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Neuropsychological predictors of patient-reported cognitive decline after deep brain stimulation in Parkinson's disease

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Abstract

Background: Deep brain stimulation (DBS) is effective for treatment of motor complications of dopaminergic therapy in Parkinson's disease (PD) but occasionally has been associated with multi-domain cognitive decline. Patient- and caregiver-reported cognitive decline are clinically meaningful and increasingly recognized as important to consider when evaluating therapeutic interventions for PD.

Objective: To assess presurgical neuropsychological and clinical factors associated with PD patient- and caregiver-reported cognitive decline in two or more domains after DBS.

Methods: A single telephone survey was used to assess patient- and caregiver-reported cognitive decline in five domains at both one and four months after DBS surgery. Decline in two or more domains was considered multi-domain cognitive decline (MDCD). Baseline demographic, clinical, and neuropsychological factors were compared in those with or without MDCD. Preoperative neuropsychological measures were evaluated as risk factors and regressed on the presence of MDCD, with demographic covariates, using multiple logistic regression.

Results: Preoperative performance in verbal recognition memory, language knowledge, and verbal processing decline were associated with post-operative, patient-reported MDCD in the first four weeks. MDCD at four months after DBS was associated with worse preoperative verbal reasoning, verbal recall, and semantic verbal fluency. Caregiver-reported MDCD one month after DBS was associated with poorer baseline verbal memory recognition accuracy/discriminability, visuospatial problem solving, and constructional praxis.

Conclusion: Poor presurgical performance in verbal memory recognition, language processing, and visuospatial performance are associated with patient- or caregiver-reported decline following

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DBS surgery. Posterior cortical dysfunction seems to portend significant self-reported cognitive decline following deep brain stimulation.

Keywords

Parkinson's disease; Cognitive impairment; Deep brain stimulation; Neuropsychology

Introduction

Cognitive impairment is observed in approximately 24% of newly diagnosed Parkinson's disease (PD) patients (Muslimovic, Post, Speelman, & Schmand, 2005), with up to 46% of patients developing dementia by 10 years of disease (Williams-Gray et al., 2013). Paradoxically, effective treatment of Parkinson's movement symptoms can occasionally exacerbate cognitive dysfunction (Rothlind et al., 2014; Swainson et al., 2000), so clinicians must carefully weigh the risk of worsening cognition against the potential to improve motor function when considering treatment options.

The clinical effectiveness of deep brain stimulation (DBS) in the treatment of PD patients who have developed motor complications of medical therapy is well established (Deuschl et al., 2006; Weaver et al., 2009), and results in a robust improvement in quality of life (Williams et al., 2010). Whereas dramatic declines in cognitive function following DBS rarely occur, isolated declines in phonemic verbal fluency (Saint-Cyr, Trepanier, Kumar, Lozano, & Lang, 2000; Trepanier, Kumar, Lozano, Lang, & Saint-Cyr, 2000) are frequently reported following subthalamic nucleus (STN) DBS while isolated declines in other cognitive processes have been found (Pillon et al., 2000; Saint-Cyr, et al., 2000; Trepanier, et al., 2000; Witt et al., 2008). Assessing a more global decline in a large cohort randomized to receive either "best medical therapy" or DBS (Follett et al., 2005; Weaver, et al., 2009), 11% of DBS patients experienced "multi-domain" cognitive decline (i.e. at least one-third of tests in two or more domains being impaired), compared to only 3% of medical therapy patients (Rothlind, et al., 2014). Only minor differences in cognition were found between those implanted in either the STN or globus pallidus pars internus (Rothlind, et al., 2014). Importantly, quality of life improved only one-fourth as much among DBS patients with multi-domain cognitive decline when compared to those without multi-domain cognitive impairment after DBS (Rothlind, et al., 2014). This suggests that a subset of PD patients who are appropriate candidates for DBS go on to develop multi-domain cognitive decline at a higher rate than if they had not undergone surgery. One important step in maximizing the quality of life benefit from DBS would be to identify risk factors for elevated risk of postoperative cognitive decline.

