Parkinson's Disease With Mild Cognitive Impairment May Has A Lower Risk Of Cognitive Decline After Subthalamic Nucleus Deep Brain Stimulation: A Retrospective Cohort Study

hutao xie
Capital Medical University
Yutong Bai
Capital Medical University
Yin Jiang (jiangyin0802@foxmail.com)
Capital Medical University
Jianguo Zhang
Capital Medical University

Research Article

Keywords: Parkinson's disease, Subthalamic nucleus, Deep brain stimulation, Cognitive decline, Mild cognitive impairment, Montreal Cognitive Assessment

Posted Date: March 9th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1407482/v1

Abstract

Objective: The cognitive outcomes induced by subthalamic nucleus deep brain stimulation (STN-DBS) remain unclear, especially in PD patients with mild cognitive impairment (MCI). This study explored the cognitive effects of STN-DBS in PD patients with MCI.

Methods: This was a retrospective cohort study that included 126 PD patients who underwent STN-DBS; all patients completed cognitive and motor assessments before and at least 6 months after surgery. Cognitive changes were mainly evaluated by the Montreal cognitive assessment (MoCA) scale and the seven specific MoCA domains, including visuospatial, executive function, naming, attention, language, abstract, delayed recall, and orientation. Motor improvement was evaluated by the UPDRS-III. Cognitive changes and motor improvements were compared between PD-MCI and normal cognitive (NC) patients. Logistic regression analyses were performed to explore predictors of postoperative cognitive change.

Results: At the time of surgery, 61.90% of the included PD patients had MCI. Compared with the PD-MCI group, the PD-NC group had a significantly higher proportion of cases with postoperative cognitive decline during follow-up of up to 36 months (mean 17.34 ± 10.61 months), including in global cognitive function, attention, memory, visuospatial, and executive function. Covariate-adjusted binary logistic regression analyses showed that preoperative global cognitive status was an independent variable for postoperative cognitive decline. We also found that preoperative cognitive specific function could predict its own decline after STN-DBS, except for the naming and orientation domains.

Conclusion: PD-MCI patients are at a lower risk of cognitive decline after STN-DBS compared with PD-NC patients before surgery.

1. Introduction

Subthalamic nucleus (STN) deep brain stimulation (DBS) has become a well-established treatment for alleviating motor symptoms and reducing the dose of dopaminergic medicine in patients with advanced Parkinson's disease (PD)[1,2]. But accumulated evidence has shown that STN-DBS has negative effects on cognitive function in patients with both normal cognitive (NC) and mild cognitive impairment (MCI)[3–10]. MCI represents a transitional cognitive status from normal cognition (NC) to dementia, and it is common in PD patients, with a prevalence as high as 40%[5,11,12].

There are relatively few studies on the cognitive outcomes of STN-DBS in PD-MCI patients, and the existing studies have primarily focused on the rate or risk of progression to dementia. These studies have generally shown that PD-MCI patients are at greater risk of developing dementia compared with PD-NC patients[3–5, 13]. However, postoperative cognitive decline that does not reach sufficient severity for dementia diagnosis, although does diminish patients' quality of life, has largely been ignored.

The aim of this retrospective cohort study was to investigate whether the rate of postoperative cognitive decline (not only dementia) was higher in PD-MCI patients compared with PD-NC patients after STN-DBS.

We also explored potential baseline parameters that could predict postoperative cognitive decline after STN-DBS.

2. Methods

2.1. Patient selection

This was a single center retrospective cohort study. PD patients who underwent STN-DBS between January 2016 and June 2020 were consecutively collected from the database of Beijing Tiantan Hospital (Beijing, China). The inclusion criteria included: (1) idiopathic PD diagnosed according to the UK brain bank criteria; (2) no dementia based on the Mini-Mental State Exam (MMSE) norm for elderly Chinese citizens (MMSE > 20 for individuals with 1–6 years of education and MMSE > 24 for individuals with 7 or more years of education) [14]; (3) bilateral synchronous STN-DBS treatment was performed at Beijing Tiantan Hospital; and (4) complete clinical assessment and follow-up for at least 6 months after STN-DBS. The exclusion criteria included: (1) illiteracy; (2) previous relevant medical history affecting cognitive function (e.g., stroke, brain tumor, hydrocephalus, and brain trauma); (3) serious surgical related complications (e.g., intracerebral hemorrhage); (4) the DBS lead had been revised or replaced; or (5) only online follow-up. The study was approved by the Beijing Tiantan Hospital Ethical Committee (IRB number: KY2020-139-01) and conducted in accordance with the latest version of the Declaration of Helsinki, all patients provided signed written informed consent.

