PAPER

Defining a role for the subthalamic nucleus within operative theoretical models of subcortical participation in language

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Objective: To investigate the effects of bilateral, surgically induced functional inhibition of the subthalamic nucleus (STN) on general language, high level linguistic abilities, and semantic processing skills in a group of patients with Parkinson's disease.

Methods: Comprehensive linguistic profiles were obtained up to one month before and three months after bilateral implantation of electrodes in the STN during active deep brain stimulation (DBS) in five subjects with Parkinson's disease (mean age, 63.2 years). Equivalent linguistic profiles were generated over a three month period for a non-surgical control cohort of 16 subjects with Parkinson's disease (NSPD) (mean age, 64.4 years). Education and disease duration were similar in the two groups. Initial assessment and three month follow up performance profiles were compared within subjects by paired *t* tests. Reliability change indices (RCI), representing clinically significant alterations in performance over time, were calculated for each of the assessment scores achieved by the five STN-DBS cases and the 16 NSPD controls, relative to performance variability within a group of 16 non-neurologically impaired adults (mean age, 61.9 years). Proportions of reliable change were then compared between the STN-DBS and NSPD groups.

Results: Paired comparisons within the STN-DBS group showed prolonged postoperative semantic processing reaction times for a range of word types coded for meanings and meaning relatedness. Case by case analyses of reliable change across language assessments and groups revealed differences in proportions of change over time within the STN-DBS and NSPD groups in the domains of high level linguistics and semantic processing. Specifically, when compared with the NSPD group, the STN-DBS group showed a proportionally significant ($p<0.05$) reliable improvement in postoperative scores achieved on the word test-revised (TWT-R), as well as a reliable decline ($p<0.01$) in the accuracy of lexical decisions about words with many meanings and a high degree of relatedness between meanings.

Conclusions: Bilateral STN-DBS affects certain aspects of linguistic functioning, supporting a potential role for the STN in the mediation of language processes.

Operative theoretical models of subcortical participation in language highlight what is currently recognised as the "direct" basal ganglia pathway to represent the neural turnpike underpinning cortico-subcortical-cortical linguistic processes,[1 2] failing to consider a role for the subthalamic nucleus (STN). Following the inception of these models, however, a "direct-indirect" pathway dichotomy has been endorsed as the scheme for functional organisation within the basal ganglia,[3 4] and most recently, tracing studies have revealed multiple "indirect" basal ganglia circuits, in addition to the classical indirect pathway, which incorporate or influence STN activity.[5 6]

It has been hypothesised that the STN regulates activity within thalamocortical projection neurones by way of excitatory influences on the principal output nuclei of the basal ganglia.[5] In relation to working theories of subcortical participation in language, it has been postulated that the striatum, internal globus pallidus (GPi), and a chain of thalamic nuclei (including the ventral anterior and lateral nuclei, pulvinar, centrum medianum (CM), and nucleus reticularis (NR)) facilitate the activation, integration, transfer, or modulation of cortically generated, context specific linguistic information through cortico-subcortical-cortical circuits.[1 2 7] Evidently, indirect circuitry components—such as external globus pallidus (GPe)-STN, STN-GPe,[8] cortex-STN,[9] GPe-GPi/substantia nigra reticulata (SNr), GPe-NR,[6] centrum medianum-parafascicular complex (CMPFC)-STN,[5] and GPi-CM[10] projections—suggest major ramifications for basal ganglia mediated thalamocortical activity subserving language processes.

Three theories of subcortical participation in language have influenced contemporary thinking about the role of subcortical structures in mediating language processes.[1 2 7] Despite defined functions for the striatum, globus pallidus, and thalamus within response-release semantic feedback,[1] lexical decision,[2] and selective engagement[7] models, each theoretical construct has so far failed to recognise a potential role for the STN in language.

A recent resurgence in the application of advanced neurosurgical techniques to the treatment of Parkinson's disease[11 12] is providing a means whereby theories about STN involvement in language may be tested. Deep brain stimulation (DBS) is one such technique. The precise mechanism underpinning DBS remains unknown; however, the therapeutic effects appear to be equivalent to those resulting from ablative lesions,[13 14] involving functional inhibition of the target structure by three possible mechanisms: depolarisation block, neural jamming, or the activation of inhibitory afferents.[15]

Bilateral deep brain stimulation involving the subthalamic nucleus (STN-DBS) is thought to interfere with the integrity of the indirect pathway, so that the direct pathway largely

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Abbreviations: DBS, deep brain stimulation; GPe, external globus pallidus; GPi, internal globus pallidus; MDRS, Mattis dementia rating scale; NR, nucleus reticularis; RCI, reliable change index; RD, reliable decline; SNr, substantia nigra reticulata; STN, subthalamic nucleus; TWTR, the word test revised

Box 1 Language assessment battery

Battery 1: Gross language

- Neurosensory Centre comprehensive examination for aphasia (NCCEA)[20]
- Boston naming test (BNT)[21]

