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ORIGINAL ARTICLE - FUNCTIONAL NEUROSURGERY - MOVEMENT DISORDERS

Predictive potential of preoperative electroencephalogram for neuropsychological change following subthalamic nucleus deep brain stimulation in Parkinson's disease

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Abstract

Background Deep brain stimulation of the bilateral subthalamic nucleus (STN-DBS) improves motor fluctuation and severe dyskinesia in advanced Parkinson's disease (PD). Effects on non-motor symptoms, such as neurocognitive side effects, can also influence the quality of life of both patients with PD and caregivers. Predictive quantitative factors associated with postoperative neurocognitive deterioration therefore warrant further attention. Here, we evaluated preoperative electroencephalogram (EEG) as a predictive marker for changes in neurocognitive functions after surgery.

Methods Scalp EEG was recorded preoperatively from 17 patients with PD who underwent bilateral STN-DBS. Global relative power in the theta, alpha, and beta bands was calculated. Cognitive function was assessed with neuropsychological batteries preoperatively and 1 year after STN-DBS.

Results Performance on the Symbol Search subtest of the WAIS III declined 1 year after DBS. The theta band was chosen for analysis with a 40% cutoff point for increased (≥ 40%) and decreased (< 40%) power. No significant differences between the two groups in baseline performance on most neuropsychological batteries were found, except for the Digit Symbol Coding subtest of the WAIS III. Changes in visual spatial functions were significantly different between groups. The increased theta band power group demonstrated a significant deterioration in performance on the WAIS III Matrix Reasoning subtest and the copy and immediate recall tasks of the Rey-Osterrieth complex figure test.

Conclusions These findings suggest that preoperative increases in theta power are related to postoperative deterioration of visuospatial function, which indicates the predictive potential of preoperative quantitative EEG for neurocognitive changes after STN-DBS.

Keywords Deep brain stimulation · Parkinson's disease · Subthalamic nucleus · Neurocognitive function · Visuospatial function

Introduction

Deep brain stimulation (DBS) is an established therapy for advanced Parkinson's disease (PD), with relatively strict inclusion criteria to obtain optimal improvement of motor function [12, 45]. However, the effects of DBS on non-motor manifestations, such as the new onset of cognitive deterioration [24], have become a critical issue in recent years.

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Global cognitive function has been assessed in various studies with the Mini-Mental State Examination (MMSE) or the Mattis Dementia Rating Scale. Smeding et al. reported the worsening of global cognition 1 year after surgery [41], while most other studies found no significant changes [47, 53]. Previous studies reported an estimated incidence of dementia of 35.7~89 per 1000 persons per year after subthalamic nucleus (STN) DBS [5, 17]. In addition, deterioration in verbal fluency [32] and in Stroop test performance has been frequently reported [23, 49]. As impairments in neuropsychological functions affect daily life and quality of life (QOL), considerable efforts have been made to identify preoperative risk factors for cognitive deterioration following DBS. Smeding et al. suggested that impaired attention, advanced age, and a low L-dopa response at baseline could predict cognitive decline, whereas a high L-dopa response at baseline could be a predictive factor for improvement in QOL [41]. Recent reports demonstrated that word fluency, apathy scale scores, and the mental health domain of health-related QOL are independent preoperative prognostic factors for cognitive decline [29]. Thus, predicting postoperative neuropsychological deterioration is a critical theme in DBS surgery for PD. Deterioration of some cognitive measures after surgery is sometimes mitigated by improvement of others. A meta-analysis conducted by Combs et al. concluded that the subtle cognitive decline produced by DBS appears to be relatively well tolerated [8]. Moreover, as the reported decline of cognitive domains was observed at the population level, cohort differences caused by individual preoperative risk factors might also play an important role.

Electroencephalogram (EEG) is a non-invasive technique that requires minimal patient cooperation and does not depend on verbal or motor responses that may be affected in PD. It primarily measures dendritic potentials from vertically oriented pyramidal neurons and can thus be used to examine the frequency and mode of oscillatory brain activity. Studies on EEG characteristics of patients with PD indicated that diffuse slowing of EEG is present in many patients with PD [39], and that those patients frequently show cognitive impairment [26]. Furthermore, Klassen et al. utilized quantitative EEG measurements and suggested that a lower background rhythm frequency and increased relative power in the theta band might be potential predictive biomarkers for dementia incidence in PD [19]. However, the correlation between preoperative quantitative EEG measures and postoperative changes in neuropsychological testing performance in patients with PD has not been studied in detail. Here, in the present study, we aimed to clarify whether patients who show preoperative slowing on EEG would develop neuropsychological deterioration after DBS. We also evaluated the predictive value of preoperative EEG for neuropsychological deterioration in patients with PD following STN-DBS.