2.2. Surgical procedures

All operations were performed by the same surgical team, and the surgical process was as described in previous studies in detail[15,16]. Briefly, under local anesthesia, DBS electrodes (model 3389, Medtronic, Dublin, Ireland, or model L301, Pins Medical, Beijing, China) were implanted with the Leksell micro stereotactic system (Elekta Instrument AB, Stockholm, Sweden). Microelectrode recording and macro stimulation tests were performed for trajectory selection. Then, an implantable pulse generator was implanted into the subclavian region under general anesthesia. Computed tomography scans were performed 1 day after surgery to eliminate complications such as intracranial hemorrhage. The implantable pulse generator was turned on 1 month after the operation. Since then, each patient underwent a regular adjustment of stimulation parameter settings and medication until symptoms were optimally controlled, usually at 6 months after surgery.

2.3. Clinical assessment

Clinical assessments primarily included cognitive function assessment (i.e., MMSE [Chinese version] and Montreal cognitive assessment [MoCA; Beijing version]), motor function assessment (i.e., Unified Parkinson's Disease Rating Scale [UPDRS] or Movement Disorder Society [MDS]-UPDRS). All clinical assessments were conducted by the same movement disorder team. Preoperative assessments were conducted up to 2 weeks before surgery, and regular clinical assessments were conducted at 6 months and 1 year after surgery, and then annually thereafter. All cognitive function assessments were performed

in the preoperative on-medication (med-on) and postoperative on-medication (med-on)/on stimulation (stim-on) states. Motor function assessments were performed as preoperative: off-medication (med-off) and med-on and postoperative: med-on/stim-on and med-on/stim-off. Med-off status was defined as at least 12 h after the patient withdrew from dopaminergic medications and med-on was defined as 1 h after the patient had taken dopaminergic medications. We also calculated the post- and pre-operative improvement rates of MDS-UPDRS-Ⅲ in PD patients using the formula described in previous studies[16]. Levodopa equivalent daily doses (LEDDs) were also recorded.

2.4. Dichotomy of postoperative cognitive decline in individual patients

PD-MCI was defined by MoCA scores (≤ 19 for individuals with 1–6 years of education and ≤ 24 for individuals with 7 or more years of education based on the norms for elderly Chinese citizens[17]) following MDS diagnostic criteria level I[18]. Based on the changes in MoCA score after STN-DBS, patients were divided into the cognitive-decline and non-cognitive-decline groups. A decrease in MoCA score of > 1.5 standard deviations (SDs) from baseline was defined as individual cognitive decline. Considering that MoCA scores are integers, we rounded 2 points as the cut-off[17]. Additionally, we subtracted 1 point as the cut-off for each specific domain, such as in visuospatial and executive function, naming, attention, language, abstract, delayed recall, and orientation.

2.5. Potential predictors of postoperative cognitive decline

We collected baseline information from PD patients as potential predictors of cognitive decline, including gender, age at surgery, age of onset, disease duration, education, Hoehn–Yahr stage (med-off), MDS-UPDRS-Ⅲ (med-off), levodopa responsiveness, symptom onset side, LEDD, MoCA, MMSE, and preoperative global cognitive status. This study used 50-years-old as the cut-off value for age of onset, and PD patients were divided into early-onset PD (< 50) and late-onset PD (≥ 50)[19]. Hoehn–Yahr stage was only collected in the med-off state. Levodopa responsiveness was calculated as (UPDRS-Ⅲ [med-off] − UPDRS-Ⅲ [med-on]) ÷ UPDRS-Ⅲ [med-off] × 100%. It should be noted that because some patients were assessed with UPDRS and others with MDS-UPDRS (the scale used for each patient was consistent during follow-up), UPDRS-Ⅲ scores were uniformly converted to MDS-UPDRS-Ⅲ using the previously reported method[20].

2.6. Statistical analysis

Descriptive statistics were used to describe baseline and follow-up demographic data. Continuous variables are described as mean (± SD) and median (range), while categorical variables are expressed as percentages. Intergroup comparisons of demographic data between patients were performed by applying either the independent t-test for continuous variables or the chi-square test for binary variables.