Meeting criteria for PD with mild cognitive impairment (PD-MCI) before surgery does not predict subsequent dementia in the near-term after DBS (Merola et al., 2014). Moreover, if all patients who meet the criteria of MCI were excluded from DBS, many patients who could have a dramatic reduction in motor disability would go untreated so PD-MCI classification may not be clinically useful in DBS surgical risk stratification.

Neuropsychological evaluation is routinely performed preoperatively to guide decisions regarding DBS candidacy and brain electrode target. However, only a few studies have

evaluated which components of the neurocognitive assessment or other baseline characteristics predict postoperative cognitive decline. A lower preoperative composite score on the Trail Making Test (part B) and Stroop Color-Word Test (interference trial) (Smeding, Speelman, Huizenga, Schuurman, & Schmand, 2011), impaired list learning (Yaguez et al., 2013), lower Full Scale I.Q. (Yaguez, et al., 2013), older age at disease onset (Heo et al., 2008), higher educational level (Heo, et al., 2008), and older age at surgery (Funkiewiez et al., 2004; Rothlind, Cockshott, Starr, & Marks, 2007; Smeding, et al., 2011) have all been associated with cognitive decline after DBS surgery. Only two of these studies evaluated cognitive performance predictors of post-DBS cognitive decline and it is not clear to what degree the objective postoperative decline was clinically meaningful in these studies. Yaguez et al., (2013) found that immediate story recall was the cognitive performance measure most affected by STN DBS, so they sought to assess preoperative cognitive predictors of a decline in the performance of this task. Bivariate correlations were statistically significant between postoperative immediate story recall and several preoperative cognitive measures, but other demographic variables (possible confounders) were not assessed simultaneously in the same model simultaneously. Furthermore, the outcome of measure of interest was impairment in one cognitive task, and because we know from a larger study of DBS cognitive outcomes that multi-domain cognitive decline drives the most significant impact on quality of life (Rothlind, et al., 2014), the prediction of isolated decline in immediate story recall is of unclear clinical significance. Smeding, Speelman, Huizenga, Schuurman, & Schmand (2011) reported cognitive predictors of postoperative cognitive decline in multiple measures using a multivariate normative comparison method, but did not directly assess subjective cognitive decline as the outcome measure of their analysis, allowing only an inference for patient-centered clinical decision-making. A clinically meaningful interpretation of objective cognitive changes can be complicated by the observation that subjective experience of cognitive impairment in PD is driven by objective declines in some domains more than others (Mills et al., 2016). Because of this, and in an effort to find predictors of cognitive decline reported as meaningful by the patients, we used subjective postoperative cognitive decline as the outcome in this study.

In order to identify preoperative risk factors for postoperative patient- and caregiver-reported multi-domain cognitive decline (PR- and CR-MDCD), we compared demographics and preoperative neuropsychological test scores of patients who did or did not develop postoperative multi-domain cognitive decline (PR- and CR-MDCD) at two time points: a) after lead implantation surgery but before activation of stimulation and b) after 3 months of stimulation.

Methods

Subjects:

Patients who underwent neuropsychological evaluation in the Johns Hopkins Division of Medical Psychology as part of an evaluation for DBS for Parkinson's disease (Defer, Widner, Marie, Remy, & Levivier, 1999) during the past 4 years were eligible. Subjects were excluded if they were not fluent in English or unable to provide phone consent. Because DBS is a standard therapy for patients with troublesome motor complications of therapy, we

did not include a control group of PD patients who elected to not undergo DBS surgery; these patients rarely have similar neuropsychological baseline exams as those who do choose to have surgery. Also, because the efficacy of DBS versus “best medical therapy” has already been described in sample randomized to treatment (Weaver, et al., 2009), we did not feel the impact of our study would justify the ethical implications of repeating a randomized design. Our study complies with the Declaration of Helsinki and was approved by the Johns Hopkins University School of Medicine Institutional Review Board (IRB# 00053338).

Measures:

We administered a phone questionnaire (see Supplementary Materials) to the DBS patient and to the main caregiver on one occasion. During that interview, we queried cognitive decline after surgery both before activation of stimulation (during the first month after surgery) and during the first three months of stimulation (months 2–4 after surgery). These time points were chosen to isolate the effects of surgery and chronic stimulation. The phone questionnaire queried perceived deficits in episodic memory, language, executive function, and visuospatial function. Participants and caregivers categorized each domain as “improved”, “unchanged”, “slightly worse”, “moderately worse”, or “severely worse”.