Battery 2: High level linguistics

- Test of language competence–expanded (TLC-E)[22]

  Subtests:

  a. **Ambiguous sentences** (for example, providing two essential meanings for ambiguous sentences (such as, *Right then and there the man drew a gun*))

  b. **Making inferences** (for example, using causal relations or chains in short paragraphs to make logical inferences)

  c. **Recreating sentences** (for example, formulating grammatically complete sentences using key semantic elements within defined contexts (such as, defined context = *At the ice cream store*; key semantic elements = *some, and, get*)

  d. **Figurative language** (for example, interpreting metaphorical expressions (such as, *There is rough sailing ahead for us*) and correlating structurally related metaphors (such as, *We will be facing a hard road*) according to shared meanings)

  e. **Remembering word pairs** (for example, recalling paired word associates)

- The word test-revised (TWT-R)[23]

  a. **Associations** (for example, identifying semantically unrelated words within a group of four spoken words (eg, knee, shoulder, ***bracelet***, ankle) and providing an explanation for the selected word in relation to the category of semantically related words (eg, *The rest are parts of the body*))

  b. **Synonym generation** (for example, generation of synonyms for verbally presented stimuli (eg, *afraid = scared*))

  c. **Semantic absurdities** (for example, identifying and repairing semantic incongruities (eg, *My grandfather is the youngest person in my family = My grandfather is the oldest person in my family*)

  d. **Antonym generation** (for example, generating antonyms for verbally presented stimuli (eg, *alive = dead*))

  e. **Formulating definitions** (for example, identify and describe critical semantic features of specified words (eg, *house = person + lives*))

  f. **Multiple definitions** (for example, provision of two distinct meanings for series of spoken homophonic words (eg, *down = position/feathers/feeling*)

- Conjunctions and transitions subtest of the test of word knowledge (TOWK)[24] (for example, evaluation of logical relations between clauses and sentences (eg, *It is too cold to play outside now. We will play outside* (**until/when/where/while**) *it gets warmer*)
- Wiig-Semel test of linguistic concepts (WSTLC)[25] (for example, comprehension of complex linguistic structures (eg, *John was hit by Eric. Was John hit?*))
- Animal and tool verbal fluency

Battery 3: Semantic processing

- Lexical decision task incorporating written legal non-words (that is, pronounceable but meaningless letter strings (eg, BELF)) and real word stimuli (eg, TRAP) classified by number of meanings and meaning relatedness[26]

assumes control of GPi/SNr outputs.[16] With respect to language, the resultant thalamic disinhibition was hypothesised to result in the following:

- extraneous verbal output as a result of disturbed preverbal semantic monitoring mechanisms and heightened anterior language cortex activity[1];
- lexical selection deficits and speech initiation difficulties resulting from disturbed thalamic gating mechanisms and the random excitation of inhibitory cortical interneurones[2]; or
- any combination of language comprehension and production deficits as a result of indiscriminate or inappropriate thalamic engagement of cortical regions subserving linguistic processes.[7]

Our aims in the study were therefore to evaluate the effects of bilateral STN-DBS on language functioning; and to discuss postoperative language profiles within the context of working theories of subcortical participation in language.

METHODS

Participants

Five individuals with idiopathic Parkinson's disease (mean (SD) age, 63.2 (4.8) years; level of formal education, 11.4 (3.0) years; disease duration 10.8 (4.1) years), considered appropriate candidates for bilateral surgical implantation of deep brain electrodes within the dorsolateral STN (as determined by a qualified neurologist and neurosurgeon), served as experimental subjects for this research. Biographical details of these patients are listed in table 1, including age, sex, education, disease duration, disease severity, and drug regimens. The Hoehn and Yahr staging of Parkinson's disease[17] provided the basis for rating disease severity on a scale of 1 (unilateral disease) to 5 (wheelchair

Table 1 Biographical summary of characteristics of subjects given bilateral subthalamic nucleus deep brain stimulation

Subject	Sex	Age (years)	Formal education (years)	Disease duration (years)	Age at onset (years)	Disease severity		Primary symptom	Side affected	Drug treatment (preop daily dose (mg))	Drug treatment (postop daily dose (mg))
						Pre	Post				
1	M	62	14	16	46	4.0	2.5	Bradykinesia	BL (L>R)	Sinemet (1000) Comtan (600)	Sinemet (1000)
2	F	62	10	13	49	3.0	3.0	Tremor	BL (R>L)	Madopar (750) Symmetrel (200)	Madopar (500)
3	M	68	8	4	64	5.0	4.0	Bradykinesia	BL	Symmetrel (300) Sinemet (1100) Madopar (250)	Sinemet (825) Madopar (125)
4	M	68	15	14	54	2.0	2.0	Tremor	BL (R>L)	Madopar (500) Tambacor (100) Betaloc (50)	Cabaser (1 mg)
5	M	56	10	10	46	2.0	2.0	Tremor	BL (R>L)	Madopar (750)	Madopar (750)

