RESEARCH PAPER

Neuropsychological changes following deep brain stimulation surgery for Parkinson's disease: comparisons of treatment at pallidal and subthalamic targets versus best medical therapy

Johannes C Rothlind,[1] Michele K York,[2] Kim Carlson,[3] Ping Luo,[3] William J Marks Jr,[4] Frances M Weaver,[5,6] Matthew Stern,[7] Kenneth Follett,[8,9] Domenic Reda,[3] for the CSP-468 Study Group

▶ Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/jnnp-2014-308119).

For numbered affiliations see end of article.

Correspondence to
Dr Johannes C Rothlind, PhD MHS 116B, San Francisco VAMC, 4150 Clement Street, San Francisco, CA 94121 USA; johannes.rothlind@va.gov

Received 19 March 2014
Revised 30 June 2014
Accepted 30 July 2014
Published Online First 2 September 2014

ABSTRACT

Background Deep brain stimulation (DBS) improves motor symptoms in Parkinson's disease (PD), but questions remain regarding neuropsychological decrements sometimes associated with this treatment, including rates of statistically and clinically meaningful change, and whether there are differences in outcome related to surgical target.

Methods Neuropsychological functioning was assessed in patients with Parkinson's disease (PD) at baseline and after 6 months in a prospective, randomised, controlled study comparing best medical therapy (BMT, n=116) and bilateral deep brain stimulation (DBS, n=164) at either the subthalamic nucleus (STN, n=84) or globus pallidus interna (GPi, n=80), using standardised neuropsychological tests. Measures of functional outcomes were also administered.

Results Comparison of the two DBS targets revealed few significant group differences. STN DBS was associated with greater mean reductions on some measures of processing speed, only one of which was statistically significant in comparison with stimulation of GPi. GPi DBS was associated with lower mean performance on one measure of learning and memory that requires mental control and cognitive flexibility. Compared to the group receiving BMT, the combined DBS group had significantly greater mean reductions at 6-month follow-up in performance on multiple measures of processing speed and working memory. After calculating thresholds for statistically reliable change from data obtained from the BMT group, the combined DBS group also displayed higher rates of decline in neuropsychological test performance. Among study completers, 18 (11%) study participants receiving DBS displayed reliable decline by multiple indicators in two or more cognitive domains, a significantly higher rate than in the BMT group (3%). This multi-domain cognitive decline was associated with less beneficial change in subjective ratings of everyday functioning and quality of life (QOL). The multi-domain cognitive decline group continued to function at a lower level at 24-month follow-up.

Conclusions In those with PD, the likelihood of significant decline in neuropsychological functioning increases with DBS, affecting a small minority of patients who also appear to respond less optimally to DBS by other indicators of QOL.

Trial registration number NCT00056563 and NCT01076452.

To cite: Rothlind JC, York MK, Carlson K, *et al*. *J Neurol Neurosurg Psychiatry* 2015;**86**:622–629.

INTRODUCTION

Deep brain stimulation (DBS) improves motor symptoms and quality of life (QOL) in Parkinson's disease (PD),[1–3] but it has also been associated with decrements in neuropsychological function, including reductions in verbal associative fluency, working memory, and learning and recall efficiency.[3–7] Reliable change (RC)[8 9] and other statistical methods[5] have been utilised to document higher rates of decline following DBS.[10–13] Available studies have suggested considerable heterogeneity in neuropsychological outcomes in patients with PD 6–12 months after surgery, with some individuals showing large changes and others showing no change or even improved test performance.[12] Questions remain about the rate of more robust DBS-related cognitive decline determined through aggregation of results across multiple outcome measures.

The clinical significance of declines in neuropsychological test performance following DBS surgery also remains unclear. In prior naturalistic studies of PD, impairment in neuropsychological functioning has been found to impact everyday functioning and QOL.[14] However, the few studies that have examined clinical correlates of declines in neuropsychological function following DBS have not found an association with QOL.[5 7]

The aims of the present study are to (a) compare DBS at subthalamic nucleus (STN) and globus pallidus interna (GPi) targets to best medical therapy (BMT) with regard to treatment-related change in neuropsychological test performance over a 6-month follow-up, including differences in rates of RC on specific tests and more globally across broad domains of neuropsychological function and (b) explore the clinical significance of changes in neuropsychological test performance through an examination of their association with changes in QOL following treatment.

METHODS

Study sites and patients

The details regarding the recruitment and assessment of patients, surgical interventions and follow-up have been described previously.[3 15] In

brief, 316 patients were enrolled at seven Veterans Affairs and six affiliated university medical centres. Patients with idiopathic PD who were at least 21 years of age were eligible if they had disease that was assessed as stage 2 or higher on the basis of the Hoehn and Yahr Disability Scale while not receiving antiparkinsonian medication, had a response to levodopa, had persistent and disabling symptoms (eg, motor fluctuations and/or dyskinaesia) despite optimal medical therapy, had at least 3 h per 24 h period with poor motor function or symptom control and had been on stable medical therapy for at least 1 month. Exclusions included clear evidence of dementia (MMSE <25 or Mattis dementia rating scale (DRS) >2 SD below the mean of healthy age-matched peers).

Interventions

Patients randomised to BMT were managed by study movement disorders neurologists, applying state-of-the-art care to achieve best symptom control and optimal functioning. Patients randomised to DBS were further randomised to bilateral DBS surgery at either the STN or GPi and underwent surgery within 1 month of the study baseline evaluation. Lead implantation was accomplished using stereotactic techniques with MRI or CT guidance, with initial targets based on standard coordinates for STN and GPi and further refinements made using intraoperative physiological mapping and test stimulation.

Assessment procedures

The study utilised a battery of neuropsychological tests to assess multiple broad domains of neuropsychological functioning at baseline and after 6 months of treatment with either BMT or DBS (cataloged in table 2). Patients were assessed in the on-medication state at baseline and follow-up, and those in the DBS group were also in the on-stimulation state. Alternate forms of the learning and memory challenges were administered at the two assessments in a counterbalanced order to limit the effect of repeated exposure to the same stimuli. Patients also completed the Parkinson Disease Questionnaire-39 (PDQ-39) at each study session. Patients provided written informed consent.