The primary outcome measure was the presence of patient- or caregiver-reported multi-domain cognitive decline (PR-MDCD or CR-MDCD, respectively), defined as any reported decline in two or more of the above cognitive domains. Multi-domain cognitive decline was chosen as an outcome that is more likely to reduce the degree of quality of life improvement provided by DBS (Rothlind, et al., 2014). The DBS patient participants were also administered the Modified Telephone Interview for Cognitive Status (TICS-M) (Brandt, Spencer, & Folstein, 1988), a phone-based measure of global cognitive function. The predictor variables scores on preoperative neuropsychological measures that were assessed about three months prior to DBS surgery (Supplementary Table 1) and non-modifiable demographic variables.

Statistical Analyses:

To evaluate test validity in this population of PD patients and their caretakers, associations between objective performance on cognitive testing and subjective report of specific domain dysfunction were analyzed by logistic regression. Convergent validity was assessed by determining whether specific baseline cognitive impairments predicted both PR- and CR-MDCD. We also evaluated inter-rater reliability between patient- and caregiver reports of cognitive decline in individual domains at each time point by calculating percent agreement and the kappa statistic.

Baseline demographic and clinical variable summary measures were compared between those who described the presence or absence of multi-domain cognitive decline (MDCD) one month after surgery using independent t-tests or Fisher’s exact test. Univariate summary measures of baseline cognitive test performance were also calculated and compared between those with and without MDCD, as reported by patients or caregivers, to gauge the effect of surgery.

Preoperative neuropsychological measures were evaluated as risk factors for the presence of MDCD using multiple logistic regression, adjusting for time from surgery to survey administration (months), education level (stratified as less than high school diploma, high school/GED, associate's degree, bachelor's degree, master's degree, doctoral degree), and DBS target (STN, GPi, or Vim thalamus) (*StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP*). Separate models were used to assess neuropsychological risk factors for each of four outcomes: patient-reported cognitive decline at one or four months after surgery and caregiver-reported cognitive decline at one or four months following surgery.

Results

Subjects

Eighty two patients were identified in the neuropsychological evaluation database who had undergone DBS for a diagnosis of PD in the last four years (Figure 1). Of these, 49 PD patients and 43 caregivers participated in the survey. In the case of 37 PD patients, both patient and caregiver were surveyed. Only one patient refused, while 25 could not be reached after two telephone call attempts. Those who could not be reached appeared similar in preoperative PD severity preoperatively but were more likely to live remotely from our center, either across state lines or internationally. Patients with and without MDCD were called after a similar amount of time following surgery (39.0 ± 9.6 versus 39.8 ± 4.2 years, $p=0.94$) making this variable less likely to be a confounder. Nevertheless, we included this as a covariate in our multiple logistic regression models to control for this variability within and between outcome groups. Patients were implanted in the following targets: left subthalamic nucleus (STN) (4), right STN (1), bilateral STN (35), bilateral globus pallidum internus (GPi) (8), left ventral intermediate thalamus (2).

One month after surgery (prior to DBS activation) 14, 12, 16, and 14% of patients reported improvement in memory, executive, language, and visuospatial function, respectively. This increased to 16 to 26% across these four domains by 4 months after surgery while over 50% of patients reported no change in cognition in all domains at 1 or 4 months after DBS. The most frequent caretaker-reported cognitive decline was in language (16% at 1 month and 15.4% at 4 months), but because verbal fluency decline is well-documented and of controversial clinical significance relative to QoL as an isolated decline in this setting (Borden et al., 2014), this was another reason to use a more global measure of cognitive decline across multiple domains as the outcome of interest, as this is more likely to impact quality of life gained from DBS (Rothlind, et al., 2014).

