduced for the STN group but increased for the GPi group. Black bars = stimulation on; white bars = stimulation off.

On the RNG test, the group $\times$ stimulation interaction was significant for χ^2 [$F(1,11) = 11.9$, $P = 0.005$] and approached significance for the RNG index [$F(1,10) = 3.9$, $P = 0.076$]. While these measures showed significant improvement of performance, i.e. towards greater randomness of the output with stimulation in the STN group [χ^2 : $t(6) = 2.8$, $P = 0.032$, RNG index: $t(6) = 2.2$, $P = 0.068$], the opposite effect was obtained for the GPi group, which was not statistically significant [χ^2 : $t(5) = 2.2$, $P = 0.074$; RNG index: $t(5) = 0.69$, $P = 0.520$], however (Fig. 1C). In the STN group, the χ^2 and RNG indices were improved with DBS, respectively for six (85.7%) and five (71.4%) of the seven patients, while in the GPi group, in five of the six patients (83.3%) these scores were worse with DBS. The main effects of group [χ^2 : $F(1,11) = 0.11$, $P = 0.74$; RNG: $F(1,10) = 0.01$, $P = 0.097$] or stimulation [χ^2 : $F(1,11) = 0.38$, $P = 0.55$; RNG: $F(1,10) = 0.40$, $P = 0.54$] were not significant for either of these two measures. For the two seriation measures of the RNG test, count score 1 and count score 2, none of the main or interaction effects were statistically significant ($P > 0.05$).

For the number of perseverative errors on the WCST, the group $\times$ stimulation interaction [$F(1,8) = 9.2$, $P = 0.016$] was significant, but the main effects of group [$F(1,8) = 0.03$, $P = 0.86$] and stimulation [$F(1,8) = 0.06$, $P = 0.81$] were not. The significant interaction was due to the fact that the numbers of perseverative errors on the WCST were

significantly reduced by STN stimulation from a mean of 3.2 (SD = 2.2) to a mean of 1.0 (SD = 1.4) [$t(4) = 2.9$, $P = 0.04$], whereas for the patients with GPi stimulators the mean number of perseverative errors was 1.0 (SD = 0.7) with the stimulators off, and 3.6 (SD = 3.2) with the stimulators on, a change that was not significant [$t(4) = 1.6$, $P = 0.137$] (Fig. 1D). The main effect of group or stimulation and the group $\times$ stimulation interaction were not significant ($P > 0.05$) for either the number of categories correctly sorted or the number of non-perseverative errors on the WCST. However, *post hoc* paired *t*-tests showed that the number of categories correctly sorted was significantly higher [$t(4) = 2.8$, $P = 0.05$] and the number of non-perseverative errors were significantly lower [$t(4) = 2.7$, $P = 0.05$] with stimulation in the STN group, whereas in the GPi group the changes were not significant ($P > 0.05$). In the STN group, four of the five patients (80%) who had completed the WCST showed improved performance as indicated by a higher number of categories correctly sorted and fewer perseverative and non-perseverative errors with stimulators on compared with off. For the remaining case, performance was unchanged by stimulation.

Although there was a trend for stimulation to improve performance on the semantic version of the word fluency task, neither this nor the change in the phonemic version showed any significant main or interaction effects ($P > 0.05$).

We examined the association between the change in the

clinical measures (UPDRS and Hoehn and Yahr ratings) and the percentage change scores for the various measures of cognitive function using Spearman correlation coefficients. For the sample as a whole, the improvement in the UPDRS scores was significantly associated with improvement in the number of perseverative errors on the WCST ($r = 0.66$, $P = 0.038$) and on TMT B ($r = 0.64$, $P = 0.048$). The improvement in the Hoehn and Yahr ratings also showed significant correlation with improvement in the number of categories correctly sorted on the WCST ($r = 0.67$, $P = 0.036$). The other associations were not significant.