Statistical analyses

To reduce the number of tests in the neuropsychological battery, and to confirm and further guide grouping of neuropsychological tests, an exploratory factor analysis was conducted. Since it is reasonable to assume that factors exhibit some degree of correlation, an oblique method of rotation, specifically promax rotation, was used. A test was deemed to significantly load on a factor if its standardised regression coefficient was >0.3. The number of factors was chosen by examining a scree plot to determine the number of factors with the largest eigenvalues and then examining the eigenvalues of each factor. Five factors were extracted that correspond to broad domains that we have labelled processing speed, working memory, learning and memory, executive function and language (see online supplementary appendix A).

To compare rates of abnormal cognitive decline across treatment groups, we first calculated RC CIs and practice-adjusted thresholds for RC[8 16] based on the test–retest data of the BMT group. For each test, thresholds were based on 90% CIs surrounding the mean change scores observed in the BMT sample, with adjustment for mean change score on that test. To generate even more robust psychometric criteria for cognitive decline over the study interval, study participants who displayed a statistically RC on at least one-third of the individual measures used to assess a specific domain were classified as having displayed a RC in that domain (see online supplementary appendix A). The standard for a single-domain decline was adjusted for each instance of statistically reliable improvement by requiring one additional instance of reliable decline in that domain. In order to identify the potential effects of treatment on the rate of more robust (multi domain) cognitive decline, we further classified individual study participants based on whether they displayed multi-domain cognitive decline, defined as a statistically reliable decline on at least one-third of the measures in two or more of the five broad domains.

To examine mean group differences in cognitive outcomes at 6 months, multiple t-test were carried out to compare STN and GPi DBS targets (and the combined DBS group) to BMT on individual neuropsychological scores. Non-parametric analyses (χ^2 tests) were utilised to compare rates of single-task, single-domain and multi-domain decline across treatment groups. Univariate analyses (t tests) were employed to determine whether multi-domain cognitive decline is associated with changes in activities of daily living (ADLs) or other aspects of QOL following DBS, as assessed using the PDQ-39.

To address missing data we conducted various sensitivity analyses involving study completers, including multiple imputation of individual neuropsychological scores and a worst case scenario where all missing outcomes correspond to decline in a particular test. Results based on the analysis of domains did not change appreciably with these sensitivity analyses.

RESULTS

Three hundred and sixteen patients with PD were enrolled in the study. Initially, 255 patients were randomised to receive BMT (n=134) or bilateral DBS (n=121). Following the termination of recruitment to the BMT arm of the study, an additional 56 patients were randomised to GPi or STN DBS, including five already randomised to BMT (figure 1). Participant withdrawals and missed visits are further described in figure 1. In sum, 182 individuals were assigned to DBS, with 164 included in the present analysis. Of the original group, two died before 6-month follow-up, nine participants withdrew consent and three other participants were lost to follow-up. Three others randomised to the DBS arm missed their 6-month visit for unspecified reasons. Of the nine participants who withdrew consent, seven did so due to medical or psychological problems occurring during the study. The reasons that two others withdrew consent and three participants were lost to follow-up are unknown.

Eighty-four per cent of the study participants were men, 69% were married and most (>95%) were Caucasian. The mean age for the combined sample was 61.7 (SD=8.8) years (range 37–83 years). GPi and STN groups did not differ on any variables at baseline (see table 1). As documented previously,[3] the BMT subgroup had been diagnosed with PD and treated with PD medication for a significantly longer period of time than the DBS group.

Neuropsychological outcomes

Comparison of the GPi and STN groups revealed no significant differences in baseline neuropsychological test performance. In comparing the outcome following DBS for the two surgical targets, just 3 of the 25 change scores showed a statistically significant group difference. These group differences were small and did not fall in a consistent pattern, with performance on one test (Stroop word reading) declining to a greater extent within the STN group than GPi, and performance on the

