Right on track: Towards improving DBS patient selection and care

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CHAPTER 7

Quantitative EEG reflects non-dopaminergic disease severity in Parkinson's disease

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Abstract

Objective

In Parkinson's Disease (PD), measures of non-dopaminergic systems involvement may reflect disease severity and therefore contribute to patient-selection for Deep Brain Stimulation (DBS). There is currently no determinant for non-dopaminergic disease severity. In this exploratory study, we investigated whether quantitative EEG reflects non-dopaminergic disease severity in PD.

Methods

Sixty-three consecutive PD patients screened for DBS were included (mean age 62.4 ± 7.2 years, 32% females). Relative spectral powers and the Phase-Lag-Index (PLI) reflecting functional connectivity were analysed on routine EEGs. Non-dopaminergic disease severity was quantified using the SENS-PD score and its subdomains; motor-severity was quantified using the MDS-UPDRS III.

Results

The SENS-PD composite score correlated with a spectral ratio ((δ + θ) /(α1 + α2 + β) powers) (global spectral ratio Pearson's r=0.4, 95% Confidence Interval (95%CI) 0.1 to 0.6), and PLI in the α2 band (10-13 Hz) (r=-0.3, 95%CI -0.5 to -0.1). These correlations seem driven by the subdomains cognition and psychotic symptoms. MDS-UPDRS III was not significantly correlated with EEG parameters.

Conclusions

EEG slowing and reduced functional connectivity in the α2 band were associated with non-dopaminergic disease severity in PD.

Significance

The described EEG parameters may have complementary utility as determinants of non-dopaminergic involvement in PD.

Introduction

Parkinson's Disease (PD) is a multisystem neurodegenerative disorder, caused by progressive degeneration of both dopaminergic and non-dopaminergic neurons.[1] Dopaminergic neurons account primarily for the characteristic motor symptoms of PD, whilst non-dopaminergic neurons account for non-motor symptoms such as impaired cognition, psychiatric manifestations or sleep disturbances. PD is typically treated with oral dopaminergic medication, which alleviates motor symptoms. However, medication-related motor complications occur in the majority of patients within 10 years of disease.[2] Patients refractory to oral treatment may be eligible for Deep Brain Stimulation (DBS), which ameliorates motor complications and improves quality of life.[3] DBS is particularly effective in patients perceiving substantial motor improvement of upon dopaminergic treatment.[4] However, non-dopaminergic symptoms such as cognitive impairment,[5] depression,[6] speech intelligibility [7] and axial symptoms [8] may deteriorate post-DBS. This indicates the need for accurate assessment of non-dopaminergic disease severity during the preoperative selection process.

Clinical, neuropsychological and psychiatric evaluations are used to rule out severe cognitive decline or psychiatric comorbidity. However, several factors including intelligence, education, and personality limit the interpretability of clinimetric assessments.[9] Moreover, questionnaires and performance tasks are susceptible to misinterpretation, social desirability bias, or fatigue.[10] Therefore, there is a need for complementary measures reflecting disease severity in PD to aid the identification of DBS candidates.

Quantitative Electroencephalography (qEEG) is an inexpensive and widely available tool which measures brain activity directly. Previous studies applied qEEG to examine clinical domains in PD, such as cognition,[11,12] response to treatment [13] or motor impairment.[13,14] Global oscillatory slowing of the EEG spectrogram is a highly suitable biomarker for cognitive impairment in PD.[11] Recent advances in neurophysiology have provided more complex markers such as connectivity parameters and graph theory estimations, which quantify brain network disorganization. The Phase-Lag Index (PLI), which reflects functional connectivity, was suggested as a potential biomarker of PD dementia.[15] To our knowledge the relation of qEEG parameters to measures of non-dopaminergic severity in PD has not been investigated so far. We aimed to investigate whether qEEG correlates with clinical measures of disease severity, in order to ultimately provide neurophysiological determinants of disease severity.

Methods

Study participants

All consecutive PD patients who were referred for preoperative screening to the DBS centre of Leiden University Medical Center (LUMC) and Haga Teaching Hospital between September 2015 and July 2017 were included in the study. All patients fulfilled the Movement Disorders Society PD criteria for clinically established PD.[16] Written informed consent was obtained from all patients. A formal ethical evaluation of this study was waived by the local medical ethics committee.