We also examined how change in the speed of movement initiation as measured with an unwarned visual simple reaction time task completed by the subjects on the same day with the stimulators on and off (Brown *et al.*, 1999) correlated with change in executive function with DBS. As the STN and GPi samples were small, the majority of these associations were not statistically significant. However, in the STN group, change in movement initiation had Spearman correlation coefficients which were positive and ranged from 0.50 to 0.80, with percentage change scores in the PVSAT, TMT, missing digit, Stroop control and interference tasks, and negative correlations with percentage change in the RNG index ($r = -0.50$), VCLT total errors ($r = -0.50$), WCST non-perseverative errors ($r = -0.62$) and phonemic word fluency ($r = -0.70$). In the GPi group, percentage change in movement initiation had a positive correlation with percentage change in phonemic word fluency ($r = 0.94$, $P = 0.05$) and the RNG chi-square index ($r = 0.94$, $P < 0.005$), both of which were significant; and two other positive correlations above 0.50 with percentage change on the Stroop interference task ($r = 0.54$) and count score 1 measure of the RNG test ($r = 0.60$). For the GPi group, none of the negative correlations were above 0.50.

Discussion

DBS was effective in controlling the symptoms of Parkinson's disease since both STN and GPi stimulation led to a significant reduction of UPDRS scores. The impact of DBS on the measures of executive function and working memory used can be classified into four groups. First, those on which both the patients with DBS of the STN or GPi showed improvement with the stimulators on compared with off. These were the PVSAT, missing digit, TMT A and B and their difference score, and the control Stroop task. Secondly, the VCLT, on which both groups showed deterioration with the stimulators on compared with off. Thirdly, the tests on which performance was not significantly altered with stimulation in either group, which were the word fluency and measures of seriation on the RNG test. Finally, the STN and GPi groups showed differential change on the TMT B, TMT difference score (STN group more improved with stimulation) and perseverative errors on the WCST and two of the measures (χ^2 and RNG index) of RNG (STN group improved, GPi group worse with stimulation). It is also important to note

that although for some of the tests (e.g. TMT), the number of valid observations was small as some patients could not complete the test with the stimulators off, nevertheless, there was a consistent trend for the STN group to show a greater effect of stimulation than the GPi group, both clinically and in terms of impact of DBS on executive function, and, on virtually all of the tests used, the change in performance with stimulation of the GPi was not statistically significant. One reason for such differential effects of DBS of the STN and GPi may be that, as previously shown (Bejjani *et al.*, 1997; Krack *et al.*, 1998b), the effect of DBS of the GPi is complex, with stimulation of its dorsal versus ventral portions producing opposite effects on akinesia (improved by DBS of the dorsal GPi, worse with DBS of the ventral GPi) and dyskinesias (improved by DBS of the ventral GPi, worse with DBS of the dorsal GPi).

Improved speed of responding, which has been documented in an associated study involving the majority of the present sample (Brown *et al.*, 1999), may have contributed to the significant change observed on the timed tests such as TMT A and B, the Stroop control task and the PVSAT. This is confirmed by the non-significant correlations of improvement on these tests and improvement in movement initiation. However, the significant improvement on the more complex TMT B or TMT B – A difference score and the PVSAT cannot be due solely to improved motor speed, but also suggests faster or more efficient cognitive processing. In the MPTP monkey, lesions of the STN have been reported not only to reduce parkinsonian signs such as improving spontaneous activity and reducing freezing, but also to result in improved attention to external stimuli (Aziz *et al.*, 1991; Wichmann *et al.*, 1994). The differentially greater improvement of the group with DBS of the STN on the cognitively more demanding Trail B which requires switching of attention between two types of stimuli, numbers and letters, and the Trail B – A difference score may reflect such an enhanced attentional effect.

The PVSAT and the missing digit tests are externally paced, but both require holding one (PVSAT) or more (missing digit) items of information 'on line' across an interval of several seconds. Both groups showed improved performance on these tests with stimulation. With PET, the missing digit significantly activated the DLPFC (Brodmann areas 9 and 46) bilaterally and the posterior premotor cortex bilaterally (Petrides *et al.*, 1993a). The SMA and lateral premotor cortex are among the areas that are activated during the paced serial addition test (de Jong *et al.*, 1996). Recent evidence from animal experimentation has shown that in the motor circuit, there are multiple and separate projections from the GPi to the motor cortex, SMA and lateral premotor cortex (Hoover and Strick, 1993). Improvement of performance on these tests with stimulation may relate to changes in activity in the lateral and medial premotor cortex which are cortical sites of projection of the outflow from the GPi and the STN in the motor circuit. Animal studies have shown that the lateral premotor cortex and the SMA are

essential for response selection on the basis of external or internal cues, respectively (Passingham, 1993), and it is possible that they are engaged in a similar way during PVSAT and missing digit tests.