Questionnaire Performance

Patient-reported deficits in specific cognitive domains on the questionnaire were associated with performance on objective cognitive tests in those domains, demonstrating construct validity. For instance, pre-surgical patients' report of impaired visuospatial function was associated with objective visuospatial performance: better performance on the DRS construction task by 1 point reduced the likelihood of reporting visuospatial function by an OR of 0.19 ($p=0.02$) and worse performance on the Brixton Spatial Anticipation Test by 1

point increased likelihood of reporting visuospatial/executive dysfunction by an OR of 1.15, $p=0.014$. Neither pure executive function nor verbal memory tasks were associated with patient-reported visuospatial dysfunction. Convergent validity is also suggested by the observation that patients and their respective caregivers both reported MDCD in those with baseline deficits in verbal recognition accuracy. However, using the subjective ratings as continuous variables, patient-caregiver inter-rater reliability was only fair on average (Kappa range: 0.076 – 0.526, Table 1), suggesting differences between patients and their caregivers in the recognition of cognitive decline. The highest agreement was found in the memory (Kappa = 0.305, 0.506, 0.225 at baseline, 1-, and 4 months postop) and language (Kappa = 0.400, 0.333, 0.273 at baseline, 1-, and 4 months postop) domains.

Patient-reported multi-domain cognitive decline

Baseline demographic and clinical variables are shown for patients who reported PR-MDCD and those who did not ($N=41$) one month after surgery (Table 2). Those with PR-MDCD at one month tended to be older (71.4 ± 3.4 vs. 65.7 ± 1.1 , $p=0.06$), have higher education (Fisher's exact across all groups, $p=0.22$), have higher UPDRS Part III OFF scores (44.4 ± 6.6 vs. 35.9 ± 2.4 , $p=0.20$), and have more anticholinergic use (14.3% vs. 2.5%, $p=0.39$), though none of these trends was statistically significant. Performance on the TICS given at the time of the phone interview was not different between those who did or did not report PR-MDCD at 1 month (31 ± 2.8 vs. 30.7 ± 0.73 , $p=0.20$) or at 4 months after surgery (28.7 ± 2.4 vs. 31.3 ± 1.2 , $p=0.26$). In a multivariable regression analysis, none of these variables, or DBS target, was an independent risk factor for one month post-DBS PR-MDCD (overall model: $R^2=0.18$, $p=0.23$).

Mean preoperative performance on each neuropsychological measure component score was compared between those with and without PR-MDCD at one month following surgery (Supplementary Table 2). Baseline Dementia Rating Scale (DRS) measures of initiation (35.9 ± 0.21 vs. 33.7 ± 1.7 in no MDCD vs. MDCD, $p=0.01$) and construction (5.85 ± 0.07 vs. 4.57 ± 0.75 , $p<0.01$), total DRS score (136.5 ± 0.97 vs. 129.4 ± 4.2 , $p=0.02$), and Hopkins Verbal Learning Test (HVLT) total immediate recall and recognition scores were lower in the group that developed PR-MDCD at one month after surgery. Higher discrepancy score on the Speed and Capacity of Language Processing Test (SCOLP), a marker for decline in language function relative to premorbid intellect, was found in those who developed PR-MDCD at one month ($1.28\pm.44$ vs. 5.86 ± 1.14 in non- MDCD vs. MDCD, $p<0.01$), as well as the Trail Making Test, and the Brixton Spatial Anticipation Test (22.9 ± 1.3 vs. 30.3 ± 4.4 , $p=0.045$). Mood function assessed by the Geriatric Depression Scale – 30 was no different in patients who did or did not report MDCD (7.57 ± 0.84 vs. 5.57 ± 1.59 , $p=0.350$) one month after surgery. Multiple logistic regression analyses adjusting for time from surgery to survey, education, and DBS target revealed a smaller set of preoperative cognitive tasks where performance was associated with patient-reported, postoperative PR-MDCD (Table 3, complete results in Supplementary Table 3.) PR-MDCD at one month was associated with lower preoperative performance on verbal recognition memory (i.e. discrimination accuracy on the yes/no recognition trials of the HVLT-R) and with language knowledge and processing decline (SCOLP Spot-the-Word and discrepancy scores). PR-MDCD at four months after DBS was associated with baseline verbal memory (HVLT delayed recall),

verbal reasoning (DRS conceptualization) and semantic verbal fluency. Depression severity was not associated with PR-MDCD at one or four months. This suggests that baseline verbal memory and language processing are most strongly associated with PR-MDCD that persists to four months after surgery.