Disease severity is given by the Hoehn and Yahr scale score.[17]
F, female; L, left; M, male; postop, postoperative; preop, preoperative; R, right; BL, bilateral.

bound or bedridden unless aided). Preoperatively the five STN-DBS subjects achieved a mean (SD) Hoehn and Yahr rating of 3.2 (1.3), indicating mild to moderate bilateral disease. Postoperatively, the mean Hoehn and Yahr score declined to 2.7 (0.8), indicating a subtle improvement in motor performance in the presence of mild bilateral disease. Preoperative magnetic resonance imaging (MRI) revealed no brain abnormalities, and extensive preoperative neuropsychological testing showed executive functioning to be largely intact, with no evidence of co-morbid dementing illness or indicators of anxiety or depression.

Controls were first, a cohort of 16 non-surgical patients with Parkinson's disease (NSPD) (mean (SD) age, 64.4 (8.4) years; level of education, 12.0 (4.1) years; disease duration, 7.3 (5.5) years; Hoehn and Yahr score, 2.25 (0.82)); and second, 16 non-neurologically impaired (NC) subjects (age, 61.9 (9.0) years; level of formal education, 12.6 (4.5) years). Both the surgical and control subjects were native English speakers with no reported previous history of head injury, cerebrovascular accident, cerebral tumour or abscess, co-existing neurological disease, substance abuse, psychiatric disorder, or speech and language disorder (for Parkinson's disease subjects, before the onset of the disease). Subjects in the NC group were required to demonstrate perceptually normal speech as judged by a qualified speech pathologist and to score within the normal range of cognitive functioning[18] on the Mattis dementia rating scale (MDRS).[19] NSPD subjects were also required to score within the range of normal cognitive functioning on the MDRS, and those with more than mild perceived dysarthria severity were excluded from the study to avoid possible misinterpretation of verbal responses.

Procedure

Linguistic evaluation

All subjects underwent a comprehensive language assessment comprising three distinct test batteries evaluating general and high level linguistic functioning, in addition to on-line semantic processing (box 1).

The surgical subjects were assessed up to one month before and three months after the implantation of bilateral deep brain electrodes within the dorsolateral subthalamic nucleus, during active stimulation. Each of the five bilateral STN-DBS subjects were placed on a continuous stimulation schedule (that is, 24 hours a day) from the time of initial calibration. Postoperative stimulation parameters were calibrated to achieve optimal relief of motor symptoms and are summarised in table 2 with respect to left-right electrode orientation. The NSPD subjects were assessed over the same time interval (that is, an initial assessment and a three month follow up assessment). Furthermore, all participants with Parkinson's disease were assessed in perceived ''on'' periods (that is, when receiving optimal drug treatment as determined by the individual subjects).

All testing was undertaken in a quiet distraction-free environment according to standardised testing instructions. Subject fatigue levels were monitored throughout the assessments and multiple testing sessions were provided to compensate for fatigue effects when required.

Table 2 Summary of postoperative electrode configuration and stimulation parameters in subjects with bilateral subthalamic nucleus high frequency deep brain stimulation: left side

Subject	Electrode configuration	Stimulation contacts	Frequency (Hz)	Pulse width (μs)	Voltage (V)
Left side					
1	Bipolar	0–1	100	60	3.0
2	Unipolar	2–	130	60	3.7
3	Unipolar	3–	160	60	2.0
4	Bipolar	1+0–	160	60	3.3
5	Bipolar	0–1	160	60	2.8
Right side					
1	Bipolar	0–1	100	60	2.5
2	Unipolar	1–	130	60	3.9
3	Unipolar	3–	160	60	2.0
4	Bipolar	1+0–	130	60	2.9
5	Bipolar	0–1	160	60	3.0

0, most distal electrode; 3, most proximal electrode (relative to point of attachment).

Table 3 Comparison of initial and three month follow up language assessment scores in the bilateral subthalamic nucleus deep brain stimulation (STN-DBS) and non-surgical Parkinson's disease (NSPD) groups