What processes are common to TMT B, the WCST and the RNG test, on all of which the STN group showed differentially greater improvement with stimulation than the GPi group? In addition to the necessity of holding information 'on line', some of the other processes that are necessary for performance of these tasks are: intrinsic generation of responses partly through suppression of habitual responses (e.g. connecting numbers serially on TMT B, or repeated sorting by one stimulus dimension on the WCST, or habitual counting on the RNG task), monitoring of one's output and switching attention between different stimulus attributes or items in a set. These are all processes that are dependent on the integrity of the DLPFC. As the STN has connections to both the GPi and SNr output pathways from the basal ganglia, it is possible that stimulation of the STN differentially affects the DLPFC which is a target of the thalamic projection from the SNr. This would be in line with the PET results of Limousin and colleagues, who found that greater activation of the DLPFC was the only area that differentiated effective stimulation of the STN and GPi (Limousin *et al.*, 1997). However, it should also be noted that word fluency which also engages some of these processes was not significantly altered with DBS in the present study, unlike the significant deterioration on this test observed by Troster and colleagues and Ardouin and colleagues (Troster *et al.*, 1997; Ardouin *et al.*, 1999). Such variations of the impact of DBS on different tasks of executive function and across studies may relate to the precise positioning of the stimulating electrodes in individual cases.

In rats made parkinsonian by injection of the neurotoxin 6-hydroxydopamine into the striatum, Baunez and colleagues reported that subsequent bilateral lesions of the STN alleviated the motor deficits, but resulted in lasting deficits of premature responding in simple and choice reaction time tasks (Baunez *et al.*, 1995; Baunez and Robbins, 1997). In the present study, patients were non-significantly slower and made a greater number of self-corrected errors on the interference condition of the Stroop with stimulation of the STN even though colour naming on the control Stroop task was significantly faster. This is reminiscent of the premature responding reported by Baunez and colleagues.

For both groups of patients with DBS of STN or GPi, performance on the VCLT was worse with stimulation, with the change being significant for the STN group only. With the stimulators on, the patients required more trials to reach criterion, and fewer patients reached criterion. This task requires learning by trial and error. As contextual information such as positional information is reduced and the associations between colours and abstract designs are completely arbitrary, such conditional associative learning tasks require strategic regulation of behaviour by internal representations of prior episodic information (Levine *et al.*, 1997). Such tasks

originally were shown to be sensitive to lesions of the lateral premotor cortex in animal studies (Halsband and Passingham, 1982; Petrides, 1982) and were adapted for administration to human subjects by Petrides who demonstrated their sensitivity to frontal pathology in man (Petrides, 1985). Functional imaging has shown that compared with control tasks, performance of conditional associative learning tasks is associated with significant activation of Brodmann area 8 and the anterior cingulate (Petrides *et al.*, 1993b) or the dorsal premotor area and the cingulate cortex (Mitz *et al.*, 1993), among other areas. Therefore, conditional associative learning tests appear to involve more posterior frontal areas (Brodmann areas 8 and 6), and probably different sections of the premotor cortex than those engaged by the PVSAT and missing digit tests, which showed improvement with DBS.

The findings of Canavan and colleagues and Gotham and colleagues are relevant to the present results (Gotham *et al.*, 1988; Canavan *et al.*, 1989). Canavan and colleagues examined the effect of bilateral lesions of the VA and VLo nuclei of the thalamus, which receive projections from the GPi and SNr, in four monkeys. After bilateral thalamotomy, acute post-surgical akinesia quickly receded, but an impairment of relearning a conditional learning task was found (Canavan *et al.*, 1989). Gotham and colleagues assessed patients with Parkinson's disease on a version of the VCLT identical to that used in the present study both on and off medication. Compared with controls, patients showed a significant increase in errors during learning only when assessed *on* medication. Furthermore, a significant positive correlation was obtained between total errors on this test and levodopa dosage, suggesting that levodopa levels optimal for control of motor symptoms of the disorder may be associated with overstimulation of the frontal cortex where dopamine transmission is relatively intact, with a consequent decline in cognitive function (Gotham *et al.*, 1988). These results suggest that the processes required for performance of conditional associative learning tasks are sensitive to bilateral lesions of the VA in the monkey (Canavan *et al.*, 1989), bilateral high frequency electrical stimulation of the STN or GPi in Parkinson's disease (present study) and possible dopaminergic overstimulation of the frontal cortex in Parkinson's disease (Gotham *et al.*, 1988). In contrast to our results with DBS, Trepanier and colleagues did not find any effect of pallidotomy on VCLT (Trepanier *et al.*, 1998). However, they evaluated their sample on medication and used a VCLT with only four pairs of association compared with our six, which makes our VCLT task more demanding and may account for the deterioration that we observed.