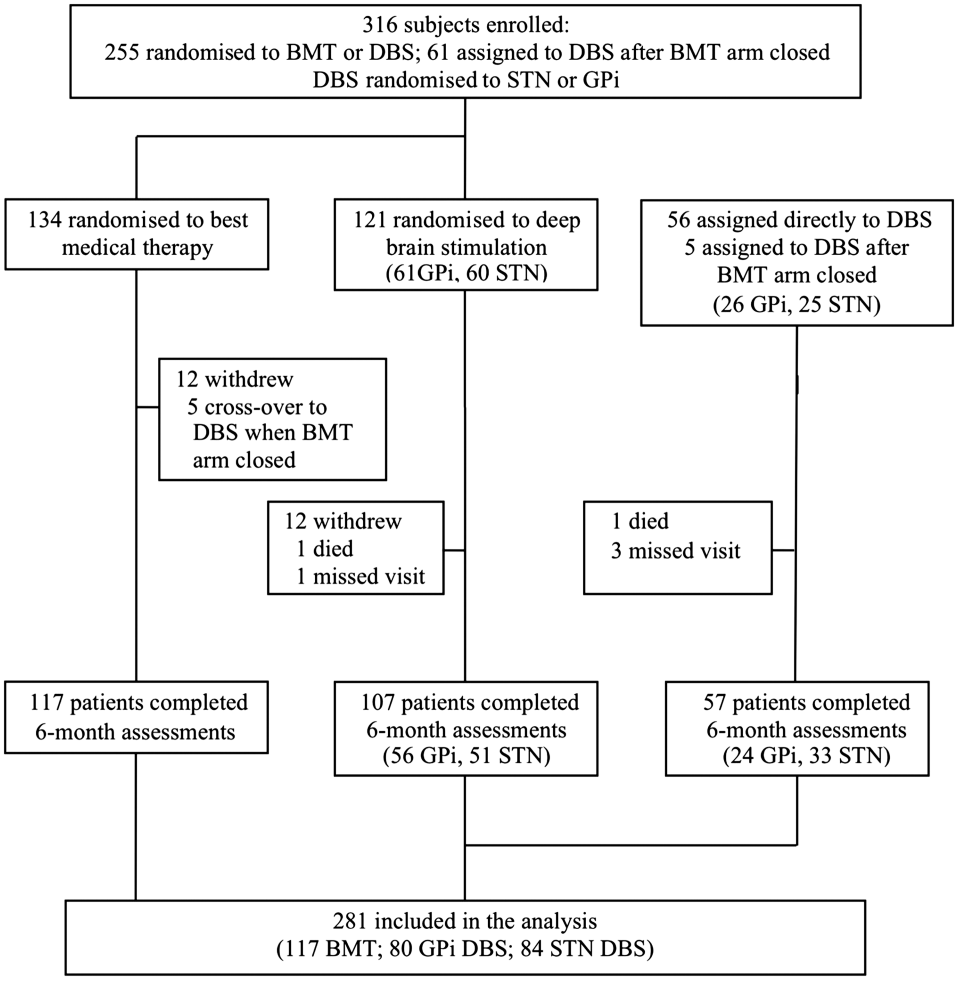

Figure 1 Enrolment and outcome assessment (BMT, best medical therapy; DBS, deep brain stimulation; GPi, globus pallidus interna; STN, subthalamic nucleus).

Hopkins Verbal Learning Test (HVLT) declining more in the GPi group (see table 2).

Because the two DBS groups showed a similar level of change overall, results for the two surgical targets were subsequently pooled, and the combined DBS group was compared with the BMT group. In these group-level analyses, the DBS group showed statistically significantly greater decline (or lack of improvement) at 6 months on multiple measures of processing speed and working memory (see table 2). Follow-up analysis of covariance adjusting for isolated small baseline group differences did not alter the main study findings.

RC results for individual tests

Rates of RC did not differ significantly between the two surgical groups with the exception of the Digit Symbol coding task, on which a significantly higher rate of decline was observed in the STN DBS subgroup (11.1% compared with 1.3% in GPi DBS; p=0.04). Within the combined DBS group, elevated rates of statistically reliable decline were observed for several measures of processing speed and working memory (see table 3). There were no significant group differences in rates of improvement, except for the significantly lower rate of improvement displayed by the combined DBS group on the Wisconsin card sorting test

Table 1 Baseline demographic and clinical features

	BMT (n=116)		GPi DBS (n=80)		STN DBS (n=84)		
	Mean	SD	Mean	SD	Mean	SD	p Value
Age (years)	62.3	8.9	61.3	8.9	61.3	8.5	0.68
Education (years)	14.8	3.0	14.3	3.1	15.2	3.3	0.17
Years since diagnosis	12.8	5.5	11.0	4.7	11.0	5.0	0.02
Years on PD medication	12.2	5.3	10.4	4.6	10.1	4.4	0.004
Hoehn-Yahr off medication	3.3	0.9	3.2	0.8	3.4	0.9	0.48
Hoehn-Yahr on medication	2.4	0.5	2.3	0.7	2.3	0.6	0.73
Blinded on med UPDRS III	23.2	10.5	22.2	12.4	21.2	11.8	0.49
Blinded off med UPDRS III	43.1	11.2	41.6	12.6	42.8	16.7	0.72
Total levodopa dosage (mg)	1290.1	550.2	1284.0	490.7	1291.5	549.8	>0.99

BMT, best medical therapy; DBS, deep brain stimulation; GPi, globus pallidus interna; PD, Parkinson's disease; STN, subthalamic nucleus; UPDRS, unified Parkinson's disease rating scale.

Table 2 Group differences: baseline and change in neuropsychological test performance at 6 months

