Does Quantitative Electroencephalography Refine Preoperative Cognitive Assessment in Parkinson's Disease Patients Treated with Deep Brain Stimulation? A Follow-Up Study

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Keywords

Quantitative electroencephalography · Deep brain stimulation · Parkinson's disease · Cognitive decline · Neuropsychological testing · Screening

Abstract

Objective: Deep brain stimulation (DBS) in Parkinson's disease (PD) is associated with an increased risk of post-operative cognitive deterioration. Preoperative neuropsychological testing can be affected and limited by the patient's collaboration in advanced disease. The purpose of this study was to determine whether preoperative quantitative electroencephalography (qEEG) may be a useful complementary examination technique during preoperative assessment to predict cognitive changes in PD patients treated with DBS. **Methods:** We compared the cognitive performance of 16 PD patients who underwent bilateral subthalamic nucleus DBS to the performance of 15 PD controls (matched for age, sex, and education) at baseline and at 24 months. Cognitive scores were calculated for all patients across 5 domains. A preoperative 256-channel resting EEG was recorded from each patient. We computed the global relative power spectra. Correlation and linear regression models were used to assess associations of preoperative EEG measures with post-operative cognitive scores. **Results:** Slow waves (relative delta and theta band power) were negatively correlated with

post-operative cognitive performance, while faster waves (alpha 1) were strongly positively correlated with the same scores (the overall cognitive score, attention, and executive function). Linear models revealed an association of delta power with the overall cognitive score ($p = 0.00409$, adjusted $R^2 = 0.6341$). Verbal fluency (VF) showed a significant decline after DBS surgery, which was correlated with qEEG measures. **Conclusions:** To analyse the side effects after DBS in PD patients, the most important parameter is verbal fluency capacity. In addition, correlation with EEG frequency bands might be useful to detect particularly vulnerable patients for cognitive impairment and be supportive in the selection process of patients considered for DBS.

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Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disease characterized by motor and non-motor manifestations [1, 2]. PD has long been considered primarily a motor disease with the cardinal symptoms of tremor at rest, rigidity, akinesia, and postural instability, upon which diagnosis and treatment are based [2–4].

However, the non-motor manifestations of PD have gained increasing recognition [3]. Non-motor manifestations generally constitute the prodromal phase of PD years

Table 1. Values represent the median and interquartile range

	PD patients with DBS	PD patients without DBS	<i>p</i> value
<i>n</i>	16	15	
Age, years	66 (63, 68.5)	64 (63, 68.5)	ns
Gender (female)	5	4	ns
Education	14 (12, 16.5)	14 (12, 17)	ns
MMSE	28 (28, 29.5)	29 (28.5, 30)	ns
Disease duration	8.5 (3.5, 13.5)	6 (4, 9)	ns
LED	709.5 (442.75, 1,560)	653 (477.5, 760)	ns
UPDRS-II	8 (8, 11.25)	8 (5, 10)	ns
UPDRS-III	17 (7.75, 20.25)	13 (10, 19.5)	ns
UPDRS-IV	4 (1.75, 4.75)	2 (1, 4)	ns
Duration of FU, months	24.50 (16.50, 40)	24 (23, 25.5)	ns

DBS, deep brain stimulation; PD, Parkinson's disease; MMSE, Mini-Mental Status Examination; UPDRS-II–IV, Unified Parkinson's Disease Rating Scale (tested in on status); LED, levodopa equivalent dose; FU, follow-up.