Methods and materials

Patient population

A total of 17 patients (10 men, seven women) with advanced PD who underwent bilateral STN-DBS were enrolled in our study. All participants were affected by severe motor complications from dopaminergic medications, such as fluctuations and/or dyskinesia. All patients underwent implantations of bilateral STN-DBS at Chiba University Hospital, performed by the same surgical team. To standardize the patient background, the following inclusion/exclusion criteria were applied: (i) younger than 75 years of age; (ii) no dementia (global cognition evaluated at 25 points or more on the MMSE); (iii) no psychiatric problems (screened by a psychiatrist); and (iv) neuroradiologically verified absence of vascular lesions. The median disease duration was 12.9 years (interquartile range (IQR 10.5~16.8 years), and, at the time of surgery, the median age was 66 years (IQR 60~68). Preoperatively, the mean (± standard deviation, SD) UPDRS (Unified Parkinson's Disease Rating Scale) Part III score was 16 ± 7.5 in the "on" medication state, and 41.7 ± 13.8 in the "off" medication state. The mean L-dopa equivalent dose (LED) was 1022 ± 189 mg. The mean MMSE score was 29.2 ± 1.4, which represents a normal level. This retrospective study that involved only routine diagnostic procedures before and after surgery was approved by the Ethics Committee of Chiba University Graduate School of Medicine (2823). All participants provided written informed consent, obtained in the "on" medication state.

Preoperative EEG recording and processing

Scalp EEG was recorded according to the 10–20 International system, using a digital EEG instrument (DAE-1100, Vita CL02, Nihon-Kohden, Tokyo, Japan), from the following positions: Fp1, Fp2, F3, F4, C3, C4, A1, A2, P3, P4, O1, O2, F7, F8, T3, T4, T5, T6, Fz, Cz, and Pz. The ground electrode was placed on the forehead. All electrode impedances were kept below 5 kΩ. Preoperative EEG was obtained with each subject in resting-awake condition with their eyes closed. The high-frequency filter was set at 60 Hz, with a time constant of 0.3 s.

Data were processed offline using Neuroworkbench® software (Nihon-Kohden, Tokyo, Japan). We chose an average electrode reference for digital re-referencing. Consecutive, non-overlapping 3- to 5-s epochs were created and visually inspected for artifacts; individual files yielded 15 epochs. These epochs were passed through a hamming window, processed using fast Fourier transform (FFT), and each electrode was averaged. Approximately 75-s periods of data were used for analysis. Frequency bands were set as follows: delta, 1.5–3.9 Hz; theta, 4–7.9 Hz; alpha, 8–12.9 Hz; and beta, 13–30 Hz. Klassen et al. have demonstrated that high relative

theta band power was related to PD dementia in a long-term follow-up [19]. We therefore focused on relative theta band power in this study. The global relative EEG power for the theta frequency band was calculated using all electrodes except Fp1 and Fp2, as a percentage of the overall summed EEG power across all chosen frequency bands (alpha, beta, theta), and the mean value was chosen as the cutoff point for the group assignment.

Assessment of neuropsychological status

We evaluated language, attention and working memory, processing speed, and visuospatial function preoperatively as well as 1 year after STN-DBS. The neuropsychological batteries used included the Japanese versions of the Wechsler Adult Intelligence Scale III (WAIS III), the Rey-Osterrieth complex figure test (ROCFT), and the Trial Making Test (TMT).

We obtained the full-scale WAIS III scores from all patients and selected the subtests for evaluating language, attention and working memory, processing speed, and visuospatial function. Language was assessed by the Vocabulary and Similarities subtests of the WAIS III. The TMT Part A (TMT-A) provides a baseline measurement of psychomotor speed and visual search, while the TMT part B (TMT-B) is administered as a measure of set-shifting and inhibition [4, 14, 44]. In this study, we used the Japanese version of the TMT, where the TMT part B (TMT-B) is modified by changing letters from the Roman alphabet into Kana (Japanese phonogram); another difference is the direction of the paper we used for examination: it was arranged side-to-side, not end-to-end as in the English version. We used the TMT-B and the Arithmetic, Digit Span, and Letter-Number Sequencing subtests of the WAIS III for evaluation of attention and working memory [33], while the TMT-A along with the Digit Symbol Coding and Symbol Search of the WAIS III were chosen to evaluate processing speed [8]. As the Digit Symbol Coding subtest is a multifaceted test, its memory and motor skill components have been studied, and Kreiner et al. suggested that a large part of the performance on the Digit Symbol Coding subtest depends on motor skills [20]. The subtests Matrix Reasoning and Block Design of the WAIS III assess visual and inductive reasoning, and visuospatial and motor skills construction, respectively [25, 28]. The ROCFT is a widely used neuropsychological test for the evaluation of visuospatial constructional ability and visual memory [40]. The copy task and immediate recall task were evaluated in this study. We used the Block Design and Matrix Reasoning subtests as well as the ROCFT for evaluation of visuospatial functions.