	STN-DBS (n = 5)				**NSPD (n = 16)**			
Test variable	**Initial assessment score (mean (SD))**	**Three month follow up assessment score (mean (SD))**	***t***	**p Value**	**Initial assessment score (mean (SD))**	**Three month follow up assessment score(mean (SD))**	***t***	**p Value**
$\text{NCCEA}_{\text{TOT}}$	514.7 (30.2)	518.3 (40.1)	−0.59	0.586	544.5 (15.7)	551.8 (21.2)	−2.50	0.025
BNT	45.6 (6.2)	48.6 (6.7)	−1.20	0.298	51.8 (5.7)	52.7 (4.3)	−1.21	0.246
Tools	12.6 (3.0)	11.0 (5.3)	−1.12	0.327	13.1 (4.8)	16.5 (5.0)	−2.94	0.011
Animals	15.2 (5.9)	14.8 (4.1)	0.15	0.889	18.0 (4.3)	18.6 (3.5)	−0.84	0.417
TLCE_{TOT}	139.8 (26.2)	150.8 (24.7)	−3.57	0.023	172.4 (19.2)	178.3 (17.6)	−2.27	0.038
TWTR_{TOT}	73.2 (8.6)	75.8 (10.9)	−0.92	0.412	83.0 (4.2)	83.1 (4.2)	−0.18	0.860
TOWK	21.0 (4.9)	21.0 (6.4)	0.00	1.000	25.4 (2.8)	25.1 (2.5)	0.72	0.484
WSTLC	43.8 (2.2)	44.8 (3.9)	−0.77	0.486	47.0 (2.1)	47.0 (3.0)	0.00	1.000
ACC MH	9.8 (0.5)	9.5 (1.0)	0.40	0.718	9.7 (0.6)	9.8 (0.5)	−0.37	0.718
ACCML	9.5 (0.6)	9.3 (1.0)	0.40	0.718	9.6 (0.5)	9.9 (0.3)	−1.46	0.164
ACCFH	9.0 (1.4)	9.0 (0.8)	0.00	1.000	9.6 (0.7)	9.4 (0.8)	0.72	0.485
ACCFL	10.0 (0.0)	8.0 (2.0)	2.00	0.139	9.6 (0.6)	9.7 (0.7)	−0.44	0.669
ACCLNW	28.5 (19.0)	32.3 (4.3)	−0.91	0.430	33.6 (10.4)	31.5 (13.3)	0.53	0.602
RTMH	1025.8 (915.1)	1281.1 (1200.4)	−4.51	**0.000***	871.2 (383.8)	835.9 (262.5)	1.32	0.191
RTML	922.6 (212.4)	1219.1 (893.1)	−2.45	0.019	891.4 (386.2)	849.7 (338.7)	1.29	0.200
RTFH	1095.4 (212.4)	1331.1 (804.9)	−2.29	0.028	1036.9 (1539.9)	866.0 (275.5)	1.40	0.165
RTFL	920.3 (354.8)	1104.4 (380.9)	−3.38	**0.002***	847.3 (335.9)	860.3 (436.0)	−0.43	0.671
RTLNW	1214.6 (737.2)	1584.2 (840.4)	−12.32	**0.000***	1182.9 (850.7)	113.0 (626.3)	1.75	0.080

*Significant at $p<0.003$ after Bonferroni adjustment.
ACCFH, accuracy few/high words; ACCFL, accuracy few/low words; ACCMH, accuracy many/high words; ACCML, accuracy many/low words; ACCLNW, accuracy legal non-words; animals, animal fluency; BNT, Boston naming test; $\text{NCCEA}_{\text{TOT}}$, Neurosensory Centre comprehensive examination for aphasia total score; RTFH, reaction time few/high words; RTFL, reaction time few/low words; RTLNW, reaction time legal non-words; RTMH, reaction time many/high words; RTML, reaction time many/low words; TLCE_{TOT}, test of language competence expanded total score; tools, tool fluency; TWTR_{TOT}, the word test revised total score; WSTLC, Wiig-Semel test of linguistic concepts total score.

Normal control baseline data were acquired and employed as a normative reference point to which surgical and NSPD performances could be compared. Using this reference point, reliable change indices (RCIs) relative to clinically significant performance changes over time in the STN-DBS and NSPD groups were calculated (discussed in detail below).

Statistical analysis

Assessment data were analysed using parametric tests of statistical significance (that is, related measures *t* tests, including a Bonferroni adjustment) and the calculation of RCIs.[27] The RCI represents a standardised difference score[28] which defines clinically significant change relative to a normal control population (that is, the level of postoperative functioning was predicted to fall within the range of a control population, where range is defined as a fixed measure of variance above or below that control group mean).[27] RCIs were calculated using the formula $\text{RCI} = X_2 - X_1/S_{\text{diff}}$,[29 30] where X_1 represents a subject's initial assessment score, X_2 represents a subject's score at the three month follow up assessment phase, and S_{diff} represents the standard error of difference relative to the distribution of scores within the NC sample. S_{diff} was calculated using the following formula:

$$\sqrt{(2\,(S_E{}^2))}$$

where S_E represents the standard error of the mean.

For the purposes of the current research, a *t* score of 2.131 (α level 0.05; $df = 15$) was established as the criterion for clinically significant change over time (that is, the period from the initial to the follow up assessment) within the STN-DBS and NSPD groups relative to the normative sampling distribution.