before the onset of the motor phase [4–6]. Cognitive impairment is a common non-motor manifestation of PD with a significant impact on the quality of life [7–10]. First-line treatment for PD consists of pharmacological treatment. Potential drawbacks of medical treatment are dyskinesias or disease refractory to pharmacological management. Deep brain stimulation (DBS) is a surgical remedy for medically intractable PD. The 2 main DBS targets for PD are the subthalamic nucleus (STN) and the globus pallidus internus. Although there is no consensus on the optimal target choice [11, 12], there is a broad consensus that dementia is a clear contraindication for DBS, but there is no consensus with regards to mild cognitive impairment. DBS has proven to be an effective treatment for the motor symptoms of PD, but post-operative cognitive decline is recognized as a potential complication, despite thorough preoperative neuropsychological testing [13–17]. Thus, it is of critical importance to identify additional and reliable examination techniques to predict the post-operative cognitive course of patients considered for DBS. Although electroencephalography (EEG) is considered a useful method to predict cognitive decline in PD [18–23], it is not a component of the standard preoperative evaluation for DBS [24]. A background rhythm frequency that is below the median value (i.e., <8.5 Hz) has been found to be associated with a higher incidence over time of cognitive impairment in PD [18–24]. The objective of our study was to determine whether any aspects of the preoperative quantitative EEG correlate with the post-operative cognitive state in PD patients treated with STN-DBS and therefore potentially provide a complementary screening technique to increase selection accuracy of patients considered for DBS.

Patients and Methods

Demographics

Twenty-seven patients were initially included in our study. One male patient was excluded when his DBS system had to be explanted because of a brain abscess. Twenty-six patients underwent baseline neuropsychological testing.

Twenty-six patients had a preoperative EEG. Ten patients were excluded from the final analysis (3 women and 7 men) for artefact contamination (sleepiness/sleep, motion artefacts). Thus, 16 patients (5 women and 11 men) were included in the final analysis. These were matched to 15 PD patients treated conservatively (i.e., without DBS) for age, gender, education, Mini-Mental Status Examination (MMSE), disease duration, levodopa equivalent dose (LED), and Unified Parkinson's Disease Rating Scale (UPDRS) II–IV (Table 1). The control group (patients from our clinic) did not differ for age, gender, education, MMSE, LED, UPDRS, disease duration, and follow-up.

DBS Surgery

All patients with PD who undergo evaluation for DBS by our DBS team are eligible for participation in the study. Whether or not DBS is indicated for each patient is determined by the team based on clinical criteria alone, and this determination does not form a part of the study. Patients are selected for DBS treatment based on the established criteria modified [25] after Coleman and Ostrem [26].

Inclusion Criteria for the DBS Group

1. Idiopathic PD according to the UK Brain Bank Criteria
2. Motor impairment despite state-of-the-art therapy
3. Robust improvement on L-dopa (>30% in the UPDRS-III score except tremor)
4. Awareness of risks and realistic expectations of surgical outcome by the patient

Exclusion Criteria for the DBS

1. Comorbidity with any other neurological or psychiatric disease
2. Mental incompetence to provide informed consent to participate in the study (MMSE <24)

3. Contraindications for DBS seen in MRI scan

Stimulating electrodes were stereotactically implanted into the STN. Patients were awake for the deep brain procedure. In the second part of the procedure performed under general anaesthesia, the permanent electrodes were connected to a subcutaneously implanted impulse generator, which was usually placed superficial to the pectoralis fascia just inferior to the clavicle.

Neuropsychological Assessment

The neuropsychological assessment has been described in detail in a previous publication [24]. Briefly, the patients completed a comprehensive battery of neuropsychological tests. They were tested preoperatively on medications and post-operatively on medications with the stimulation turned on. The median disease duration was 8 years for the DBS patients and 6 years for the control group, at which time point the precognitive assessments were performed.

The tests were assigned to 5 cognitive domains: attention and information processing speed (Stroop Colour-Word Test, Trail Making, and Digit Span), executive functions (Stroop Colour-Word, Trail Making Test, and Wisconsin Card Sorting), fluency (semantic verbal fluency [VF] test, phonemic VF, and 5-point test), long-term memory (wordlist long-delayed recall, verbal learning: discrimination), working memory (Corsi blocks from the German version of the revised Wechsler Memory Scale, divided attention), and visuospatial functions (block design test, Rey Osterrieth Complex Figure Copy). Mood assessment was based on the UPDRS I, UPDRS II, and UPDRS IV for the analysis of neuropsychological measures, and z-scores (corrected for age, sex, and education) of each variable were averaged per each domain to obtain domain scores. Greater values represent better performance. The median follow-up range (at which time point the assessment occurred) was for both groups 24 months (Fig. 1).