The Japanese version of the WAIS IV was not available until 2018, and we therefore used the WAIS III for neuropsychological evaluation. Patients were evaluated before surgery, with the IPGs turned on, and while receiving their regular medication at the postoperative follow-up.

Surgical procedures

For surgical target and trajectory planning, a preoperative MRI scan was performed to visualize the STN, and stereotactic software (Surgiplan Elekta Instruments, Stockholm, Sweden) was utilized to verify anatomical landmarks: the anterior commissure, the posterior commissure, and the midsagittal plane were used to determine the coordinates for the intended STN targets. Before the patient was transferred to the operating theater, the placement of the Leksell G frame was performed, and CT scans and MR images were obtained. The tentative targets were placed 4.0–5.0 mm below the anterior commissure-posterior commissure (AC-PC) line, 11.5–13.0 mm lateral to the midline, and 2.5–3.0 mm posterior to the AC-PC midpoint; they were adjusted based on the red nucleus as internal fiducial marker [3], and the STN was visualized on T2-weighted images and fluid-attenuated inversion recovery (FLAIR) images. Intraoperative microelectrode recordings confirmed high activity in the subthalamic nucleus (STN).

Bilateral implantation of intracranial leads (Model 3387, Medtronic, Minneapolis, MN, USA) was performed under local anesthesia, and placements of the electrodes was determined according to the microelectrode recordings, motor benefits, and side effects. The electrodes were then connected to implantable pulse generators (IPGs; Activa; Soletra, Medtronic, USA), which were implanted under general anesthesia. Following surgery, CT scans were taken on the same day to confirm electrode location. One day after surgery, stimulation parameters were progressively adjusted by telemetry. To obtain optimal clinical effects, stimulation parameters were set as follows: average voltage 2.99 ± 0.40 V on the right side, 3.01 ± 0.40 V on the left side. Pulse width and frequency were set to 60 μs and 130 Hz, respectively.

Statistical analysis

We conducted two different sets of analyses using JMP Ver.12 (SAS Institute Inc., Cary, NC, USA). A power spectrum analysis was performed to assess the relationship between the results of the neurocognitive tests and preoperative EEG, while pre- and post-surgical mean scores of neuropsychological tests were also compared. All data are presented as means and SD. To evaluate postoperative changes in individual patients, we subtracted individual baseline scores from postoperative scores. The Wilcoxon test was used for paired samples, Bonferroni correction was applied, and the level of significance for all tests was set at 0.05. The relationship between postoperative score changes on the neuropsychological tests and relative theta band power was analyzed using linear regression analysis.

Results

EEG analyses and group assignment

A power spectrum analysis was performed, and the mean band power of each band was as follows: theta 43 ± 15%, alpha 35 ± 12%, beta 23 ± 10%. The theta band was chosen for analysis by using 40% as a cutoff point according to the mean value; the increased theta band power group had a theta band power ≥ 40% ($n = 10$), while the decreased theta band power group had a theta band power < 40% ($n = 7$).

All patients showed good motor responses to DBS, their UPDRS motor scores significantly improved (16 ± 7.5 vs. 8.4 ± 4.8), and their LED was significantly reduced (1022 ± 189 mg vs. 585 ± 175 mg) 1 year after surgery (Table 1). We did not find statistical differences when comparing UPDRS motor scores before and after surgery in the "on" medication state between the two groups, and no statistical difference was found comparing LED between the two groups. Sex ratio, age at assessment, and disease duration were not statistically different between the two groups (Table 1).