RESULTS

Parametric statistical comparisons

Multiple repeated measures *t* tests were conducted within the STN-DBS and NSPD groups for all assessment variables. Mean initial and three month follow up total assessment scores achieved by the two groups across language tasks are summarised in table 3. Significant performance differences over time were restricted to the STN-DBS group after application of related measures *t* tests with Bonferroni adjustment correcting for multiplicity of comparisons. At an α level of 0.003 (as determined by Bonferroni adjustment), the STN-DBS group showed a significant postoperative decline in performance on the reaction time component of the lexical decision task. Specifically, there were postoperative prolongations in reaction times for many/high words ($p<0.001$), few/low words ($p<0.01$), and legal non-words ($p<0.001$).

Measures of reliable clinical change

The performance heterogeneity of Parkinsonian populations and the fact that significant individual differences may be concealed within group comparisons[31 32] has led to an exploration of alternative methods of data analysis for such experimental cohorts. McCarter *et al* promoted the RCI as a means of investigating clinically important changes in datasets relating to small Parkinsonian populations that may fail to generate significant differences in performance when subjected to groupwise statistical comparisons.[28 33 34] Thus, in addition to groupwise comparisons, RCIs were calculated relating to differences between the initial and the three month assessment scores across measures of general language, high level linguistics, and semantic processing for each STN-DBS and NSPD subject who participated in the study. The scores were then related to performance variability within the NC group.

Percentages of reliable change (that is, reliable improvement and reliable decline) for the STN-DBS and the NSPD groups for general language, high level linguistics, and semantic processing are summarised in table 4. Significant differences in proportions of change were identified between the STN-DBS and NSPD groups on the TWT-R and accuracy of lexical decisions. Specifically, the STN-DBS subjects showed a greater proportion of reliable improvement (80%) on the TWT-R than the NSPD subjects (19%) ($p<0.05$).

Table 4 Percentage of assessment scores indicating reliable change or no reputable change from the initial to three months' follow up assessments in bilateral subthalamic nucleus stimulation (STN-DBS) and non-surgical Parkinson's disease (NSPD) groups

Language assessment	STN-DBS (n = 5)			NSPD (n = 16)			Proportions test (RI)		Proportions test (RD)	
	%RI	%RD	%NRC	%RI	%RD	%NRC	z	p Value	z	p Value
General language total score	30	10	60	28	3	69	−0.48	0.630	−0.57	0.571
NCCEA	20	0	80	38	6	56	0.20	0.840	−0.67	0.506
BNT	40	20	40	19	0	81	0.36	0.719	0.63	0.529
High level linguistics total score	44	23	33	30	16	54	0.04	0.971	−0.31	0.754
Tools	0	40	60	43	7	50	1.24	0.214	1.09	0.275
Animals	40	20	40	29	14	57	−0.09	0.929	−0.39	0.700
TLCE	60	0	40	38	6	56	0.35	0.727	−0.67	0.506
TWTR	80	2	0	19	13	68	1.98	**0.048***	−0.34	0.735
TOWK	40	40	20	13	31	56	0.68	0.494	−0.17	0.864
WSTLC	40	20	40	38	24	38	−0.45	0.655	−0.42	0.672
Semantic processing: accuracy	10	25	65	11	9	80	−0.76	0.445	0.17	0.867
MHACC	0	100	0	13	13	74	−0.01	0.993	3.05	**0.002****
MLACC	25	25	50	38	12	50	−0.01	0.996	−0.01	0.995
FHACC	0	0	100	0	0	100	−0.31	0.761	1.22	0.221
FLACC	0	0	100	0	0	100	−0.01	0.996	−0.31	0.761
LNWACC	25	0	75	6	19	75	0.37	0.709	0.33	0.745
Reaction time	20	70	10	27	35	38	−0.28	0.783	0.86	0.389
MHRT	25	75	0	12	44	44	−0.01	0.995	0.70	0.485
MLRT	25	75	0	19	25	56	−0.35	0.730	1.49	0.136
FHRT	25	75	0	31	31	38	−0.31	0.761	1.22	0.221
FLRT	25	25	50	38	31	31	−0.01	0.996	−0.31	0.761
LNWRT	0	100	0	38	46	16	1.07	0.284	1.62	0.105

*Significant difference between proportions at $p<0.05$; **significant difference between proportions at $p<0.01$.
Animals, animal fluency; BNT, Boston naming test; FHACC, few/high words accuracy; FHRT, few/high reaction time; FLACC, few/low words accuracy; FLRT, few/low reaction time; LNWACC, legal non-words accuracy; LWNRT, legal non-words reaction time; MHACC, many/high words accuracy; MHRT, many/high reaction time; MLACC, many/low words accuracy; MLRT, many/low reaction time; NCCEA, neurosensory comprehensive examination for aphasia; NRC, no reliable change; RD, reliable decline; RI, reliable improvement; TLCE, test of language competence expanded; tools, tool fluency; TOWK, test of word knowledge; TWTR, the word test revised; WSTLC, Wiig-Semel test of linguistic concepts.