EEG Data

For each patient in the DBS group, a 256-channel EEG of circa 15 min length was acquired at rest (Netstation 300; EGI Inc., Eugene, OR, USA, sampling rate 1,000 Hz). Subjects were instructed to stay awake in a relaxed state. A semi-automated process was applied, in which each EEG recording was first visually inspected for sleep/sleepiness and EMG artefacts. The preselected segments were filtered, and artefacts due to eye movement, muscle contraction, drops in vigilance (sleep/sleepiness), electrodes, and ECG were removed further with MATLAB-based TAPEEG [27]. In the post-processing stage, 12 epochs of 4 s each were extracted from the cleaned EEG segments and spectral powers were calculated. To quantify EEG, spectral analysis is used to decompose a complex EEG signal into its component frequencies through Fourier transformation. Spectral power can be assessed globally (over the whole scalp) and over definite scalp regions. Using a high-density electrode system enables us to aggregate nearby signals thus potentially reducing noise. We obtained the spectral powers for the 10 regions of interest and also assessed spectral power globally. Thus, we analysed features in 6 frequency ranges and 11 locations, obtaining a total of 66 spectral features.

Relative power, which assesses the relative contribution of a particular frequency to the EEG signals, is calculated by dividing the absolute power in a given frequency band by the total power. We calculated median relative spectral powers in the following frequency ranges (Hz): 1–4 (delta), 4–8 (theta), 8–10 (alpha 1), 10–13 (alpha 2), 8–13 (alpha), and 13–30 (beta).

Fig. 1. Z-scores represent age-, sex-, and education-corrected and combined test scores (averaged per each domain to obtain domain scores). VF (a), executive function (b), and attention (c) of patients with PD treated with STN-DBS (DBS, orange line) versus treated conservatively (non-DBS, blue line) over 2 years. The performance in VF tests (a) in the DBS group was significantly reduced after 2 years ($p < 0.05$) as compared to the control group. No other interaction between time $\times$ group was statistically significant. DBS, deep brain stimulation; PD, Parkinson's disease; STN, subthalamic nucleus; VF, verbal fluency.

Statistics

Continuous variables were visually inspected for normality of distribution and statistically tested with the Kolmogorov-Smirnov test. In accordance with the results, parametric or nonparametric analyses were performed. All p values < 0.05 were considered statistically significant. MANOVA was used for a multivariate comparison for all selected difference scores between intervention conditions (DBS, non-DBS).

Table 2. Median baseline (BL) scores of the neuropsychological evaluation, cognitive scores after intervention, and change scores (CS), which indicate change between BL and tests after intervention

	BL (median, IQR)		FU (median, IQR)		CS	
	PD-DBS patients	PD patients non-DBS	PD-DBS patients	PD patients non-DBS	PD-DBS patients	PD patients non-DBS
Overall cognitive score	-0.28 (-0.55, -0.12)	-0.05 (-0.33, -0.10)	-0.41 (-1.00, -0.05)	-0.35 (-0.47, 0.03)	-0.18 (-0.50, 0.21)	-0.23 (-0.34, 0.04)
Attention	-0.55 (-0.85, -0.21)	-0.34 (-0.87, 0.03)	-1.11 (-1.92, -0.65)	-0.74 (-1.19, -0.49)	-0.39 (-0.77, -0.08)	-0.35 (-0.94, 0.08)
Executive function	-0.51 (-0.96, 0.02)	0.30 (0.12, 0.68)	-0.76 (-1.16, -0.33)	-0.12 (-0.41, 0.44)	-0.26 (-0.80, 0.14)	-0.10 (-0.77, 0.09)
Memory	-0.19 (-0.47, 0.05)	-0.43 (-0.91, 0.32)	0.03 (-0.38, 0.49)	-0.71 (-1.16, 0.06)	0.06 (-0.44, 0.77)	-0.19 (-0.41, 0.24)
Fluency	-0.20 (-0.48, 0.44)	-0.07 (-0.32, 1.13)	-0.68 (-1.13, -0.02)	0.11 (-0.40, 0.74)	-0.42 (-1.47, 0.02)	0.14 (-0.29, 0.39)
Visuoconstruction	-0.99 (-1.53, 0.67)	0.43 (0.10, 1.29)	0.44 (-0.09, 1.00)	0.63 (0.25, 0.77)	0.02 (-0.81, 0.13)	0.02 (-0.62, 0.42)