The impact of DBS on measures of upper limb movement paralleled the effects of dopaminergic medication reported in previous studies, with movement execution and force production showing the greatest improvement, and movement initiation and preparation improving to a lesser degree (Brown *et al.*, 1999). Dopaminergic medication produces a less consistent effect on cognitive function in Parkinson's disease. While some aspects of executive function and working

memory are improved with such medication (Girotti *et al.*, 1986; Gotham *et al.*, 1988; Cooper *et al.*, 1992; Lange *et al.*, 1992), others remain unchanged (Girotti *et al.*, 1986; Lange *et al.*, 1992) or even become impaired (Gotham *et al.*, 1988) following medication. The heterogeneous nature of the effects of DBS on the various measures of executive function and working memory in the present study is also reminiscent of the divergent results produced by levodopa medication.

In the light of current models of frontostriatal circuits as partially segregated, the question arises as to why DBS of the GPi or STN, which specifically targets the motor circuit between the medial pallidum and the SMA, should produce any effects on cognitive function which would be expected to be mediated by some of the other circuits such as the complex circuit between the caudate and the DLPFC (Alexander *et al.*, 1986). One possibility is that the localization of the implanted electrodes is not precisely or solely targeting the motor circuit. This is unlikely as, in almost every case, stimulation produced a significant improvement of motor function. A second possibility is that as the precise mechanisms of action of DBS are not fully understood; the neuronal zone within which the functional effects of stimulation is active may be quite diffuse, extending across both motor and cognitive circuits. In the case of the STN, another explanation may be the indirect projection to the DLPFC via the connection to the SNr (Ilinsky *et al.*, 1985; Barbas *et al.*, 1991). A final possibility is that the frontostriatal circuits are not as anatomically and functionally segregated as presumed. There is some evidence that the anatomical segregation of the circuits is not complete (Percheron and Filion, 1991). Also, within the framework of frontostriatal loops as 'split circuits', between-circuit interactions can occur via the 'open' loop elements of the closed circuits (Joel and Weiner, 1994).

The results lend some support to each of the two opposing predictions set out in the Introduction. The improved performance on some of the tests of executive function and working memory with effective stimulation of the STN or GPi is in accord with current models of frontostriatal connectivity and its impairment in Parkinson's disease. According to these models, DBS would alter excessive inhibitory outflow from the basal ganglia in Parkinson's disease and thus would be associated with 'releasing the brake' over frontal cortical function, which would, in turn, be associated with improvement in aspects of motor and cognitive function dependent on these frontal areas. It is feasible to suggest that the cognitive processes that improve with DBS are not dependent directly on striatal processes, but are simply facilitated by enhanced cortical activation. Conversely, the significant deterioration in learning of arbitrary conditional associations lends some support to the proposal of Marsden and Obeso that following subcortical surgery, patients with Parkinson's disease should exhibit some deficits in situations that require changing behaviour in novel contexts (Marsden and Obeso, 1994). In these aspects of executive function, the striatum may play a more central

role, providing important information for subsequent cortical processing. Although the impact of DBS of the STN and GPi is considered mainly in terms of changes in the activity of the frontostriatal circuits, some of the observed effects may be mediated through other pathways such as the outputs of the STN and GPi to the brainstem (Smith *et al.*, 1990). It is also possible that the projections that the STN receives from other cortical areas (Monakow *et al.*, 1978) could influence the activity of these areas through an antidromic conduction.

Despite worsening of VCLT and improvement of some aspects of attention and working memory with DBS, none of the patients reported any changes in concentration, attention or memory, either spontaneously or on direct questioning. Therefore, the *clinical* significance of these cognitive changes in everyday life is difficult to determine. The present study compared the effects of DBS of the STN or GPi after a relatively short interval of 2–26 months after surgery. It is possible that chronic DBS for many years may have more long-term effects on the STN or GPi, the cognitive sequel of which may also be different from the current findings. This is an issue that requires longitudinal follow-up of patients with chronic DBS in order to assess the long-term efficacy of the procedure in controlling the symptoms of Parkinson's disease and its impact on cognitive and motor function.

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