Caregiver-reported multi-domain cognitive decline

We also evaluated baseline demographic and clinical variables stratified by the presence or absence of CR-MDCD (Table 4). Again, there were no statistically significant differences between these strata of CR-MDCD. However, those with CR-MDCD tended to be less well educated (14.7% of no CR-MDCD vs. 0% with CR-MDCD had doctoral degrees, $p=0.83$). Only two respondents had surgery under general anesthesia and neither reported CR-MDCD. TICS score at the time of survey administration post-operatively was similar between those with CR-MDCD compared to those not reporting CR-MDCD (28.7 ± 2.4 vs. 31.3 ± 0.90 , respectively, $p=0.26$). The baseline UPDRS Part III score OFF medication tended to be lower in those who developed caregiver-reported CR-MDCD, though not statistically significant (mean score 26.3 ± 0.8 vs. 34.1 ± 1.2 , $p=0.12$).

Performance on baseline cognitive measures was compared with univariate analyses between those patients whose caregivers did and did not report CR-MDCD one month after surgery (Supplementary Table 4). Patients with lower performance on the construction scale of the DRS (5.82 ± 0.07 vs. 5.20 ± 0.34 for non-MDCD vs. MDCD, $p=0.02$), the Brief Visuospatial Memory Test (BVM-T) total immediate recall (16.2 ± 1.3 vs. 10.4 ± 1.8 , $p=0.03$), and Brixton Spatial Anticipation Test (23.0 ± 1.35 vs. 31.8 ± 3.5 , $p<0.01$) were more likely to have their caregivers report new MDCD at one month after surgery. Depression severity was in the “normal” range on the GDS-30 and not significantly different between those with and without CR-MDCD (6.85 ± 0.82 vs. 7.90 ± 2.54 , $p=0.607$).

To evaluate the effect of baseline cognitive task performance on caregiver-reported cognitive outcomes while controlling for education, time from surgery to survey, and DBS target, we regressed each cognitive task on the presence or absence of CR-MDCD at one and four months (Table 5, complete results in Supplementary Table 5). Baseline depression severity did not predict subsequent CR-MDCD. Baseline verbal recognition memory (HVLT-R), visuospatial problem solving (Brixton), and visuospatial construction (DRS construction) were associated with the presence of CR-MDCD one month following surgery when adjusting for the variables above. However, only worse baseline visuospatial problem solving (Brixton) was associated with an increased odds of CR-MDCD at four months following surgery (aOR=1.12, 95%CI: 1.01,1.24, $p=0.03$).

Discussion

In order to determine whether neurocognitive tests could predict post-DBS MDCD, we evaluated associations between baseline neuropsychological test scores and the presence of patient- and caregiver-reported cognitive decline following DBS surgery. We found that patients with baseline deficits in delayed verbal recall and recognition, verbal reasoning, language knowledge, and verbal processing decline were more likely to report decline in at least two cognitive domains at one month following DBS (before stimulation was activated).

Baseline delayed verbal recall, verbal reasoning, and semantic fluency were associated with patient-reported MDCC after 3 months of stimulation. Caregivers reported post-DBS MDCC at one month in patients with baseline deficits in verbal recognition memory, visuospatial problem solving and constructional praxis.

Pattern of baseline deficits predisposing to PR- and CR-MDCC

Most PD patients display some degree of impairment on thorough neuropsychological evaluation (Weintraub et al., 2015). Under the “dual syndrome hypothesis” (Kehagia, Barker, & Robbins, 2013), non-demented PD patients can be roughly divided into those who exhibit chronic but relatively restricted deficits in cognitive functions emanating from frontostriatal dysfunction, including working-memory and set-shifting, and those who exhibit more pervasive dysfunction affecting posterior cortical regions, such as verbal memory and visuospatial impairment (van Balkom et al., 2016). The patients in this latter group are at higher risk for dementia in the near future (Williams-Gray et al., 2009). The pattern of baseline cognitive dysfunction associated with PR- and CR-MDCC following DBS surgery in our study includes neuropsychological tests that are associated with posterior cortical regions such as the mesial temporal lobes for verbal memory, temporal poles for word knowledge, and parietal lobes for visuospatial processing and recognition. This is most likely explained by the observation that dysfunction in posterior cortical regions signals wide-spread α -synuclein deposition and dysfunction in multiple neurotransmitter systems that support normal cognition and cognitive compensation in PD (Kehagia, et al., 2013).