First, we investigated whether there were differences in cognitive decline after STN-DBS between the two groups using the chi-square test. Second, we evaluated baseline variables that could predict cognitive decline using univariate logistic regression models. Because no consistent predictors have been identified

in previous studies, we included all available parameters as an exploratory analysis, the stepwise forward approach was used to input these measurements as independent variables into the multivariable logistic regression model. Then, we also used the logistic regression model to explore possible baseline cognitive variables that could predict decline in cognitive specific domains following STN-DBS. Two tailed *p*-values < 0.05 were considered significant. All statistical analyses were performed using The R Project for Statistical Computing (version 3.6.1; https://www.rstudio.com/). Reported *p*-values were corrected for multiple comparisons in the domain analysis using the Bonferroni method (initial α = 0.05).

3. Results

3.1. Baseline characteristics of the PD-MCI and PD-NC groups

Initially, 227 PD patients who met the inclusion criteria were selected from the database of Beijing Tiantan Hospital. According to the exclusion criteria, 101 patients were excluded; thus, 126 PD patients were ultimately included. The detailed workflow is shown in Figure. 1. Among the included patients, 61.90% had MCI status at the time of surgery. As shown in Table 1, the PD-MCI group had lower MMSE (PD-MCI:26.73 ± 2.12, PD-NC: 28.15 ± 1.90) and MoCA (PD-MCI: 19.33 ± 3.39, PD-NC: 25.19 ± 1.79) scores, decreased scores in the specific cognitive domain of MoCA, and fewer years of education. The two groups did not differ significantly in any other baseline characteristics.

3.2. Individual cognitive decline and motor improvement at latest follow up between the PD-MCI and PD-NC groups

As shown in Table 2, postoperative follow-up ranged from 6 to 36 months (mean: 17.52 [10.83] months, median: 12 months), there were no significant differences between the PD-MCI and PD-NC groups. There was a higher percentage of patients with decreased MoCA scores in the PD-NC group than in the PD-MCI group (p = 0.005). Furthermore, the PD-NC group showed a higher proportion of declines in specific MoCA domains including attention, delayed recall, visuospatial, and executive function. Both groups had an excellent rate of improvement in MDS-UPDRS-Ⅲ after surgery, with no significant difference found between the two groups.

3.3. Preoperative predictors of postoperative cognitive decline

Two potential baseline predictors of cognitive decline were entered into multivariate logistic regression models: global cognitive status (odds ratio [OR]: 2.89, 95% confidence interval [CI]: 1.37–6.10, p = 0.005) and UPDRS-Ⅲ (med-off) (OR: 0.98, 95%CI: 0.97–1.00, p = 0.084; Table 3). The multivariate logistic regression model was adjusted twice: (1) for age and gender (adjust Ⅰ model); and (2) for age, gender, age of onset, education, Hoehn–Yahr stage (med-off), and symptom onset side (adjust Ⅱ model). After adjusting other factors, the pattern remained unchanged, and the stepwise forward regression model

showed that global cognitive status (PD-NC) at baseline was an independent variable (adjusted OR: 2.961, 95%CI: 1.191–7.357, p = 0.020) for postoperative cognitive decline (Table 4). The multivariate logistic regression model showed that at baseline, PD-MCI patients had a significantly lower probability of cognitive decline after STN-DBS than PD-NC patients.

Furthermore, we established a logistic regression model to explore predictors of cognitive decline in specific MoCA domains. These data indicated that preoperative cognitive specific function could predict its own decline after STN-DBS, except for the naming and orientation domains (Figure. 2). All results were corrected for multiple comparisons using the Bonferroni method (initial α = 0.05).

4. Discussion

In this study, we compared the postoperative cognitive decline of PD patients with different preoperative cognitive status. The results showed that the percentage of patients with postoperative cognitive decline was higher in the PD-NC group compared with the PD-MCI group, including global cognition, visuospatial, executive function, attention, and delayed recall (memory). Potential predictors of cognitive decline were also explored, which revealed that patients with preoperative NC status had a significantly higher probability of cognitive decline after STN-DBS than patients with preoperative MCI status.