Global effects of STN-DBS on neuropsychological assessments

Pre- and postoperative mean scores are shown in Table 2. The preoperative scores of the ROCFT were slightly lower than the normative data from the Japanese population [50], and preoperative mean times to complete the TMT were in the normal range of the same age group according to a previous study using the same Japanese version of the TMT [43]. Scores on language and attention and working memory indicated no significant changes between pre- and postoperative status. For processing speed, the patients' performance on the Symbol Search subtest was significantly poorer 1 year after STN-DBS. Regarding visuospatial functions, the ROCFT

Table 2 Neuropsychological tests results between preoperative and postoperative state

Tests	Before DBS	1 year after DBS	*P* value
Language			
Vocabulary	11.24 ± 2.80	10.47 ± 2.72	0.07
Similarities	10.65 ± 3.00	10.82 ± 2.48	0.79
Attention and working memory			
Arithmetic	9.76 ± 3.67	9.59 ± 2.79	0.86
Digit span	10.59 ± 2.92	10.88 ± 3.06	0.66
Letter-number sequencing	10.23 ± 3.15	10.35 ± 2.85	1.00
TMT-B	193.79 ± 86.57	212.35 ± 91.01	0.55
Processing speed			
Digit symbol coding	7.65 ± 2.37	7.06 ± 2.14	0.18
Symbol search	7.94 ± 2.51	6.29 ± 2.82	< 0.01
TMT-A	122.11 ± 61.77	92.69 ± 50.68	0.07
Visuospatial function			
Block design	7.76 ± 3.42	7.35 ± 2.91	0.46
Matrix reasoning	9.24 ± 2.41	8.88 ± 2.67	0.57
ROCFT copy	32.84 ± 3.57	28.28 ± 5.44	0.01
ROCFT-immediate recall	14.28 ± 6.60	13.38 ± 7.81	0.53

TMT, trail-making test; *ROCFT*, Rey-Osterrieth complex figure test

Values are shown as mean ± standard deviation

Table 1 Demographic data and clinical characteristics of patients

Variables	Total	Relative theta band power < 40%	Relative theta band power ≥ 40%	*P* value
Number of patients	17	7	10	n.s
Age at surgery (mean)	65.2 ± 5.3	66.1 ± 5.2	64.5 ± 5.6	n.s
Sex (male/female)	10/7	3/4	7/3	n.s
PD duration (years)	13.6 ± 3.5	11.8 ± 2.1	14.9 ± 3.7	n.s
MMSE (mean)	29.2 ± 1.4	29.0 ± 1.5	29.3 ± 1.3	n.s
LED preoperative (mg)	1022 ± 189	1091.6 ± 166.3	973.5 ± 196.5	n.s
LED postoperative (mg)	585 ± 175	590.7 ± 194.3	581.5 ± 170.4	n.s
Preoperative UPDRS part III ON	16 ± 7.5	16.9 ± 3.2	15.4 ± 7.3	n.s
Preoperative UPDRS part III OFF	41.7 ± 13.8	40.3 ± 14.7	42.7 ± 13.9	n.s
Postoperative UPDRS part III ON	8.4 ± 4.8*	8.6 ± 5.4	8.3 ± 4.7	n.s
Postoperative UPDRS part III OFF	13.2 ± 7.3*	14.6 ± 9.0	12.2 ± 6.1	n.s

Values are shown as mean ± standard deviation

LED, L-dopa equivalent dose; *PD*, Parkinson's disease; *MMSE*, mini-mental state examination; *UPDRS*, Unified Parkinson's Disease Rating Scale; *n.s*, no significant difference

*Preoperative score vs. Postoperative score, $P < 0.05$

copy task demonstrated significant deterioration 1 year after DBS.

Effects of EEG slowing on neuropsychological assessments

In the power spectrum analysis, we found no significant differences between the increased theta band power group and the decreased theta band power group in terms of baseline performance on most neuropsychological batteries, except for the Digit Symbol Coding subtest of the WAIS III, which demonstrated a significant difference between the two groups: the scores of the patients in the increased theta band power group were significantly lower than those of the patients in the decreased theta band power group ($P < 0.05$) (Table 3). We found significant differences between the two groups regarding the changes in the Matrix Reasoning subtest of the WAIS III as well as the ROCFT copy task and immediate recall (Table 3). The group difference in Matrix Reasoning performance was small; however, the ROCFT demonstrated substantial changes. These deteriorations in visuospatial function were associated with increased theta band power in patients with PD. There was no significant difference in relative theta band power regarding the changes in language, attention and working memory, and processing speed. Linear regression analyses of the Matrix Reasoning subtest and the ROCFT copy test, according to relative theta band power, demonstrated a significant correlation between EEG slowness and postoperative score changes (Fig. 1A–C).