	BMT						GPi DBS						STN DBS					
		Baseline		Change				Baseline		Change				Baseline		Change		
Measure	N	Mean	SD	Mean	SD	Per cent	N	Mean	SD	Mean	SD	Per cent	N	Mean	SD	Mean	SD	Per cent
Processing speed																		
WAIS-III digit symbol	114	43.7	16.7	0	10.1	0.1	75	47.1	15.8	−1.9	8	−4.1	81	47.9	15.7	−2.9	10.2	−6.1*
WAIS-III symbol search	115	22.2	8.2	0.2	5.3	0.9	78	23	7.8	−1.3	5.4	−5.5	84	23.6	8.2	−2.5	6.5	−10.7*
Trail making test A	115	45.1	25.1	1	18	2.2	79	44	20.1	4.1	37.2	9.3	84	49	30.5	−0.7	24.2	1.5
Trail making test B	112	131.2	76.7	9.1	60.9	6.9	79	125.2	73.6	11.6	59.4	9.3	81	127.7	69.1	9.7	50.8	7.6
Animal naming	115	19.9	5.9	−0.9	4.8	−4.8	79	20.5	5.6	−2.7	5.3	−13.3	83	20	5.8	−2.3	4.5	−11.3*
Grocery naming	116	21.6	6.4	0.7	5.8	3.3	80	23.2	6.3	−2.6	5.3	−11.1	84	23.5	6.1	−4.1	6.2	−17.3*
Stroop word reading	110	83	17.6	−1.1	10.6	−1.4	76	84.9	19.4	−1.2	14.5	−1.4	78	87.4	15.5	−5.2	11.3	−5.9†
Stroop color naming	109	58.3	13.2	−0.7	9.3	−1.2	76	60.4	13.3	−3.4	11.9	−5.7	78	59.3	10.8	−4.7	9.6	−7.8*
Stroop color word	109	31	9.7	0.5	8.4	1.6	76	33.2	10.1	−2.1	9.3	−6.4	78	32.9	8.3	−2.8	6.3	−8.4*
Working memory																		
WAIS-III digits forward	116	10.1	2	−0.2	1.8	−2.3	79	10.4	2.4	−0.3	2	−3	84	10	2.2	−0.2	1.8	−2.3
WAIS-III digits backward	116	5.9	1.7	0.1	1.6	2.2	79	6.4	2	−0.3	2	−4.2	84	6	1.8	−0.1	1.7	−2
WAIS III letter-number	114	8.4	2.6	0.4	1.8	4.3	79	9.2	2.8	−0.6	2.6	−6.2	81	9.4	2.6	−0.7	2.2	−7.5*
Phonemic fluency (F,A,S)	114	35.9	14.2	0.5	8.6	1.3	79	36.7	13.3	−5	10.8	−13.6	83	37.2	15.4	−4.6	9.7	−12.4*
WAIS III arithmetic	114	13	3.7	−0.1	2.3	−1.1	77	13.6	3.4	−0.7	1.9	−5	82	13.1	3.4	−0.5	2.2	−3.4
WAIS III similarities	113	22.6	5.8	0.8	3.3	3.8	77	22.6	5.3	−0.7	3.2	−3.2	83	23.3	5.3	−0.7	3.4	−2.9*
Language																		
Boston naming test	114	56.1	4.2	0.4	1.9	0.6	79	55.1	4.5	0.5	2.2	1	81	55.4	4.7	0.4	2.4	0.7
Learning and memory																		
HVLT trials 1–3 total	115	21.7	5.4	−0.2	4.6	−0.8	79	21.9	4.5	−0.8	4.4	−3.7	82	21.1	5.6	0.9	4.7	4.0†
HVLT-R delayed recall	115	6.7	3.4	−0.2	3	−2.5	79	7	3.1	−1.1	3	−15.3	82	6.5	3.6	0.1	3	1.9†
HVLT-R recognition	115	9.8	2	0.2	2.4	2.1	78	9.8	1.8	0	2.1	−0.3	81	9.9	1.9	0.1	2	1
BVMT-R trials 1–3 total	116	16.8	7	0.1	6.3	0.3	79	16.3	7.4	−0.2	6.6	−1.2	83	17	7.7	−0.7	7.6	−4.3
BVMT-R delayed recall	116	6.8	3.1	0.4	2.7	6.4	78	7	3.1	−0.8	2.6	−11.3	83	6.9	3.2	−0.2	2.7	−3.3*
BVMR-R discrimination	116	5	1.2	0.2	1.5	3.1	79	5.1	1.2	−0.1	1.2	−2	83	5.2	1	−0.1	1.6	−2.3
Executive functioning																		
WCST total errors	114	24.9	11.7	−0.4	11.3	−1.7	79	23.7	10.7	0	8.7	−0.2	81	23.1	9.3	−0.2	9.5	−0.9
WCST preservations	114	17.3	12.4	−2.1	11	−12	79	15.6	11.6	−0.2	12.4	−1.1	81	14.4	8.2	0	9.2	−0.1
Stroop interference index	109	6	5.6	0.7	7.5	11	76	7.2	7.4	0.1	8.9	1.7	78	5.6	7.3	1.5	6.9	26.7

All means in Table 2 refer to raw, unadjusted scores.
*p Value for BMT versus GPi and STN<0.05.
†p Value for GPi versus STN<0.05.
BMT, best medical therapy; BVMT, brief visuospatial memory test; DBS, deep brain stimulation; GPi, globus pallidus interna; STN, subthalamic nucleus; WAIS, Wechsler adult intelligence scale.

Table 3 RC parameters, practice-adjusted thresholds for RC, and rates of reliable decline by group

	Test–retest coefficient	Mean difference	SD	RC 90%	Adjusted RC (90%)		Per cent declining	
					Lower 5%	Upper 5%	BMT	DBS
Processing speed								
WAIS-III digit symbol*	0.81	0.0	10.06	16.54	−16.52	16.57	5.2	6.1
WAIS-III symbol search†	0.80	0.2	5.3	8.72	−8.53	8.91	5.2	13.4
Trail making test A	0.73	1.0	17.91	29.47	−30.44	28.49	2.6	7.3
Trail making test B	0.76	9.1	59.02	97.07	−106.18	88.0	5.2	5.5
Animal naming†	0.65	−0.9	4.79	7.88	−8.83	6.93	2.6	11.0
Grocery naming†	0.61	0.7	5.82	9.57	−8.86	10.27	7.8	18.9
Stroop word reading†	0.82	−0.7	10.56	17.37	−18.50	16.23	4.3	11.0
Stroop colour naming	0.76	−1.1	9.26	15.23	−15.93	14.53	4.3	8.5
Stroop colour word	0.68	0.5	8.29	13.63	−13.12	14.13	2.6	4.9
Working memory								
WAIS-III forward	0.63	−0.2	1.75	2.88	−3.12	2.65	2.6	6.1
WAIS-III backward	0.66	0.1	1.56	2.57	−2.44	2.70	4.3	7.3
WAIS III letter-number†	0.76	0.4	1.80	2.97	−2.61	3.33	3.4	19.4
Phonemic fluency (F,A,S)†	0.82	0.8	8.63	14.19	−13.73	14.65	6.3	16.5
WAIS III arithmetic	0.82	−0.1	2.28	3.6	−3.90	3.62	5.2	7.3
WAIS III similarities	0.83	0.5	3.31	5.45	−4.60	6.30	6.9	12.8
Language								
Boston naming test	0.90	0.4	1.85	3.04	−2.68	3.40	6.3	8.5
Learning/memory								
HVLT trials 1–3 total	0.64	−0.2	4.58	7.53	−7.69	7.36	3.4	6.1
HVLT-R delayed recall	0.59	−0.2	3.01	4.95	−5.12	4.79	3.4	3.7
HVLT-R recognition Discrimination	0.24	0.2	2.41	3.97	−3.76	4.17	6.0	3.7
BVMT-R trials 1–3 total	0.62	0.1	6.24	10.27	−10.21	10.32	5.2	8.5
BVMT-R delayed recall	0.64	0.4	2.73	4.50	−4.07	4.93	3.4	5.5
BVMR-R discrimination index	0.23	0.2	1.47	2.41	−2.26	2.57	5.2	4.3
Executive functioning								
WCST total errors	0.49	−0.4	11.30	18.58	−18.17	18.99	5.2	6.7
WCST perseverative Responses‡	0.55	−2.1	10.93	17.98	−15.90	20.06	6.9	3.1
Stroop interference index	0.12	0.7	7.52	12.37	−11.71	13.03	3.4	3.7

*Decline more common in subthalamic nucleus (11.1%) than globus pallidus interna (1.3%; p<0.05).
†BMT versus DBS difference significant (p<0.05).
‡No difference in rate of decline, but BMT showed higher rate of *improvement* (7.9% vs 2.5%; p<0.05).
BMT, best medical therapy; DBS, deep brain stimulation; RC, reliable change.