Our data showed that with an average disease duration of 9.41 years, the prevalence of MCI was 61.90% at the time of surgery, which was consistent with previously studies. For example, Kim et al. reported that prevalence of MCI was 63.1% among 103 non-demented PD patients with a disease duration of 10.6 years[4], and Park et al. reported a 69.08% rate of MCI among 304 PD patients with an average disease duration of 13 years[13]. Notably, the prevalence of MCI was high in our cohort compared with a meta-analysis of 7053 non-surgery PD patients that had a pooled prevalence of PD-MCI of 40%[12]. The differences between their results and those presented herein may be attributable to differences in the patient cohort. In our study, patients mostly had advanced PD, longer disease duration, increased disease severity, and needed surgery. Overall, MCI is highly common among PD patients undergoing DBS surgery, so more attention should be paid to this patient population.

In this study, the percentage of patients with postoperative cognitive decline among all PD patients at the last follow-up (mean 17.52 months) was 40.48%, which was very close to the rate reported by Odekerken et al. (39.3%), where patients were not classified as PD-NC or PD-MCI at baseline and cognitive decline after 12 months was defined as a significant deterioration of three or more cognitive tests according to the reliable change index[6]. Our findings are also in accordance with those reported by Smeding et al., which showed that at the individual level, compared with the control group, 36% of patients in the STN-DBS group showed cognitive decline at 12-month follow up[7]. Our results also confirmed previous findings that patients showed a significant postoperative cognitive decline in terms of global cognitive function, language, attention, memory, visuospatial and executive function[7,21].

Previous studies have indicated that PD-MCI patients are at greater risk of developing dementia compared with PD-NC patients. Gruber et al. reported that patients with MCI (46.4%) had a markedly higher prevalence of developing dementia following STN-DBS compared with NC patients (22.2%) after 6.3 years follow-up[5]. The postoperative median time for PD-MCI patients to develop dementia was 6.03 years compared with 11.08 years for those with PD-NC[3]. There have also been several predictive studies that have reported an increased risk of dementia for MCI subjects compared with NC individuals following STN-DBS[4,13]. However, our study showed that the proportion of patients with cognitive decline in the PD-NC group (56.25%) was higher than in the PD-MCI group (30.77%). Meanwhile, multivariate logistic regression results also confirmed that the risk of cognitive decline after STN-DBS in the PD-NC group was increased compared with the PD-MCI group. The difference between our data and previous studies may be due to the following reasons: (1) we primarily focused on postoperative cognitive decline, not only cases that progressed to dementia; and (2) we used the MoCA scale for cognitive assessment, while other studies have used the MDRS[5], MMSE[4,13], and other comprehensive scales[3].

The interesting findings above can possibly be explained as follows. Postoperative cognitive decline may be attributable to both disease progression and side effects of STN-DBS[4,13]. First, postoperative deterioration in executive function, visuospatial, and memory (delayed recall) might be primarily due to natural PD progression[3,21]. Indeed, non-amnestic single domain impairment predominates in PD-MCI[18], with executive function, visuospatial, and attention as the most frequently affected cognitive domains[22–24]. MCI patients had impairments in these cognitive domains at baseline; thus, their postoperative deterioration was not as obvious as in the PD-NC group. Second, has been confirmed that STN-DBS primarily deteriorates the language domain, particularly verbal fluency, and may slightly damage executive function, memory, attention, and global cognitive function[8–10]. Therefore, postoperative language deterioration might be a side effect of STN-DBS, as there were obvious declines in both groups and no significant difference between the two groups in our study.

This study also found that the preoperative status of specific MoCA domains, except for the naming domain, could predict their own decline after STN-DBS. Our findings are generally consistent with prior studies[6,25]. This finding might be explained by the low rate of patients with a postoperative decrease in naming (MCI: 11.54%, NC: 6.25%, total: 9.52%).

There were a few limitations to this study. First, this was a single center retrospective study with its inherent defects, including being subject to bias, even though patients were enrolled consecutively. Our findings need to be confirmed by further prospective longitudinal studies. Second, only MoCA was used to diagnose MCI. But comprehensive neuropsychological assessments are not always available or feasible in clinical practice, MCI as defined by simplified evaluations also deserves consideration. Therefore, these data can be considered to provide a reference for clinicians, not to accurately reflect the detailed cognitive changes of STN-DBS on PD. Third, we did not set up a control group of medically treated patients, making it difficult to rule out the impact of disease progression on cognitive decline following STN-DBS.