We performed additional regional EEG analyses for visual spatial functions. The mean values of the theta band power of each region were used as cutoff points. Matrix Reasoning significantly correlated with increased theta band power in the temporal, occipital, and left frontal regions. Regarding the ROCFT, the copy task was related to the increased theta band power in all regions except for the left frontal region, while for immediate recall, a significant correlation with the increased theta band power was found in the temporal and occipital regions. The frontal and parietal regions did not show regional significance (Table 4).

Discussion

To our knowledge, this is the first report of neuropsychological effects of EEG slowing in patients with PD treated with STN-DBS. The results of our relative band power analysis indicate that preoperatively increased theta band power

Table 3 Change of neuropsychological tests results according to preoperative EEG

Tests	Relative theta band power < 40%		Relative theta band power ≥ 40%		*P* value baseline	*P* value change
	Baseline	Change	Baseline	Change		
Language						
Vocabulary	10.9 ± 3.3	− 0.71 ± 1.50	11.5 ± 2.5	−0.80 ± 1.55	0.59	0.88
Similarities	10.9 ± 2.9	0.86 ± 1.95	10.5 ± 3.1	−0.30 ± 1.64	0.96	0.16
Attention and working memory						
Arithmetic	9.9 ± 3.0	0.57 ± 3.2	9.7 ± 4.2	−0.7 ± 2.0	0.69	0.34
Digit span	10.0 ± 2.6	1.0 ± 1.8	11.0 ± 3.2	−0.2 ± 1.8	0.59	0.25
Letter-number sequencing	11.0 ± 3.6	0.71 ± 2.50	9.7 ± 2.9	−0.30 ± 1.16	0.35	0.32
TMT-B	209.3 ± 85.7	− 24.38 ± 64.7	180.8 ± 93.1	54.3 ± 113.7	0.17	0.34
Processing speed						
Digit symbol coding	9.0 ± 2.2	− 0.57 ± 1.3	6.7 ± 2.1	− 0.6 ± 2.8	0.03	0.55
Symbol search	8.7 ± 2.1	− 1.43 ± 2.8	7.4 ± 2.7	− 1.8 ± 1.2	0.32	0.69
TMT-A	110.1 ± 55.6	− 19.19 ± 55.1	130.5 ± 67.3	− 36.6 ± 51.1	0.31	0.34
Visuospatial function						
Block design	8.4 ± 4.0	0.43 ± 2.0	7.3 ± 3.1	− 1.0 ± 1.9	0.62	0.16
Matrix reasoning	8.3 ± 2.6	1.57 ± 1.8	9.9 ± 2.2	− 1.7 ± 2.2	0.20	< 0.01
ROCFT copy	31.1 ± 4.5	− 1.0 ± 4.4	34.2 ± 2.0	− 7.3 ± 6.4	0.12	0.04
ROCFT-immediate recall	14.4 ± 7.0	3.14 ± 3.7	14.2 ± 6.7	− 4.1 ± 6.2	0.83	0.03

Values are shown as mean ± standard deviation

TMT, trail-making test; *ROCFT*, Rey-Osterrieth complex figure test

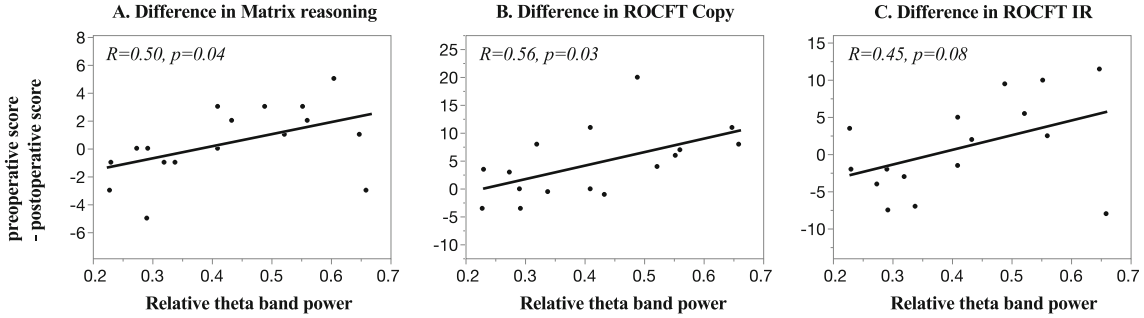

Fig. 1 Scatter graphs showing the relationships between postoperative changes on the Matrix Reasoning subtest **a**, the Rey-Osterrieth complex figure test (ROCFT) copy **b**/immediate recall **c**, and relative theta band powers. The X-, and Y-axis indicate postoperative changes in scores (preoperative score-postoperative score) and relative theta band powers, respectively. Postoperative changes on the Matrix Reasoning and ROCFT copy test were significantly correlated to relative theta band powers