Conversely, the STN-DBS group showed a greater proportion of reliable decline (100%) in the ability to identify accurately real words with many meanings and a high degree of relatedness between meanings compared with the NSPD group (13%) ($p<0.01$).

Further reliability change calculations were undertaken post hoc to identify which high level linguistic subtest scores accounted for the overall significantly reliable postoperative improvement in performance shown by the STN-DBS group on the TWT-R. Statistical comparisons of proportions of reliable improvement across the TWT-R subtests identified a greater proportion of improvement (80%) on the multiple definitions task compared with the NSPD group (12%) ($p<0.05$) (table 5).

Table 5 Comparison of proportions of reliable improvement between the bilateral subthalamic nucleus deep brain stimulation group (STN-DBS) and non-surgical Parkinson's disease group (NSPD) on subtests of the word test-revised (TWT-R)

TWT-R subtest	STN-DBS (n = 5)	NSPD (n = 16)		
	% RI	% RI	z	p Value
ASS	40	44	−0.36	0.719
SYN	60	50	−0.12	0.903
SEMAB	40	50	−0.12	0.903
ANT	40	12	0.75	0.456
DEF	60	31	0.64	0.523
MULDEF	80	12	2.38	0.017*

*Significant difference between proportions at $p = 0.05$.
ANT, antonyms; ASS, associations; DEF, definitions; MULDEF, multiple definitions; RI, reliable improvement; SEMAB, semantic absurdities; SYN, synonyms; TWT-R, the word test-revised.

Given the potential for performance heterogeneity within Parkinsonian populations and the discrepancy in comparative sample sizes used in this study, further analyses of high level linguistic performance profiles were considered necessary. A subcohort of NSPD subjects (n = 5)—matched as closely as possible to the STN-DBS subjects on variables such as age, sex, and level of education (mean age, 62.2 (2.8) years; level of formal education, 10.8 (3.4) years; disease duration, 7.0 (4.7) years)—were extracted from the original NSPD control group (n = 16) to determine whether the significant changes in the linguistic profiles of the STN-DBS group were indeed a direct result of DBS, or whether, when certain causal factors were allowed for, individuals with Parkinson's disease show similar fluctuations in language performance over time.

Reliability change indices were calculated for each of the STN-DBS and NSPD subjects with respect to their performance on TWT-R subtests. On inspection of these data, extreme heterogeneity between performances was evident, particularly within the STN-DBS group. When median values rather than means were explored, as a more resistant measure to accommodate extreme outliers,[35] quantifiable group differences were identified. Overall, the STN-DBS group showed a higher reliable change median (4.07) and a greater range of reliable decline and improvement (minimum −22.10; maximum 17.68) when compared with the NSPD group (reliable change median 0.00; range −13.26 to 5.66).

DISCUSSION

Our findings in this study support a potential role for the STN in the mediation of linguistic processes, presumably by way of excitatory projections to primary basal ganglia output nuclei responsible for the regulation of thalamocortical activity.[36 37] This hypothesis expands upon operative models of subcortical participation in language,[1 2 7] by introducing a previously disregarded basal ganglia component within an indirect cortico-striato-GPe-STN-GPi/SNr-thalamo-cortical linguistic circuit. Of particular note, bilateral STN-DBS produced significant changes across a limited number of language variables in the current study, specifically encompassing the domains of high level linguistics and semantic processing.

High level linguistics

The STN-DBS subjects as a group showed a significantly greater proportion of reliable improvement from the initial to three month follow up assessment phases when compared with the NSPD group on the TWT-R. This reliable improvement in performance was largely attributed to a proportionally significant increase in postoperative scores on the multiple definitions subtest.

Previous positron emission tomography studies of cortical activity during STN-DBS have shown enhanced activation within the supplementary motor area, anterior cingulate cortex, and dorsolateral prefrontal cortex during routine motor tasks (for example, random joystick movements) in individuals with Parkinson's disease.[38] Based on this evidence, functional inhibition of the STN as a result of DBS was predicted to have an effect on cognitive functions or tasks involving "novel" (that is, self generated) responses supported by the frontal cortex.[39] A reliable postoperative improvement shown by the STN-DBS group on the multiple definitions subtest of the TWT-R, involving the formulation of self generated or novel responses, suggested that STN-DBS may serve to enhance cortical activity (that is, in frontal and possibly temporoparietal regions), specifically subserving the production of complex divergent language in individuals with Parkinson's disease. Despite this finding, uncertainty remains as to why additional high level linguistic assessments that also required the formulation of self generated complex language (for example, synonym and antonym generation, definition formulation, semantic absurdity explanation, TLC-E, semantic and phonemic fluency) failed to reveal a similar profile of significant postoperative improvement.