Positive CS denotes an enhancement, and negative CS denotes a decline. *p* values were not adjusted for multiple testing. IQR, interquartile range; DBS, deep brain stimulation; PD, Parkinson's disease; FU, follow-up.

Correlation analysis was carried out for cognitive domains at the post-operative stage with the baseline EEG. Correlation coefficients between EEG and domain scores were adjusted for multiple testing by false discovery rate correction.

The associations between EEG measures and cognition were subsequently analysed with linear regression models. Potential confounding factors including age, sex, years of education, mental status MMSE, motor manifestations (UPDRS III), disease duration, and LED were used as additional predictors to control for their influence. The following baseline EEG variables were considered as predictors: global relative median power in the delta, theta, alpha 1, alpha 2, and beta ranges. Stepwise backwards elimination was used to consecutively eliminate non-predictive variables. Statistical analyses were performed with R (R core, 2015) [28].

Results

The 2 groups did not differ in several sample characteristics or any variable regarding disease-related motor impairment at baseline (Table 1). At follow-up, scores on the UPDRS-II and UPDRS-III subscales did not significantly differ between the 2 PD groups.

In both groups (DBS and control groups), there was worsening of the overall cognitive score with a trend towards significance over time (p time = 0.06) (Table 2). Attention declined significantly over time in both groups (p = 0.005) without significant group differences. While the VF at baseline was the same in both groups, it significantly worsened on FU in the DBS group (p group $\times$ time < 0.05). A decline over time was also seen in the executive function in both groups, with a stronger decline in the DBS group.

Looking at the baseline EEG and post-operative cognitive domains, we found strong (negative) correlations between the global relative power in the delta band at baseline with overall cognition (r = -0.74, p < 0.01), attention (r = -0.52, p < 0.05), and executive function (r = -0.73, p < 0.01) domains post-DBS (Fig. 2a-c). Global power in the theta band at baseline was correlated with a post-operative decline in fluency (r = -0.50, p < 0.05). Global relative power in the alpha band had a strong positive correlation with executive function (r = 0.82, p < 0.01) and overall cognition (r = 0.79, p < 0.01) (Fig. 3a-c). In view of these findings, we wanted to further characterize the association between the EEG measures and cognition with the aid of linear models. By using a stepwise elimination procedure, the following variables were excluded from the model explaining post-operative overall cognition: age, gender, years of education, MMSE, motor symptoms (UPDRS III), disease duration, and LED. Delta power was significantly associated with the overall cog-

Fig. 2. a–c Spearman rank correlation coefficients (r) between BL relative delta power (1–4 Hz) and FU cognition values in $N = 16$ patients with DBS surgery in STN. p values are adjusted by FDR correction. DBS, deep brain stimulation; STN, subthalamic nucleus; FDR, false discovery rate; BL, baseline; FU, follow-up.

nitive score ($p = 0.00409$, adjusted $R^2 = 0.6341$), which was not influenced by UPDRS III ($p = 0.36817$) and age ($p = 0.06401$). Global powers in the alpha 1 band (8–10 Hz) were associated with executive function ($p = 0.000134$) with a high adjusted $R^2 = 0.8037$ but confounded by MMSE scores ($p = 0.000214$). Alpha 1 power was associated with the attention domain ($p = 0.0322$, $R^2 = 0.4538$).