correlates with changes in visuospatial function 1 year after STN-DBS. Preoperative EEG slowing did not affect neuropsychological tests on language or attention and working memory. EEG slowing offers two possibilities for predicting the outcome of visuospatial function. One is predicting the vulnerability to penetration with intracranial electrodes and stimulation. The second one is predicting the progression of visuospatial decline in the natural history of PD. It may be important to know whether these results are consistent with the natural history of the disease or whether there is an influence exerted by the surgical procedure itself or the stimulation. In the current study, we tried to detect neuropsychological changes early after DBS, when the effects of disease progression might be minimum. We therefore evaluated the patients 12 months postoperatively.

Quantitative analyses of EEG have been conducted in PD. Klassen et al., for example, demonstrated that a slow background rhythm frequency and increased theta power are potential predictive biomarkers for dementia in PD [19]. Cozac et al. obtained global relative median-power spectra by fully automated processing of high-resolution EEG, and demonstrated that increased theta power is associated with the development of severe cognitive decline [9]. These studies indicate that EEG slowing indicates a risk of neurocognitive deterioration in the clinical course of PD. STN-DBS provides improvement of severe motor fluctuation and disabling dyskinesia in patients with PD, but increases the risk of cognitive decline [51]. Knowledge of the effects of preoperative EEG slowing on the patient's postoperative cognitive status is limited. Markser et al. reported that visual assessment of EEG using the Grand Total EEG (GTE) score can yield useful information for predicting cognitive deterioration after DBS [22]. The authors assessed cognitive decline using the Dem Tect [16]. While the Dem Tect has a reportedly higher sensitivity for dementia than the MMSE, it is not sensitive enough to detect the postoperative changes in detail. Considering the results of previous studies, EEG slowing is a predictor for neurocognitive impairment in patients with PD, as well as patients with PD treated with STN-DBS. The present study suggests that visuospatial functions are

Table 4 Comparison of matrix reasoning and ROCFT tests according to regional mean relative theta band power

Regional EEG	Matrix reasoning	ROCFT-copy	ROCFT-immediate recall
Left frontal $\theta < 41\%$ vs $\geq 41\%$	0.9 ± 2.2/− 1.8 ± 2.3*	− 2.0 ± 4.9/− 7.86 ± 6.52	2.1 ± 4.2/− 4.7 ± 6.7
Right frontal $\theta < 43\%$ vs $\geq 43\%$	0.7 ± 2.4/− 1.5 ± 2.4	− 1.9 ± 5.0/− 8.0 ± 6.3*	1.7 ± 4.4/4.2 ± 7.1
Left temporal $\theta < 46\%$ vs $\geq 46\%$	1.4 ± 1.8/− 1.9 ± 2.2*	− 0.9 ± 3.9/− 8.3 ± 6.1*	2.9 ± 3.5/− 4.8 ± 6.2*
Right temporal $\theta < 46\%$ vs $\geq 46\%$	1.4 ± 1.8/− 1.9 ± 2.2*	− 0.9 ± 3.9/− 8.3 ± 6.1*	2.9 ± 3.5/− 4.8 ± 6.2*
Left parietal $\theta < 37\%$ vs $\geq 37\%$	0.6 ± 2.3/− 1.7 ± 2.5	− 1.7 ± 4.8/− 9.3 ± 5.7*	1.7 ± 4.1/− 5.2 ± 7.3
Right parietal $\theta < 39\%$ vs $\geq 39\%$	0.6 ± 2.3/− 1.7 ± 2.5	− 1.7 ± 4.8/− 9.3 ± 5.7*	1.7 ± 4.1/− 5.2 ± 7.3
Left occipital $\theta < 48\%$ vs $\geq 48\%$	1.0 ± 2.0/− 1.9 ± 2.4*	− 0.7 ± 3.7/− 9.6 ± 5.3*	2.4 ± 3.6/− 5.1 ± 6.6*
Right occipital $\theta < 48\%$ vs $\geq 48\%$	1.6 ± 1.8/− 1.7 ± 2.2*	− 1.0 ± 4.1/− 7.3 ± 6.4*	3.1 ± 3.7/− 4.1 ± 6.2*

Values, change between baseline and follow-up, mean ± standard deviation; Less than mean value of relative theta band power/more than and equal to mean value of relative theta band power

θ, relative theta band power; *, $P < 0.05$

vulnerable in patients with PD with preoperative EEG slowing treated with STN-DBS.