(WCST) perseverative response measure, an index of executive function (p=0.05).

Rates of multi-domain cognitive decline

To further evaluate the extent to which individual study participants were showing cognitive decline following treatment, we aggregated RCs for each individual, classifying relevant study participants as a *decliner* in a particular domain (see table 4). Approximately 20% of participants in each treatment group declined on a single dimension (group difference NS). After aggregating further to identify instances where individuals showed statistically significant deterioration in multiple domains of neuropsychological function, non-parametric analyses documented that DBS was associated with a higher rate of multi-domain cognitive decline. Eighteen of 164 study participants in the DBS group (11%) displayed multi-domain cognitive decline, compared with just 4/116 (3%) in the BMT group (p=0.024). Further inspection of the pattern of RCs revealed that the DBS subgroup with multi-domain cognitive decline showed an average of 6.8 statistically reliable declines on individual neuropsychological tests, with an average of 0.25 tests improving. In contrast, within the DBS subgroup without multi-domain cognitive decline (n=146), a mean of 1.5 tests declined and mean of 0.9 improved.

The surgical target was not correlated with the rate of multi-domain cognitive decline (7/80 (9%) of the GPi group displayed

Table 4 Rates of reliable decline by cognitive domain

	BMT (N=116)		DBS (N=164)		
	Decline		Decline		
Cognitive domain	n	Per cent	n	Per cent	p Value
Processing speed	3	2.6	11	6.7	0.16
Working memory	5	4.3	23	14.0	0.008
Executive function*	13	11.2	20	12.3	0.85
Learning/memory	6	5.2	8	4.9	1.0
Language	7	6.0	14	8.6	0.50
Multiple domains	4	3.5	18	10.9	0.02

*Higher rate of improvement in BMT on some measures.
BMT, best medical therapy; DBS, deep brain stimulation.

Table 5 Change in PDQ-39 self-report of functioning at 6 months

	DBS−multi-domain cognitive decline (n=132)		DBS+multi-domain cognitive decline (n=15)		
	Mean	SD	Mean	SD	p Value
PDQ-39 total score	−80.3	105.3	−20.8	82.5	0.04
ADL	−17.2	19.1	−5.6	24.3	0.03
Mobility	−16.0	21.2	−5.9	23.4	0.07
Communication	−2.8	21.3	6.4	24.7	0.09
Emotional well-being	−8.2	18.8	0.0	9.7	0.09
Social support	−1.5	18.4	4.4	20.1	0.24
Cognition	−5.5	18.3	−0.8	24.6	0.34
Bodily discomfort	−9.4	19.7	−9.8	20.5	0.94
Stigma	−14.8	24.1	−14.5	21.1	0.95

ADL, activities of daily living; DBS, deep brain stimulation; PDQ-39, Parkinson Disease Questionnaire-39.

multi-domain cognitive decline, versus 11/84 (13%) in the STN group; p=0.37). While detailed analyses of factors predicting multi-domain cognitive decline are beyond the scope of the present study, we compared the DBS/no multi-domain cognitive decline and DBS/multi-domain cognitive decline groups with regard to stimulation parameters for each DBS lead at the 6-month follow-up evaluation (unipolar vs bipolar mode, amplitude, pulse width and rate). These analyses documented only one significant group difference, with pulse width for the left lead significantly lower in the individuals experiencing multi-domain cognitive decline than in the DBS/no multi-domain cognitive decline group (mean=75.9 (SD=60) vs 85.3 (SD=60), p<0.05).

QOL outcome associated with multi-domain cognitive decline

As documented previously,[3] patients who undergo DBS surgery commonly experience significant improvements on the PDQ-39. However, the multi-domain cognitive decline group in our sample did not demonstrate the same improvement in QOL seen in the DBS subgroup as a whole (p<0.05, see table 5). Multi-domain cognitive decline was a significant negative predictor of PDQ-39 total score and score on the subscale assessing ADLs.

Neurocognition and QOL at 24 months compared in individuals with and without multi-domain cognitive decline

To examine whether the more robust cognitive declines affecting the small subgroup of individuals receiving DBS treatment endure over a longer follow-up interval, we examined group differences from the 24-month study visit on two measures that are among the most commonly reported and sensitive indicators of neuropsychological decline following DBS (verbal associative fluency), and on our global indicator of QOL (PDQ-39 total score). These comparisons at 24 months reveal a significant group difference on all three measures at the longer follow-up. The Mean Animal Naming for DBS/no multi-domain cognitive decline was 17.4 (SD=5.6) vs 11.4 (SD=5.5) for DBS/multi-domain cognitive decline p<0.0001. The Mean Phonemic Fluency for DBS/no multi-domain cognitive decline group was 42 (SD=11.7) vs 30.9 (SD=8.0) for DBS/multi-domain cognitive decline (p<0.0003). The PDQ-39 total mean for DBS/no multi-domain cognitive decline group was 302.7 (SD=122.6) vs 377 (SD=136.2) for DBS/multi-domain cognitive decline (p<0.03).

DISCUSSION

The present study expands on our previously published analyses of neuropsychological outcomes associated with DBS[3], and our findings of small differences associated with STN versus GPi target.[15] The present investigation focused on a larger sample of patients with DBS than in our previous analyses of 6-month follow-up,[3] and the current analyses compared outcomes by surgical target. In contrast to our previous publications, the present study also analysed a larger number of outcomes and incorporated a wider array of group comparison methods and RC thresholds, further documenting the rate of single-test and multidimensional cognitive decline under different treatment conditions.