In conclusion, our data indicated that compared with PD-NC, PD-MCI patients had lower risk of cognitive decline after STN-DBS, and their rate of motor improvement was similar, although PD-MCI patients progressed to dementia in higher proportions than PD-NC individuals.

Declarations

Acknowledgement: none.

Study Funding:

This work was supported by the National Natural Science Foundation of China (81830033, 61761166004 and 81671104)

Author Contributions:

Conceptualization: Hutao Xie, Yutong Bai, Yin Jiang, Jianguo Zhang.

Data curation: Hutao Xie, Yutong Bai,.

Formal analysis: Hutao Xie, Yutong Bai.

Funding acquisition: Jianguo Zhang.

Investigation: Hutao Xie, Yutong Bai.

Methodology: Hutao Xie, Yutong Bai, Yin Jiang, Jianguo Zhang.

Project administration: Jianguo Zhang.

Resources: Hutao Xie, Yutong Bai, Yin Jiang, Jianguo Zhang.

Supervision: Yin Jiang, Jianguo Zhang.

Validation: Hutao Xie, Yutong Bai.

Writing—original draft: Hutao Xie, Yutong Bai.

Writing—review & editing: Yin Jiang, Jianguo Zhang.

Competing interests

The authors declare no competing interests.

Data Availability

The datasets analysed during the current study are available from the corresponding author on reasonable request.

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Tables

Table 1 Baseline characteristics and clinical information of PD patients with MCI and NC

Variables	PD-MCI group (n = 78)	PD-NC group (n = 48)	*p*-value
Gender/female (%) [a]	37 (47.44%)	17 (35.42%)	0.186
Age of surgery (years)	62.88 ± 8.45	61.69 ± 8.58	0.444
Age of onset /late onset (%) [a]	52 (66.67%)	33 (68.75%)	0.808
Duration of disease (years)	9.72 ± 4.28	8.92 ± 3.49	0.277
Education (years)	9.96 ± 2.96	11.92 ± 3.00	< 0.001*
Hoehn Yahr stage (med off)	2.96 ± 0.57	3.01 ± 0.63	0.650
LEDD (mg)	711.82 ± 368.24	749.14 ±409.51	0.598
MDS-UPDRS- (med off)	55.11 ± 19.06	58.03 ± 21.52	0.428
Levodopa responsiveness (%)	50.35 ± 19.26	52.16 ± 17.12	0.652
Symptom onset side (left/right/ bilateral) [a]	32/39/2	19/21/5	0.169
MMSE score	26.73 ± 2.12	28.15 ± 1.90	< 0.001*
MoCA score	19.33 ± 3.39	25.19 ± 1.79	< 0.001*
MoCA specific domains score			
Visuospatial and Executive score	2.37 ± 1.43	3.96 ± 1.01	< 0.001*
Naming score	2.53 ± 0.83	2.90 ± 0.31	0.004*
Attention score	4.94 ± 1.30	5.65 ± 0.56	< 0.001*
Language score	1.90 ± 0.85	2.58 ± 0.61	< 0.001*
Abstract score	0.97 ± 0.84	1.56 ± 0.54	< 0.001*
Delayed recall score	1.08 ± 1.09	2.71 ± 1.32	0.025*
Orientation score	5.42 ± 1.19	5.83 ± 0.48	< 0.001*

[a] Chi-square test; unindicated comparisons were conducted using the independent t-test; significant results are marked with*.

Abbreviations: PD-MCI, Parkinson's disease with mild cognitive impairment; PD-NC, Parkinson's disease with normal cognition; LEDD, Levodopa equivalent dose; MDS-UPDRS- (med-off), Movement Disorder Society-Unified Parkinson's Disease Rating Scale, Part (med-off); MoCA, Montreal Cognitive Assessment; MMSE, Mini-Mental State Examination (off medication).