Fig. 3. a–c Spearman rank correlation coefficients (r) between BL relative alpha power (8–10 Hz) and FU cognition values in $N = 16$ patients with DBS surgery in STN. p values are adjusted by FDR correction. DBS, deep brain stimulation; STN, subthalamic nucleus; FDR, false discovery rate; BL, baseline; FU, follow-up.

Discussion

In the present study, 2 groups of PD patients were compared regarding the prediction of EEG parameters on cognitive outcome after STN-DBS. The 2 groups were matched concerning age, gender, levodopa doses, disease duration, and motor impairment at baseline.

Preoperative neuropsychological screening is still considered the gold standard for evaluating the cognitive status of PD patients and to assess eligibility for DBS surgery. Despite thorough preoperative neuropsychological screening, post-operative cognitive decline is still a major concern after DBS surgery [13–17]. One reason for this might be that neuropsychological testing may miss subtle neuropsychological deficits and insufficient cooperation of the patient in advanced PD may contribute to gaps in testing [20, 29]. In contrast to neuropsychological testing, EEG requires minimal patient cooperation, can be rapidly performed, displays no learning effects, and is thus free of any potential test-retest bias [20]. More importantly, preclinical cortical and subcortical structural changes in PD not captured by routine neuropsychological testing may be detected by electrophysiological investigation and may account for the slowing of background EEG frequency [20].

Our study was based on extensive neuropsychological testing and high-resolution EEG data spanning global power in each of 6 frequency bands. In our study, the slowing of EEG in the delta power range significantly predicted overall worsening of cognition. We also found statistically significant correlations between delta power and attention as well as executive function post-DBS. Alpha 1 power was associated with the attention domain. Our results are in line with previous studies reporting a correlation of EEG slowing with cognitive impairment in PD [23, 24, 27, 30–32]. Preoperative (but standard) EEG was used for the assessment of the post-operative cognitive course after DBS, only once, to the best of our knowledge [24].

Markser et al. [24] reported cognitive deteriorations in 6 out of 30 patients with a lower median EEG frequency of 7.5 Hz (range 6.5–8.5), 4–12 months after STN-DBS. The remaining 24 patients who were post-operatively cognitively stable showed a higher preoperative median EEG frequency (9 Hz, range 7.5–11.5). The authors postulated that preoperative EEG may add useful information to the neuropsychological assessment to predict cognitive decline after electrode placement [24]. Multi-domain cognitive deterioration is a known complication of DBS, but outcomes are inconsistent across the reported studies, making it difficult to predict post-operative cognitive decline accurately [13–17]. The mechanisms as how DBS leads to cognitive deterioration are not fully understood but appear to be multifactorial [13–17]. Contributing factors for post-operative cognitive decline may relate to the natural progressive neurodegenerative course of PD, chronic dopaminergic therapy, current spread from the dorsolateral motor STN section into the associative cognitive central portion of the nucleus [33], and

post-operative medication reduction as well as surgery as itself [13, 16, 34, 35]. Variability in electrode trajectories and targets within the STN, as well as in stimulation parameters, might partially explain the inconsistency [16, 17, 33, 36]. Whether VF decline is a direct result of DBS is under debate [32, 37, 38]. Several mechanisms may account for VF decline such as medication dose, disease duration, and age. Parsons et al. [39] suggested that the important dopaminergic medication reduction that follows STN-DBS may account for depression and apathy, which in turn may lead to a decline in VF. Leimbach et al. [13] suggested a contrary hypothesis that VF decline may be the direct result of surgery and not an STN-DBS effect. Concerning attention, there was a significant decline over time in both groups, so this decline cannot be interpreted as a result of DBS surgery as such. The decline in VF was the only parameter which divided the DBS and non-DBS group over the follow-up period of 48 months and it is therefore exclusively attributable to the DBS surgery group. Moderate declines in VF are the most frequently observed neuropsychological declines in patients treated with STN-DBS [14, 17, 32].