The results of the current study are consistent with results from previous publications[15 17 18] in identifying only isolated, small GPi versus STN target differences in neuropsychological change after DBS. In keeping with earlier studies,[15 18] there are indications of slightly greater reductions in aspects of processing speed following STN treatment. However, the present investigation also documents greater reductions in verbal learning and recall in participants receiving DBS at the GPi target. These target differences in neuropsychological outcomes of DBS are small, and they must be interpreted with added caution given the absence of statistical correction for multiple comparisons. In the absence of formal adjustment for multiplicity, we have reported all comparisons to allow readers to perform their own adjustments. Moreover, the basis for the small target differences remains uncertain. The typically greater reductions in dopaminergic medication following STN compared with GPi DBS may play a role in the more pronounced decline in aspects of processing speed in the former group. Conversely, the slightly higher educational attainment and larger representation of women in the STN group may play a role in the target differences on the HVLT observed following treatment favouring STN, as both of these variables may be associated with stronger performance on verbal list learning and recall. Impairment in strategic aspects of learning and memory performance may also be mediated by disruption of the normal functioning of regions of anteromedial GPi,[19] perhaps influenced by lead-location and stimulation parameters. Since patients treated with DBS were only assessed with stimulation on, it is impossible to discern the extent to which the effects of therapeutic stimulation (rather than the effects of the surgical implant procedure) contributed to the neuropsychological decline in some patients in the present study. However, previous research involving counterbalanced 'on' versus 'off' stimulation comparison following DBS for PD suggests that neurocognitive performance is slightly lower with stimulation turned off.[20] This argues against stimulation parameters as a primary factor underlying the lowered performance seen on some measures following DBS surgery in our study. In the absence of further investigation regarding the underlying mechanism and functional impact of deficits on these specific measures, the finding of isolated target differences in post-treatment change in test performance does not appear to offer clear guidance to clinicians with regard to choice of surgical target.

Significantly greater mean reductions in neuropsychological functioning were observed in the combined DBS group on measures of working memory and processing speed. Verbal associative fluency is again documented to be a robust indicator of neuropsychological change following DBS, and the group

difference for animal fluency, which had been reported as a trend in earlier analyses published by our group,[3] clearly exceeds the threshold for statistical significance in the larger study sample compared here. The present study suggests small group differences in neuropsychological outcome in domains traditionally associated with integrity of frontal-subcortical circuits in human brain function. The basis for these changes will require further investigation.

Using RC thresholds, we documented that DBS is associated with a significantly higher rate of decline and/or failure to improve in performance on tests of working memory and processing speed. It is important to note that although the likelihood of statistically reliable decline was as much as five times greater in the DBS group for individual measures, the majority of individual patients receiving DBS did not display changes on individual measures or combinations of measures that would clearly distinguish them from patients treated with BMT. Instead, the majority showed a balance of isolated declines and improvements in test performance similar to the pattern observed in the BMT arm. However, by the stringent criterion for multi-domain cognitive decline established for the present study, a small but significantly higher rate of more robust cognitive decline was identified in the DBS group. The basis for the more robust decline in some study participants remains to be explored. In keeping with the results from analyses of mean group differences, surgical target did not predict multi-domain cognitive decline, and stimulation parameters themselves do not appear to have an important role. Among the numerous parameters examined, only one, increased left hemisphere mean pulse width showed a modest statistical association with multi-domain cognitive decline. However, this single statistically significant finding is probably not clinically relevant, considering the post hoc nature of the analysis, lack of adjustment for multiple comparisons in these analyses, along with the small effect, together with the small sample in which the result was obtained.

The present study is among the first to aggregate reliable declines on individual tests to generate an index of more robust decline in neuropsychological function.[10] The approach offers a way to identify individuals who may account for smaller mean group differences, and we believe that such an approach warrants further investigation as a means of identifying individuals who respond disproportionately to treatment on measures of neuropsychological function.

The current study is also among the first to document clinical correlates of more robust decrements in neuropsychological test performance following DBS. Where DBS has previously been found to be associated with improvement in QOL for the group in total, multi-domain cognitive decline appears to be a moderator of this association. Individuals in the DBS arm who experience multi-domain cognitive decline failed to show the expected improvement in QOL. These findings stand in contrast to those of previous studies that failed to demonstrate an association between neuropsychological outcomes and QOL measures.[5 21] Our findings may reflect the more stringent criteria we set for cognitive decline in our study. Small changes or isolated statistically significant reductions on a specific neurocognitive test may not be sufficiently burdensome to impact functional outcomes, particularly when assessed in the context of improvement in motor symptoms.[3] In contrast, the more robust cognitive declines affecting a small minority of individuals undergoing DBS appear to have functional significance in terms of everyday adjustment and self-ratings of QOL. Moreover, analyses of longer term follow-up data for the multi-domain cognitive decline group suggests that differences in neurocognitive and functional outcomes remain at the 2-year follow-up point. Findings of the present study suggest the added importance of understanding and acknowledging potential risk of more robust neuropsychological decline when reviewing treatment options with patients suffering from PD. In the context of DBS, multi-domain cognitive decline identified through aggregation of reliable cognitive decline may identify a subgroup in greatest need of additional clinical care and support following treatment.

Limitations and future directions

The current findings must be interpreted as a conservative indicator of the true risk of multidimensional cognitive decline following DBS. The analyses focused on study completers and did not include individuals from the DBS arm who died (n=2) or dropped out of the study secondary to medical or psychological problems (n=9). Furthermore, reasons for dropout are not documented clearly for several other cases in each arm of the study, and the possibility that neurocognitive morbidity was a greater factor in the DBS subgroup cannot be ruled out.

Restrictions in the range of baseline test scores and the modest size of the BMT study group limited our ability to stratify further prior to computing RC criteria. Use of regression-based modelling and further longitudinal research with large clinical control groups may result in more refined reliable-change parameters. Nevertheless, the thresholds for RC established through the present study (table 2) may serve as a guide for identification of unexpected cognitive changes affecting patients with similar baseline demographic and clinical characteristics, provided the same clinical measures are being compared over a comparable follow-up interval.