Table 2 Percentages of cognitive decline and rates of improved MDS-UPDRS- outcomes during the follow up between the PD-MCI and PD-NC groups

Variables	PD-MCI group (n = 78)	PD-NC group (n = 48)	*p*-value
Follow up (months)	16.08±10.48	18.78±11.43	0.324
Decline of MMSE score			0.420
YES	23（29.49%）	11（22.92%）	
NO	55（70.51%）	37（77.08%）	
Decline of MoCA score			0.005*
YES	24 (30.77%)	27 (56.25%)	
NO	54 (69.23%)	21 (43.75%)	
Decline of MoCA specific domains score			
Visuospatial and Executive score			0.011*
YES	26(33.33%)	27(56.25%)	
NO	52(66.67%)	21(43.75%)	
Naming score			0.326
YES	9(11.54%)	3(6.25%)	
NO	69(88.46%)	45(93.75%)	
Attention score			0.039*
YES	34(43.59%)	30(62.50%)	
NO	44(57.69%)	18(37.50%)	
Language score			0.538
YES	33(42.31%)	23(47.92%)	
NO	45(57.69%)	25(52.08%)	
Abstract score			0.648
YES	19(24.36%)	10(20.83%)	
NO	59(75.64%)	38(79.17%)	
Delayed recall score			< 0.001*
YES	12(15.38%)	20(41.67%)	
NO	66(84.62%)	28(58.33%)	
Orientation score			0.184

YES	21(26.92%)	8(16.67%)	
NO	57(73.08%)	40(83.33%)	
Improvement rate of MDS-UPDRS-Ⅲ (%)[a]	45.37±24.16	54.24±30.36	0.081

[a] Independent t-test; unindicated comparisons were conducted using Chi-square tests; significant results are marked with *.

Abbreviations: PD-MCI, Parkinson's disease with mild cognitive impairment; PD-NC, Parkinson's disease with normal cognition; MoCA, Montreal Cognitive Assessment; MMSE, Mini-Mental State Examination; MDS-UPDRS-Ⅲ, Movement Disorder Society-Unified Parkinson's Disease Rating Scale, Part Ⅲ.

Table 3 Impact of preoperative cognitive status, clinical and demographic data on postoperative cognitive decline (univariate logistic regression models).

Variables	OR	95% CI	*p* - value
Gender/female (%)	0.89	(0.43, 1.83)	0.753
Age of surgery (years)	1.00	(0.96, 1.04)	0.895
Age of onset /late onset	0.94	(0.44, 2.01)	0.875
Duration of disease (years)	1.02	(0.93, 1.11)	0.715
Education (years)	1.00	(0.89, 1.13)	0.952
Hoehn Yahr stage (med off)	0.78	(0.42, 1.45)	0.436
LEDD (mg)	1.00	(1.00, 1.00)	0.112
MDS-UPDRS-Ⅲ (med off)	0.98	(0.97, 1.00)	0.084*
Levodopa responsiveness (%)	1.18	(0.17, 8.27)	0.870
Symptom onset side /right	0.95	(0.45, 2.04)	0.900
Symptom onset side / bilateral	1.90	(0.39, 9.41)	0.430
preoperative cognitive status/PD-NC	2.89	(1.37, 6.10)	0.005*

Significant comparisons are marked with *.

Abbreviations: PD-NC, Parkinson's disease with normal cognition; LEDD, Levodopa equivalent dose; MDS-UPDRS-Ⅲ (med-off), Movement Disorder Society-Unified Parkinson's Disease Rating Scale, Part Ⅲ (med-off); MoCA, Montreal Cognitive Assessment; MMSE, Mini-Mental State Examination (off medication). OR, odds ratio; CI: confidence interval.

Table 4 Impact of preoperative cognitive status (PD-NC) and MDS-UPDRS- (med-off) on postoperative cognitive decline (multivariate logistic regression models)

Variables	Non-adjusted			Adjust -			Adjust -		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Preoperative cognitive status /PD-NC	2.832	(1.332, 6.020)	0.007*	2.968	(1.357, 6.492)	0.006*	2.961	(1.191, 7.357)	0.020*
MDS-UPDRS- (med off)	1.015	(0.996, 1.035)	0.113	1.019	(0.999, 1.040)	0.060	1.019	(0.994, 1.045)	0.136

Significant comparisons are marked with *; non-adjusted model adjusted for: none; adjusted model I adjusted for: age and gender; adjusted model adjusted for: age, gender, age of onset, education, Hoehn–Yahr stage (med-off), and symptom onset side.

Abbreviations: PD-NC, Parkinson's disease with normal cognition; LEDD, Levodopa equivalent dose; MDS-UPDRS- (med-off), Movement Disorder Society-Unified Parkinson's Disease Rating Scale, Part (off medication); OR: odds ratio; CI: confidence interval.