In our study, the EEG could not predict specific cognitive changes secondary to DBS, specifically, VF decline. In our view, the purpose of preoperative EEG is not the prediction of specific cognitive changes induced by DBS but rather the preoperative assessment for potential vulnerability of PD patients for long-term cognitive decline. Standard neuropsychological testing can attest a normal cognitive state; however, the adjunctive preoperative EEG may show that the very same patient has slowing of background frequency, potentially a sign of long-term cognitive decline. The risk for cognitive impairment in PD within this context is 2-fold, that is, through natural disease course and DBS. Accurate patient selection for DBS becomes more stringent. Cognitive dysfunction has also been reported as a complication of any type of surgery (in the brain or elsewhere), especially in the elderly; surgery and/or general anaesthesia might lead to the worsening of latent cognitive deficits that were not recognized preoperatively [35].

As DBS has the potential to lead to cognitive decline, tools for proper preoperative identification of patients particularly vulnerable for cognitive deterioration and in whom DBS might be inadvisable are of critical importance. The combination of a comprehensive neuropsychological assessment with EEG could improve the accuracy of preoperative screening [24].

A further important advantage of preoperative EEG is that it allows parallel assessment of increased but asymp-

tomatic cerebral excitability. In a large cohort study, it was found that PD patients had a 1.7-fold increased risk of epileptic seizures compared to subjects without PD [40].

It must be pointed out however that preoperative EEG for the assessment of cognitive function requires particular attention to the state of wakefulness of the patient during the entire EEG recording. Sleep and sleepiness will cause background frequency slowing indistinguishable from that seen in cognitive impairment [41].

The strength of our study was that it was a matched, case-control study that included a comprehensive neuropsychological assessment and the semi-automated processing of high-resolution EEG, a non-invasive, universally available technique that can be applied in routine clinical practice. A further strength was that particular attention was paid to the highest quality EEG recordings by eliminating all segments affected by sleep/sleepiness. The limitations of our study were the relatively small sample size, the short follow-up period, and the absence of a wait list control group.

Our study was designed as a matched case-control study; however, we minimized the limitations of the study design by matching the control group with the DBS group on multiple parameters. The control group did not differ in age, gender, education, MMSE, LED, UPDRS, disease duration, and follow-up.

Conclusion

Screening for impaired cognitive function by using EEG could be of value for the early, preclinical detection of potential cognitive deficits in patients under consideration for DBS. Adding electroencephalographic data to the standard neuropsychological preoperative assessment may enable more accurate detection of particularly vulnerable patients for cognitive impairment with DBS and allow parallel assessment for increased, asymptomatic cerebral excitability. Further studies on the potential usefulness of EEG for predicting post-operative cognitive decline should employ larger prospective cohorts with longer follow-up.

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Statement of Ethics

The Joint Research Ethics Committee of the Cantons of Basel City and Basel Country (Ethik Kommission beider Basel) approved this study (EKBB ref. No. 135/11). All participants were fully informed of the nature of the study and gave their written informed consent.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Christian Saleh: conception of the study, analysed the data, wrote the first draft, revised critically the final draft, and gave final approval for publication. Antonia Meyer analysed the data, wrote the draft, performed statistics, revised critically the final draft, and gave final approval for publication. Menorca Chaturvedi analysed the data, wrote the draft, revised critically the final draft, and gave final approval for publication. Selina Beltrani analysed the data, wrote the draft, revised critically the final draft, and gave final approval for publication. Ute Gschwandtner: conception of the study, analysed the data, wrote the draft, revised critically the final draft, and gave final approval for publication. Peter Fuhr: conception of the study, analysed the data, wrote the draft, revised critically the final draft, and gave final approval for publication.

Data Availability Statement

All data generated/analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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