Documented postoperative performance heterogeneity within stereotactic surgical populations of patients with Parkinson's disease[31 40] may provide an explanation for the inconsistent results in the current study. When RCIs relative to the performance of individual STN-DBS subjects on the TWT-R were analysed in detail, a general trend towards reliable improvement was demonstrated across constituent subtests. The presence of extreme outliers, however, could not be ignored. An RCI of 17.7 calculated for subject 5 on the multiple definitions subtest was considered to represent such an outlier which may have influenced the overall postoperative direction of reliable change observed on the TWT-R relative to the STN-DBS group. In reference to specific performance characteristics, subject 5 produced a number of preoperative stimulus bound errors,[23] whereby task responses fulfilled only one requisite definition reference criterion as opposed to two semantically distinct criteria (for example, the subject's response to test item "saw" = "*hack saw*" and "*circular saw*"; required reference criteria: tool/action + viewed/past tense). Postoperatively, subject 5 achieved a maximum score on the multiple definitions task, showing enhanced linguistic flexibility in the production of definitions constrained by semantically distinct criteria, relevant to words with more than one possible meaning (for example, postoperative response to test item "saw" = "*a tool*" *and* "*you saw it in the distance*").

An isolated mean reliable decline (RD) (mean (SD), −2.65 (11.09)) in performance was shown by the STN-DBS group on the antonyms subtest of TWT-R. This deterioration in performance was largely attributed to the RCI of −22.10 achieved by subject 3 on this task. Similarly, this outlier was also held accountable for the overall mean RD (−5.78 (8.39)) in performance shown by subject 3 across subtests of the TWT-R. This profile was in stark contrast to the mean RCIs calculated across subsets relative to the remaining four STN-DBS subjects. Stimulation contact parameters may provide an explanation for the results observed. Within the current study, a stimulation contact position of 0 represented the most distal electrode (that is, relative to point of attachment) and a contact position of 3 represented the most proximal electrode. Typically, contact 0 is positioned at the target site,[41] or in this case, the dorsolateral STN. Deep brain stimulation has been reported to produce spherical electrical fields with radii of approximately 3 mm.[42] Despite the fact that the spreading current of unipolar stimulation has been reported to decrease proportionally to the square of the distance from the active contact of the electrode,[43] the utilisation of more proximal stimulation contacts may have served to disturb neural structures around the target, resulting in wide ranging disruption of basal ganglia and potentially thalamic output influencing cognition. This result was in contrast with the enhanced motor outcomes observed in subject 3 during bilateral STN-DBS, as evidenced by a postoperative decrease in Hoehn and Yahr score (table 1). In addition, frequency has been defined as a critical variable with respect to the impact of STN-DBS on Parkinsonian motor dysfunction.[44] Idiosyncratically reduced overall performance on TWT-R in the presence of a relatively high stimulation frequency (160 Hz) and the recruitment of proximal electrodes in subject 3 indicate that these variables in combination may adversely influence certain cognitive skills, such as high level language.

In general, within dopamine deficient linguistic circuits (that is, in the preoperative state), STN hyperactivity may disturb thalamic regulation systems underlying the activation of cortical areas dedicated to the production of language. More specifically, GPi/SNr disinhibition as a result of excessive excitatory STN input may moderate the efficiency of indirect–direct pathway push-pull mechanisms subserving the release of semantically verified language segments as speech,[1] the synchronisation, transfer, and gating of competing lexical information for frontal processing,[2] or the engagement of cortical nets containing lexical-semantic information.[7] In relation to the current study, stimulation of the STN may largely have served to equilibrate rather than disrupt basal ganglia activity, including the potential enhancement of synaptic efficiency within neural circuits subserving certain high level cognitive linguistic processes.

Despite the fact that in-depth linguistic analyses of the impact of DBS on language in previous research are lacking, generative naming abilities (that is, performance on verbal fluency tasks) have been highlighted as one of the cognitive domains most susceptible to deterioration following this procedure, in addition to memory and executive function.[45] In the current study, within and between group statistical comparisons of the performance of subjects in the STN-DBS and NSPD groups failed to reveal significant changes in verbal fluency ability from the initial to the three month follow up assessments. Previous studies have reported a general decline in semantic[46–51] and phonemic[46 47 50–52] fluency during active bilateral STN-DBS. Other reports, however, have documented trends towards an improvement in semantic fluency,[39] in addition to a lack of overall significant change in verbal fluency.[48 52] Once again, these results highlight the extreme heterogeneity within cognitive performance profiles among parkinsonian populations, and the need to avoid generic conclusions in interpreting the results.