Figures

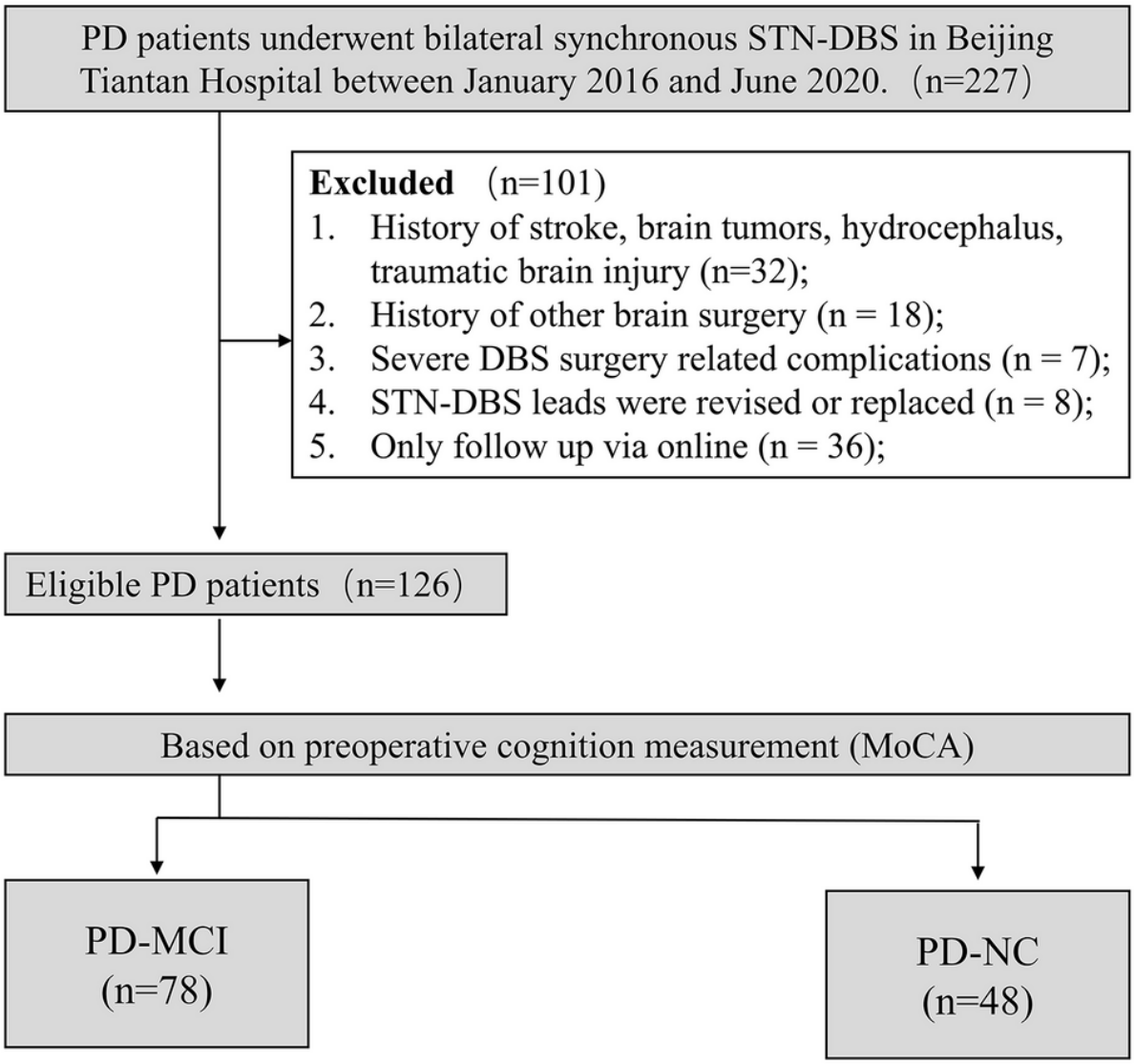

Figure 1

Flow chart of participant identification.

Abbreviations: PD-MCI, Parkinson's disease with mild cognitive impairment; PD-NC, Parkinson's disease with normal cognition; MoCA, Montreal Cognitive Assessment; MMSE, Mini-Mental State Examination.