Preoperative predictions of cognitive decline are useful for selecting subthalamic or pallidal stimulation. There is a limited number of studies that directly compare neurocognitive function between two stimulation targets, the STN and the globus pallidus internus (Gpi). Follett et al. reported a greater decline in processing speed and working memory in an STN-DBS group compared with a Gpi-DBS group at 24 months postoperatively [13]. In the same cohort, at the 3-year follow-up timepoint, STN-DBS was associated with statistically significant declines in the Mattis Dementia Rating Scale and the Hopkins Verbal Learning Test, which was not observed in the Gpi group [46]. Another study that assessed cognitive function at 12 months after surgery found that patients who underwent STN-DBS showed greater negative changes than patients in a Gpi-DBS group in mental speed (Stroop word reading and color naming), attention (TMT-B), and language (WAIS III similarities) [30]. Meanwhile, Rouaud et al. suggested that the risk of cognitive decline is lower whenever the Gpi is the target of choice [34]. Taken together, these data suggest that the STN and the Gpi have different neuropsychological risk profiles. Considering that STN-DBS tends to lead to more cognitive side effects than Gpi-DBS, the Congress of Neurological Surgeons guideline [35] recommends using Gpi stimulation rather than STN stimulation, if there is significant concern about cognitive decline, particularly with regard to processing speed and working memory in patients undergoing DBS, while taking into consideration other goals of the surgery. The Gpi might thus be an optional target for patients with PD with a risk of visuospatial deterioration.

Visuospatial function following STN-DBS surgery

The Matrix Reasoning subtest and both the ROCFT copy and the immediate recall task showed declining scores in patients with PD with increased relative theta band power (Table 3). While the analysis of mean scores of the neuropsychological tests between preoperative and postoperative states showed no significant changes in Matrix Reasoning scores, the copy task of the ROCFT demonstrated deterioration 1 year after surgery. There is a limited number of studies that have reported on visuospatial function following DBS, and some of these studies reported results similar to ours, showing that visuospatial function deteriorates after DBS [1, 2, 37]. Other studies, in contrast, reported unchanged visuospatial function after surgery (Table 5) [18, 27, 47, 49, 51]. The small sample size of our study and differences in the neuropsychological tests used for the evaluation of visuospatial function might have influenced the results. Moreover, pre- vs. post-surgical comparisons of mean scores of all patients might not be enough to reflect the changes in cognitive function. Our results suggest that EEG, as a quantitative measure, might have the potential to predict a progressive decline in visuospatial function before the decline in neuropsychological tests scores is detected.

Visuospatial dysfunction has also been shown to be related to disease severity and progression [38]. A long-term follow-up study conducted by Williams-Gray et al. reported that the decline of visuospatial function at the time of diagnosis was associated with an increased dementia risk at a 5.2-year follow-up, suggesting that dementia in PD frequently starts with visuospatial dysfunction [48]. However, in our study, preoperative baseline ROCFT scores did not show differences according to relative theta band power (Table 3). Therefore, it is possible that DBS accelerates the deterioration of cognitive function in some regions, and preoperative EEG might have the potential to predict the changes in these regions.

A regional EEG analysis indicated that Matrix Reasoning is related to increased theta band power in the temporal, occipital, and left frontal regions, which suggests a low regional sensitivity of this subtest. As for the ROCFT, our results demonstrate that there is no significant laterality between the two hemispheres, while a study investigating the relationship between regional blood flow and cognitive performance in

Table 5 Previous studies about change of visuospatial function following deep brain stimulation

Author	Year	*N*	Age M (SD)	Effect	Tasks
Saint-Cyr et al.[37]	2000	11	66.5 (7.9)	Deterioration	BEM (Batteried' efficience mnesique)
Alegret et al.[2]	2001	15	61.1 (8.3)	Deterioration	Judgment of line orientation test
Acera et al.[1]	2017	50	62.2 (8.2)	Deterioration	Judgment of line orientation test
Morrison et al.[27]	2004	17	59.9 (7.7)	Unchanged	Judgment of line orientation test
York et al.[51]	2008	23	59.5 (11.8)	Unchanged	Clock command
Witt et al.[49]	2008	60	60.2 (7.9)	Unchanged	Benton visual retention test
Kishore et al.[18]	2010	45	55.4 (10.9)	Unchanged	Judgment of line orientation test; Visual object and space perception battery
Willams et al.[47]	2011	19	62.1 (10.3)	Unchanged	Clock command

M (SD), mean ± standard deviation

individuals with Alzheimer's disease reported that right side decrease in perfusion was associated with worse performance on the ROCFT [42]. Considering the limitations on patient numbers and disease differences, further studies with lager numbers of patients that include healthy controls might be needed to clarify the brain regional sensitivity of Matrix Reasoning and the ROCFT.