For example, recognition memory, as measured by HVLT-R discrimination accuracy, was worse preoperatively in those who developed both PR- and CR-MDCC one month after DBS surgery. The majority of PD patients undergoing evaluation for DBS are in a phase of the illness where brain pathology is mainly limited to nigrostriatal degeneration causing frontostriatal dysfunction, so temporal lobe functions such as memory recognition accuracy/discriminability (i.e. cued recognition such as the HVLT discrimination score) are not usually affected in non-demented Parkinson’s disease patients (Ivory, Knight, Longmore, & Caradoc-Davies, 1999). While many patients with early or mid-stage PD have an impairment in free recall (attributed to retrieval deficits due to frontostriatal dysfunction) they do not have deficits in recognition memory that would indicate mesial temporal lobe involvement (Zizak et al., 2005), such as is more commonly seen in Alzheimer’s disease where cuing does not improve recall like it does in PD (Aretouli and Brandt, 2010; Pillon, Deweer, Agid, & Dubois, 1993). Thus, verbal memory recognition deficits may be a marker for significant cortical involvement of PD pathology or concomitant AD pathology, which may predispose patients to subsequent cognitive decline after exposure to the brain penetration and anesthesia involved in surgery.

Visuospatial dysfunction, including construction, visuospatial memory, and associative problem-solving, was also associated with CR-MDCC after surgery. These cognitive functions are uncommonly affected in early and mid-stage Parkinson’s disease (Aarsland et al., 2010), but can predict conversion to dementia in the first five years after diagnosis if present (Williams-Gray, et al., 2009). The presence of visuospatial dysfunction most likely

indicates widespread cortical pathology and thus may predispose individuals to take a larger “hit” following DBS surgery. Interestingly, this finding was true only for CR-MDCD at 1 and 4 months, not PR-MDCD. One explanation for this difference could be that patients are less likely to have insight into visuospatial dysfunction than their caregivers (e.g. driving deficits). If patients worsen in a pattern similar to their baseline deficits, they may be less likely to recognize a decline in visuospatial function compared with their caregivers.

It is notable that while phonemic verbal fluency is the most reproducible objective observed task to decline following DBS, we did not find that preoperative letter fluency predicted patient-reported multi-domain cognitive decline. Depressive symptom severity was also not associated with the odds of PR-MDCD or CR-MDCD, despite a robust literature on this association.(Hill et al., 2016; Kinsinger, Lattie, & Mohr, 2010) This may be attributable to our reluctance to perform DBS surgery in patients with uncontrolled or severe depression, as evidenced by the mean baseline GDS-30 being in the “normal” range for all subjects.

Demographic risk factors for post-DBS cognitive decline

In a multiple logistic regression analysis of demographic and clinical variables (such as education level, DBS target, age, and baseline MDS-UPDRS part III score), none were found to be independent risk factors for post-DBS cognitive decline. While older age was found to be a predictor of post-DBS cognitive decline in other studies (Rothlind, et al., 2007; Smeding, et al., 2011), there are at least two reasons why our models did not show age as a significant covariate. First, our analysis used patient-reported outcomes for the presence or absence of post-DBS cognitive decline rather than objective cognitive measures. Second, our demographic/clinical risk factor analysis included the other variables simultaneously. In fact, an analysis evaluating the association between age and one month PR-MDCD, unadjusted for other demographic/clinical variables, shows a sizeable odds ratio of borderline statistical significance (OR=1.14, p=0.07). However, this association disappears up when adjusted for education level, DBS target and baseline disease severity. Lastly, interviewees in our study were older in both groups than in prior studies (Smeding, et al., 2011; Yaguez, et al., 2013), so there may have been a ceiling effect to the relationship between age and cognitive impairment.