Semantic processing

When compared within subjects, postoperative STN-DBS reaction times achieved on the lexical decision task involving target word stimuli coded for number of meanings and degree of relatedness between meanings were significantly prolonged for all word types relative to preoperative status. A Bonferroni adjustment to account for multiplicity of comparisons, however, limited significant postoperative reaction time prolongations to legal non-words, words with many meanings and a high degree of relatedness between meanings, and words with few meanings and a low degree of relatedness between meanings. Preoperatively, the STN-DBS subjects showed the fastest reaction times to words with few and many meanings with a low degree of relatedness between meanings (table 3), followed by words with many and few meanings but with a high degree of relatedness between meanings. Slowest reaction times were observed for legal non-words. This same pattern of performance was observed postoperatively, with the exception of prolonged reaction times for all word types. It is anticipated that the use of a more stringent α level of 0.003, as determined by Bonferroni adjustment, may have concealed a general postoperative delay in relation to lexical access. Given that postoperative stimulation parameters were calibrated to achieve optimal motor outcomes, enhanced performance (that is, reduced postoperative reaction times) on the reaction time task during DBS was predicted, consistent with the findings of a number of other studies.[48 50 53] Considering the cognitive demands of the lexical decision task used in the current research, it was hypothesised that STN-DBS may, alternatively, have facilitated a generalised mental slowness[52] on a task where the execution of motor responses was dependent on complex cognitive resources.[51]

With respect to spreading activation theory, word recognition is dependent on the coherence of orthographic, phonological, and semantic features, made possible by the correlation of activation patterns between lexical (that is, orthographic/phonological input) and semantic nodes.[54] Rapid coherence (and consequently reaction time) is contingent upon strong correlations. Deep brain stimulation has been hypothesised to disrupt neural networks through the production of artificial nerve impulses, a phenomenon defined as neural jamming.[55] Our findings suggest that DBS may indeed alter the efficiency of neural communication at the lexical-semantic interface, resulting in delayed or contaminated coherence correlations, perhaps as a consequence of neural jamming.

In relation to theories of subcortical participation in language, STN-GPe disconnection as a result of STN-DBS may disturb GPe-NR exchanges, resulting in the formation of inexpedient firing modes in the thalamic nuclei subserving the efficient engagement[7] of lexical and semantic nodes. In relation to theories of motor control, it has been hypothesised that basal ganglia lesions disturb focused selection and inhibition mechanisms, resulting in prolonged reaction times.[56] More specifically, the braking (that is, inhibition) of antagonistic movement patterns, together with the facilitation (that is, the focused release) of selected movement patterns, represents the net outcome of basal ganglia activity relative to normal motor behaviour.[56] Disturbed basal ganglia outflow as a result of STN-DBS may therefore facilitate unimpeded thalamocortical activation, and in relation to language, the engagement of multiplex versus definitive lexical-semantic representations. A postlesional inability to suppress or disengage subordinate lexical-semantic alternatives would hypothetically result in increased reaction times on the lexical decision task.

Furthermore, a proportionally significant reliable decline in the accuracy of lexical decisions relating to words with many meanings and a high degree of relatedness between meanings (MH) was also observed within the STN-DBS group. In terms of language theory, words with many meanings have a probability advantage for nodal activation, given a high concentration of interrelated nodes.[57] On the basis of this premise, the postoperative performance profile observed in the current study may again reflect inefficient coherence mechanisms whereby intricate nodal networks underlying words with multiple meanings and a high degree of relatedness between meanings are more susceptible to neural disturbances facilitated by DBS. This potential phenomenon was again most easily interpreted in relation to selective engagement theory,[7] whereby lexical ‘‘engagement’’ or real word recognition is contingent upon the superordinate activation of the target word’s representation in preference to its lexical-semantic competitors.[58] In the current research we propose that MH words failed to reach postoperative recognition thresholds efficiently postoperatively with respect to the coherence of orthographic and semantic representations. We hypothesised that disruption to mechanisms facilitating the hierarchical assimilation of lexical information (presumably by way of focused selection and inhibition)[56] within convoluted neural networks as a result of DBS resulted in ‘‘incoherence’’ and the subsequent engagement of subordinate representations.

Based on contemporary theories of subcortical participation in language and the proposed mechanism of functional inhibition underlying DBS, it could be hypothesised that the postoperative linguistic profiles in the group of five STN-DBS subjects involved manifestations of extraneous verbal output (for example, semantic paraphasias), lexical selection deficits and speech initiation difficulties,[2] and possibly comprehension as well as verbal production deficits[7] resulting from STN-DBS mediated thalamocortical disinhibition. The results of the current study were not in complete agreement with these predictions. Despite this incongruity, however, our findings support the need to reconceptualise and expand on contemporary theories of subcortical participation in language in relation to defining a role for the STN.

Conclusions and directions for future research

The results of our study suggest that the subthalamic nucleus may indeed contribute to the mediation of linguistic processes by indirectly regulating thalamocortical outputs within cortico-subcortical-cortical language circuits. Our study showed significant postoperative changes in certain high level linguistic and semantic processing abilities during bilateral STN-DBS. We acknowledge that the small sample size limited the interpretation of the reported results; however, the significant postoperative changes observed provide a much needed impetus for further research on the role of the STN in mediating linguistic processes.

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