Processing speed following STN-DBS surgery

Regarding the overall effect of STN-DBS on neuropsychological tests, we demonstrate significant changes in processing speed after STN-DBS on the Symbol Search subtest. Some previous studies reported results in line with these findings. Rothlind et al. reported that patients with PD who underwent DBS with targets including the Gpi showed deterioration in Symbol Search performance at 6 months after surgery [33]. TMT-A as a subdivision of processing speed mainly reflects psychomotor speed and is also recognized as a motor-weighted factor of processing speed [7]. Although a study conducted by Jahanshahi et al. reported improvements on the TMT-A upon stimulation in the "on" state compared with stimulation in the "off" state 1 year after STN-DBS [15], most previous studies reported similar results to ours, indicating no change in pre- versus post-surgical TMT-A scores [11, 33, 36].

Preoperative EEG slowness was associated with preoperative Digit Symbol Coding scores indicating processing speed. Digit Symbol Coding is a measure of speeded transcription of symbols using a key to assess processing speed. Previous studies reported that Digit Symbol Coding, Matrix Reasoning, Symbol Search, and Letter-Number Sequencing are related to executive function [10, 31]. However, only Digit Symbol Coding scores showed significant differences according to relative theta band power. In the present study, patients with PD with low MMSE scores (< 25) were not classified as candidates for DBS surgery. MMSE is known to have low sensitivity for detecting cognitive impairment including mild cognitive impairment [52]. A remarkably wide range of cognitive impairment can be found even in patients with PD with a relatively high score on the MMSE [21]. Burdick et al. reported that greatest impairments were found on the Digit Symbol Coding test in patients with PD with high scores on the MMSE [6]. Increased relative theta band power might be associated with lower scores on Digit Symbol Coding, indicating mild cognitive impairment. There might be a possibility for the Digit Symbol Coding subtest to be used as a screening method for cognitive decline in patients with PD after STN-DBS. Further study is needed to confirm this possibility.

Limitations of our study

The current study has several limitations. The sample size was small and the effects of aging and disease progression on short-term outcomes remain unclear. Previous studies demonstrated that EEG slowing is a risk factor for developing dementia in PD, indicated by a decline in long-term follow-ups [9, 19]. Thus, we might find very early changes related to neurocognitive decline in patients with PD in spite of surgical interventions. According to a limited number of reports regarding neurocognitive functions in patients with DBS and the most appropriate medical treatment [33, 36], the likelihood of a significant decline increases with DBS. Our results suggest that patients with EEG slowing have a risk of deterioration of visuospatial functions after STN-DBS. We evaluated the patients without a control group in relatively short duration postoperatively. Further studies including a control group and a longer follow-up would be needed to confirm our results. Future work is needed in order to understand how this knowledge, in combination with preoperative EEG, could help the selection of targets and the development of strategies to minimize the impact of surgery on neuropsychological functions.

In conclusion, our quantitative EEG analyses indicate that a preoperative increase in theta band power might be associated with deterioration of visuospatial function following DBS. With further validation, quantitative EEG could serve as a metric for predicting post-surgical neurocognitive changes after STN-DBS.

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Compliance with ethical standards

Conflict of interest Maidinamu Yakufujiang, Yoshinori Higuchi, Kyoko Aoyagi, Tatsuya Yamamoto, Midori Abe, Yoji Okahara, Masaki Izumi, Osamu Nagano, Yoshitaka Yamanaka, Akihiro Shiina, Atsushi Murata, and Yasuo Iwadate declare that they have no conflict of interest. Shigeki Hirano has received research grants from Eli Lilly Japan.

Research involving human participants and/or animals This article does not contain any studies with animals performed by any of the authors.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee (the Ethics Committee of Chiba University Graduate School of Medicine) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Informed consent Informed consent was obtained from all individual participants included in the study.

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