The observation that DBS targeting, whether bilateral STN, unilateral (left) STN, bilateral GPi, or left Vim, was not associated with post-DBS MDCD is in agreement with long-term follow-up from randomized, double-blind DBS target trials, which showed minimal differences in cognitive function between those randomized to STN or GPi (Boel et al., 2016; Rothlind, et al., 2014). However, comparing cognitive outcomes based on DBS target selection, which is often decided considering cognitive and behavioral symptoms, when subjects were not randomized to target is problematic, so we included DBS target as a covariate in our modeling but did not compare outcomes directly based on this predictor. Furthermore, this study is not powered to evaluate differences in cognitive outcomes based on target given the lower number of GPi and Vim cases.

Limitations

The telephone survey used in this study does not have established validity in PD or in any other disease, but we were unable to find an existing patient-reported outcome scale that specifically queried cognitive decline after a historical surgical exposure. This questionnaire's construct validity is demonstrated by associations between baseline subjective report and objective performance in specific cognitive domains. For example, we found an association between baseline self-report of visuospatial processing deficits being correlated with Brixton performance but neither verbal executive function nor verbal memory tasks. Also, the fact that patients and caregivers both reported MDCD in the presence of baseline verbal recognition accuracy shows convergent validity. While convergent validity is only modest, with only fair patient-caregiver inter-rater reliability according the kappa statistic, this may speak to differences in the abilities of PD patients and their caregivers to detect certain types of deficits. This is itself an interesting finding and has been shown in other work comparing objective and subjective cognitive complaints in PD (Mills, et al., 2016).

The use of a retrospective questionnaire introduces the possibility of information bias through recall bias; those with more significant post-operative cognitive decline may be more likely to remember it and those with only minimal decline may be less likely to report it on our interview. Selection bias is possible if participants were more likely to have experienced cognitive decline than non-participants. We acknowledge this and propose that these biases are less relevant for the question at hand because this analysis focuses on predictors of longitudinal changes within subjects rather than identifying the incidence, prevalence, or severity of post-operative cognitive decline, measures that would be heavily influenced by selection and information biases.

Conclusion

While multi-domain cognitive impairment is rare following DBS surgery, risk stratification based on preoperative neuropsychological performance and clinical factors could help to prevent this disabling outcome. Our study suggests that lower pre-surgical performance on measures of verbal recognition memory, verbal processing decline, and visuospatial performance localizing to mesial temporal lobe, temporal pole, and parieto-occipital lobe function are associated with patient- or caregiver-reported multi-domain cognitive decline following DBS surgery. This study suggests that the risks and benefits of DBS surgery should be closely weighed in PD patients with cognitive impairments involving the mesial temporal and posterior cortices.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Flowsheet showing patient enrollment in DBS cognitive decline survey.

Table 1.

Agreement between PD patients and caregivers on report of domain-specific cognitive impairment before and after DBS surgery

Agreement between Patients and Caregivers			
Cognitive Domain	Time point	% Agreement	Kappa statistic
Memory	Pre-op	76.8	0.305
	1 month	82.1	0.526
	4 month	60.7	0.225
	Baseline	67.9	0.231
Executive	1 month	66.1	0.076
	4 month	62.5	0.143
	Pre-op	76.8	0.400
Language	1 month	73.2	0.333
	4 month	66.1	0.273
	Pre-op	78.6	0.226
Visuospatial	1 month	75.0	0.214
	4 month	73.2	0.255

Pre-op = prior to DBS surgery. 1-month = after DBS surgery, before stimulation activation. 4 months = first 3 months after stimulation activation.

Table 2.