Further investigation is needed to explore factors other than surgical target and stimulation parameters (eg, age, baseline cognitive function, treatment-related serious adverse events, change in motor function) that may contribute to the prediction of multi-domain cognitive decline and QOL after DBS. Finally, the long-term significance of statistically RCs in neuropsychological function seen following DBS remains to be explored through more detailed longitudinal investigation.

Author affiliations
[1]Mental Health Service, San Francisco VA Medical Center and Department of Psychiatry, University of California, San Francisco, California, USA
[2]Department of Neurology, Michael E. DeBakey VA Medical Center and Baylor College of Medicine, Houston, Texas, USA
[3]Hines VA Hospital, Cooperative Studies Coordinating Center, Hines, Illinois, USA
[4]Department of Neurology, San Francisco, California, USA
[5]Hines VA Hospital, Center for Management of Complex Chronic Care, Hines, Illinois, USA
[6]Loyola University Stritch School of Medicine, Maywood, Illinois, USA
[7]University of Pennsylvania Health System, Philadelphia, Pennsylvania, USA
[8]Iowa City VA Medical Center, Iowa City, Iowa, USA
[9]University of Nebraska Medical Center, Omaha, Nebraska, USA

Collaborators Past and present members of the CSP 468 Study Group are as follows: Chairpersons: KF, MD, PhD; MS, MD; FMW, PhD. Chairpersons Office: Dolores Ippolito, MPH; Gatana Stoner, RN, CCRC. Hines VA Cooperative Studies Program Coordinating Center: Tammy Barnett, MA; Ken Bukowski, BS; Rosemarie DeNicolo; Kwan Hur, PhD; Joyce Jimenez; PL, PhD; Jan Motyka, BS; DR, PhD; Theresa Simon, RN, BS; Bharat Thakkar, MS; Robert Woolson, JD, MS. Pharmacy Coordinating Center: Carol Fye, RPh, MS, CCRP; William Gagne; Crystal Harris, PharmD. National Institute of Neurological Disorders and Stroke: Jill Heemskerk, PhD; Claudia Moy, PhD; Paul Sheehy, PhD. Department of Veterans Affairs Cooperative Studies Program Central Office, VA Office of Research and Development: Timothy O'Leary, MD, PhD; Grant D Huang, MPH, PhD. MAVERIC: Louis Fiore, MD; Robert Hall, MS. Health Economist: Kevin Stroupe, PhD. Executive Committee: Kim Burchiel, MD; KF, MD, PhD; Carol Fye, RPh, MS, CCRP; Crystal Harris, PharmD; Jill

Heemskerk, PhD; Kwan Hur, PhD; William Koller, MD, PhD; WJM Jr, MD, MS; Claudia Moy, PhD; Rajesh Pahwa, MD; DR, PhD; JCR, PhD; Oren Sagher, MD; Paul Sheehy, PhD; MS, MD; FMW, PhD. Data Safety Monitoring Board: Roy Bakay, MD (Chairman); Rick Chappell, PhD; Robert Hart, MD; Robert Holloway Jr, MD, PhD; George McCabe, PhD; Margaret Schenkman, PhD; Jamal Taha, MD Study Monitors: Julia Buckelew, CCRA; Carol Fye, RPh, MS, CCRP; Marilyn Garin; Sharon Matzek, CCRA; Donna Smith, CCRA. Site Investigators: Jeff Bronstein, MD, PhD; John Duda, MD; Penelope Hogarth, MD; Kathryn Holloway, MD; Stacy Horn, DO; Eugene C Lai, MD, PhD; WJM Jr, MD, MS; Ali Samii, MD. Site Coordinators: Farah Atassi, MD, MPH; Cecilia Bello, BSN; Lisette Bunting-Perry, RN, MSN, CCRC; Tina Conn, BSN; Alice Cugley, RN, NP; Nanette Eubank, RN, CCRP; Linda Fincher, RN, BSN; Romay Franks, BSN; Tammy Harris, MSN, RN, GNP; Mariann Haselman, RN; Susan Heath, RN, MS; Miriam Hirsch, MS, RN; Virginia Janovsky, RN, MN, MS; Elaine Lanier, RN, MS; Mary Lloyd, RN; Susan Loehner, BSN, MBA; Susan O'Connor, RN; Ligaya Ordonez, BSN; Heather Maccarone, RN, BSN; Kelli Massey-Makhoul, RN; Mary Matthews, RN; Elizabeth Meyn, BSN; Keiko Mimura, RN, MSN, GNP; Wes Morrow, MS, MMSc, PAC; Tammy Searles, RN; Jamye Valotta, BSN; Usha Vasthare, PhD; Monica Volz, RN, MS; Constance Ward, RN, MSN; Rebecca Warker, APRN; Heidi Watson, BSN; Pamela Willson, PhD. Neurologists: Mark Baron, MD; Matthew Brodsky, MD; Vincent Calabrese, MD; Gordon Campbell, ANP; Amy Colcher, MD; Emad Farag, MD; Eva Henry, MD; Jyh-Gong Hou, MD, PhD; Gail Kang, MD; Galit Kleiner-Fisman, MD; Jeff Kraakevik, MD; John Nutt, MD; Jill Ostrem, MD; Aliya Sarwar, MD; Indu Subramanian, MD; Zeba Vanek, MD. Neurosurgeons: Gordon Baltuch, MD, PhD; Kim Burchiel, MD; Antonio De Salles, MD, PhD; Jorge Eller, MD; Kathryn Holloway, MD; Paul Larson, MD; Richard Simpson, MD; Philip Starr, MD, PhD. Neuropsychologists: William Carne, PhD; Tom Erikson, PhD; Jeffrey Kreutzer, PhD; Mario Mendez, MD, PhD; Paul Moberg, PhD; John Ragland, PhD; JCR, PhD; Ronald Seel, PhD; Elizabeth Soety, PhD; Daniel Storzbach, PhD; Alexander Troster, PhD; MKY, PhD. Neurophysiologist: Jurg Jaggi, PhD.