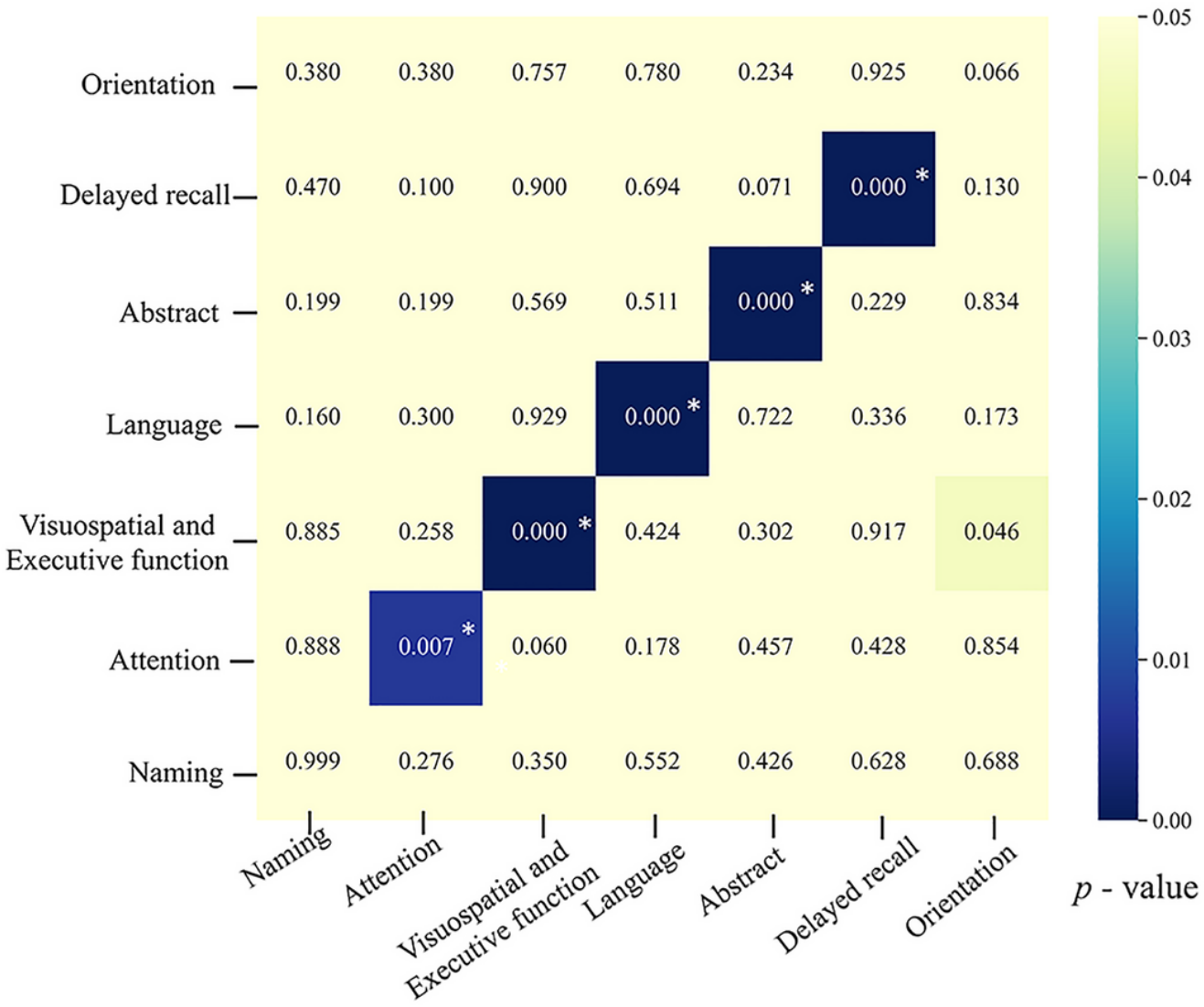

Figure 2

Heatmap showing outcomes of predictors of postoperative decline in specific MoCA domains.

The x-axis shows postoperative decline in seven different MoCA domains based on which cognitive-decline dichotomy was made. The y-axis lists seven potential predictors. The color of the blocks reflects the *p*-value from comparisons of each potential predictor between the cognitive-decline group and the non-decline group, with darker color indicating smaller *p*-values. After Bonferroni correction, $p < 0.008$ (0.05/7) was considered significant. Blocks with * indicate factors that remained statistically significant in the multivariate regression model.

Supplementary Files

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- Supplementary.docx