Demographics in patients with and without patient-reported multi-domain cognitive decline at 1 month. (mean (SE))

Clinical variables	Multi-domain cognitive decline N=8	No multi- domain cognitive decline N=41	p-value
Age (years)	71.4 (3.4)	65.7 (1.1)	0.06
Time from DBS surgery to survey (months)	39.0 (9.6)	39.8 (4.2)	0.94
Education level (%)			0.22
< HS diploma	5	28.6	
HS diploma / GED	37	28.6	
Associates	7.5	14.3	
Bachelor's	17.5	28.6	
Master's	22.5	0	
Doctoral	10	0	
DBS Target			0.91
Left STN	16.7	8.6	
Bilateral STN	66.7	71.4	
Bilateral GPi	16.7	17.1	
Left Vim	0	2.9	
TICS	31 (2.8)	30.7 (0.73)	0.90
UPDRS Part III OFF	44.4 (6.6)	35.9 (2.44)	0.20
Anticholinergic use (%)	14.3	2.5	0.39

Table 3.

Baseline neuropsychological predictors of patient-reported multi-domain cognitive decline after DBS surgery for Parkinson's disease.

Neuropsychological measure	1 month after DBS				4 months after DBS			
	aOR	95% CI		P-value	aOR	95% CI		P-value
Verbal abstract reasoning (<i>DRS conceptualization</i>)	0.770	0.54	1.1	0.14	0.154	0.03	0.84	0.03 [*]
Delayed Verbal Recall (<i>HVLT delayed recall</i>)	0.757	0.51	1.12	0.161	0.607	0.39	0.96	0.031 [*]
Verbal memory recognition accuracy (<i>HVLT discrimination</i>)	0.306	0.11	0.88	0.027 [*]	0.539	0.29	1.00	0.051
Semantic verbal fluency (<i>"Animals" and "Supermarket items"</i>)	0.939	0.83	1.06	0.295	0.767	0.61	0.94	0.028 [*]
Word knowledge (<i>SCOLP spot-the-word</i>)	1.475	1.04	2.10	0.031 [*]	1.254	0.91	1.73	0.168
Verbal processing (<i>SCOLP discrepancy</i>)	2.819	1.20	6.60	0.017 [*]	1.524	1.00	2.33	0.051

aOR = Odds ratio of having patient-reported impairment in 2 or more cognitive domains following DBS surgery, adjusted for time from surgery to survey, DBS target, education level.

^{*} Measures only shown if statistically significant at either time point ($p < 0.05$).

Table 4.

Demographics in patients with and without caregiver-reported multi-domain cognitive decline one month after DBS surgery. (mean (SE))

Clinical Variables	Multi-domain cognitive decline N=10	No multi-domain cognitive decline N=34	p-value
Age (years)	67.5 (1.59)	66.8 (1.1)	0.78
Time from DBS surgery to survey (months)	41.1 (12.4)	41.0 (4.4)	0.34
Education level (%)			0.83
< HS diploma	0.0	5.9	
HS diploma / GED	40.0	35.3	
Associates	10.0	5.9	
Bachelor's	30.0	20.6	
Master's	20.0	17.7	
Doctoral	0.0	14.7	
DBS Target			0.15
Left STN	12.5	3.3	
Right STN	12.5	0	
Bilateral STN	50	76.7	
Bilateral GPi	25	13.3	
Left Vim	0	6.7	
TICS	28.7 (2.4)	31.3 (0.90)	0.26
UPDRS Part III OFF	26.3 (0.8)	34.1 (1.2)	0.12
Anticholinergic use (%)	0	2.9	1.00

Table 5.

Baseline neuropsychological predictors of caregiver-reported multi-domain cognitive decline after DBS surgery for Parkinson's disease.

Neuropsychological measure	1 month after DBS				4 months after DBS			
	aOR	95% CI		p-value	aOR	95% CI		p-value
Verbal memory recognition accuracy <i>(HVLT discrimination)</i>	0.515	0.269	0.987	0.045 [*]	0.818	0.560	1.194	0.297
Visuospatial problem solving <i>(Brixton Spatial Anticipation Test)</i>	1.120	1.018	1.246	0.021 [*]	1.120	1.013	1.240	0.027 [*]
Constructional praxis <i>(DRS construction)</i>	0.332	0.1109	0.994	0.049 [*]	0.617	0.250	1.522	0.294

aOR = Odds ratio of having patient-reported impairment in 2 or more cognitive domains following DBS surgery, adjusted for time from surgery to survey, DBS target, education level.

* Measures only shown if statistically significant at either time point ($p < 0.05$).