Contributors JCR, WJM, FMW, MS, KF and DR and other members of the CSP468 study group had major responsibilities in the design and implementation of the study and the six authors listed by name were involved in analysis and writing of this manuscript. MKY and JCR had major responsibility for developing an analysis plan to test major hypothesis concerning neuropsychological outcomes, and they collaborated with statisticians and developed the initial drafts of the manuscript. KC and PL had primary responsibility for statistical analysis, and they collaborated in developing the analysis plan to test major hypotheses, and collaborated in writing of the manuscript.

Funding The research described in this article was financially supported by the Cooperative Studies Program, Department of Veterans Affairs Office of Research and Development, National Institute of Neurological Disorders and Stroke, and Medtronic, Inc. VA Cooperative Study #468.

Competing interests JCR has received consulting fees from Teva. MS is receiving consulting fees from Teva, Adamas, Merz, Civitas, and is an officer of the International Parkinson and Movement Disorder Society. WJMJ is receiving consulting fees from Medtronic and lecture fees from Medtronic. No other potential conflict of interest relevant to this article was reported.

Ethics approval Institutional Review Board.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Krack P, Batir A, Van Blercom N, *et al*. Five-year follow-up of bilateral stimulation of the subthalamic nucleus in advanced Parkinson's disease. *N Engl J Med* 2003;349:1925–34.
2 Deuschl G, Schade-Brittinger C, Krack P, *et al*. A randomized trial of deep-brain stimulation for Parkinson's disease. *N Engl J Med* 2006;355:896–908.
3 Weaver FM, Follett K, Stern M, *et al*. Bilateral deep brain stimulation vs best medical therapy for patients with advanced Parkinson disease: a randomized controlled trial. *JAMA* 2009;301:63–73.
4 Rodriguez-Oroz MC, Obeso JA, Lang AE, *et al*. Bilateral deep brain stimulation in Parkinson's disease: a multicentre study with 4 years followup. *Brain* 2005;128:2240–9.
5 Smeding HM, Speelman JD, Huizenga HM, *et al*. Predictors of cognitive and psychosocial outcome after STN DBS in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 2011;82:754–60.
6 York MK, Dulay M, Macias M, *et al*. Cognitive declines following bilateral subthalamic nucleus deep brain stimulation for the treatment of Parkinson's disease. *J Neurol Neurosurg Psychiatry* 2008;79:789–95.
7 Witt K, Daniels C, Reiff J, *et al*. Neuropsychological and psychiatric changes after deep brain stimulation for Parkinson's disease: a randomised, multicentre study. *Lancet Neurol* 2008;7:605–14.
8 Jacobson NS, Truax P. Clinical significance: a statistical approach to defining meaningful change in psychotherapy research. *J Consult Clin Psychol* 1991;59:12–19.
9 Troester AI, Woods SP, Morgan EE. Assessing cognitive change in Parkinson's disease: development of practice effect-corrected reliable change indices. *Arch Clin Neuropsychol* 2007;22:711–18.
10 Zahodne LB, Okun MS, Foote KD, *et al*. Cognitive declines one year after unilateral deep brain stimulation surgery in Parkinson's disease: a controlled study using reliable change. *Clin Neuropsychol* 2009;23:385–405.
11 Higginson CI, Wheelock VL, Levine D, *et al*. The clinical significance of neuropsychological changes following bilateral subthalamic nucleus deep brain stimulation for Parkinson's disease. *J Clin Exp Neuropsychol* 2009;31:65–72.
12 Mikos A, Zahodne L, Okun MS, *et al*. Cognitive declines after unilateral deep brain stimulation surgery in Parkinson's disease: a controlled study using reliable change, part II. *Clin Neuropsychol* 2010;24:235–45.
13 William A, Arzola GM, Strutt AM, *et al*. Cognitive outcome and reliable change indices two years following bilateral subthalamic nucleus deep brain stimulation. *Parkinsonism Relat Disord* 2011;17:321–7.
14 Schrag A, Jahanshahi M, Quinn N. What contributes to quality of life in patients with Parkinson's disease. *J Neurol Neurosurg Psychiatry* 2000;69:308–12.
15 Follett KA, Weaver FM, Stern M, *et al*. Pallidal versus subthalamic deep-brain stimulation for Parkinson's disease. *N Engl J Med* 2010;362:2077–91.
16 Iverson GL, Brooks BL, Collins MW, *et al*. Tracking neuropsychological recovery following concussion in sport. *Brain Inj* 2006;20:245–52.
17 Okun MS, Fernandez HH, Wu SS, *et al*. Cognition and mood in Parkinson's disease in subthalamic nucleus versus globus pallidus interna deep brain stimulation: the COMPARE Trial. *Ann Neurol* 2009;65:586–95.
18 Rothlind JC, Cockshott RW, Starr PA, *et al*. Neuropsychological performance following staged bilateral pallidal or subthalamic nucleus deep brain stimulation for Parkinson's disease. *J Int Neuropsychol Soc* 2007;13:68–79.
19 Lombardi WJ, Gross RE, Trepanier LL, *et al*. Relationship of lesion location to cognitive outcome following microelectrode-guided pallidotomy for Parkinson's disease support for the existence of cognitive circuits in the human pallidum. *Brain* 2000;123:746–58.
20 Pillon B, Ardouin C, Damier P, *et al*. Neuropsychological changes between "off" and "on" STN or GPi stimulation in Parkinson's disease. *Neurology* 2000;55:411–18.
21 Witt K, Daniels C, Krack P, *et al*. Negative impact of borderline global cognitive scores on quality of life after subthalamic nucleus stimulation in Parkinson's disease. *J Neurol Sci* 2011;310:261–6.

Neuropsychological changes following deep brain stimulation surgery for Parkinson's disease: comparisons of treatment at pallidal and subthalamic targets versus best medical therapy

Johannes C Rothlind, Michele K York, Kim Carlson, Ping Luo, William J Marks, Jr, Frances M Weaver, Matthew Stern, Kenneth Follett and Domenic Reda

J Neurol Neurosurg Psychiatry 2015 86: 622-629 originally published online September 2, 2014
doi: 10.1136/jnnp-2014-308119