Outcome measures

Motor function was assessed with the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part III (range 0-132),[17] whereas the SEverity of Non-dopaminergic Symptoms in Parkinson's Disease (SENS-PD) scale quantified non-dopaminergic disease severity (range 0-54).[18] The SENS-PD scale is a composite score comprising three items with four response options (range 0-3) from each of the following six predominantly non-dopaminergic domains: postural instability and gait difficulty (PIGD), psychotic symptoms, excessive daytime sleepiness (EDS), autonomic dysfunction, cognitive impairment and depressive symptoms.[18] These six domains represent a coherent complex of symptoms that is already present in early disease stages and increases in severity with age and advancing disease. The SENS-PD scale is a recently developed, short, reliable and valid scale that includes symptoms that do not improve with dopaminergic medication and may therefore more accurately reflect severity and progression of the underlying disease than currently used dopamine-sensitive measures. Higher scores on both the MDS-UPDRS III and SENS-PD scale reflect more severe impairment.

Patients were subdivided a posteriori into three groups of comparable size, according to the tertile in which their SENS-PD score fell: low disease severity (range 4-10), intermediate severity (range 11-14) and high severity (range 15-24).

EEG recording and pre-processing

EEGs were recorded with patients lying supine, with eyes closed, during a state of relaxed wakefulness. Light was kept at moderate intensity. Ag/AgCl EEG electrodes were placed on the scalp using 21 standard 10-20 EEG electrode positions. Additional ECG and horizontal eye movement leads were added for identification of artifacts. Data were acquired online using a Nihon Kohden EEG-1200 system, with a 500 Hz sampling rate, a 16-bit analog-to-digital converter, and band-filtered between 0.16 and 70 Hz. An EEG technician monitored signal quality throughout the entire recording; patients were alerted by acoustic stimuli

upon drowsiness. All patients used dopaminergic medication according to their individual schedule.

EEG analysis

EEG data were re-referenced towards a source derivation which approaches the surface Laplacian derivation.[19] Five consecutive, non-overlapping 4096-point epochs lasting 8.192 seconds were selected for further analysis after an artifact-free signal was visually confirmed. The individual epochs were offline converted to American Standard Code for Information Interchange (ASCII) format and further analysed using Brainwave software (BrainWave version 0.9.152.4.1, C.J. Stam; available at http://home.kpn.nl/stam7883/brainwave.html). Recordings with less than five artifact-free epochs were excluded from analysis. Analyses were performed in signal space to allow for direct analysis of the raw EEG data in Brainwave software, which is easily reproducible for most clinicians and may increase the utility of our findings.

Spectral analysis was performed off-line by processing each epoch with a Fast Fourier Transform (FFT) and averaged to produce a power spectrum for each individual electrode. The frequency bands were defined as δ (0.5 – 4.0 Hz), θ (4.0 – 8.0 Hz), α1 (8.0 – 10.0 Hz), α2 (10.0 – 13.0 Hz) and β (13.0 – 30.0 Hz). γ band power was not analysed due to frequent contamination with muscle artifacts. Relative bandpower was calculated by dividing the absolute bandpower of each frequency band by the total absolute bandpower from the FFT average per channel. Regional band powers were defined as: frontal for F3, F4, F7, F8 and Fz, temporal for T3, T4, T5 and T6, parietal for P3, P4 and Pz, central for C3, C4 and Cz, and occipital for O1 and O2. Global bandpower was defined as the average of all regional band powers. A spectral ratio was calculated by dividing the sum of the relative power in the δ and θ bands by the sum of the relative power in the α and β bands. These spectral bands were selected a priori to incorporate as much of the EEG spectrum as possible, without contaminating the results with possible artefacts that may be present in the fast frequency bands.

Functional connectivity was assessed by calculating the PLI in each frequency band. The PLI quantifies phase coupling (range 0-1) whilst being insensitive to common sources and volume conduction. PLI=0 indicates either no phase synchronization or equal in both leading and lagging throughout the epoch, PLI=1 indicates perfect phase-locking.[20]

Statistical analysis

Baseline demographic, clinical, and test variables were not-normally distributed and were thus compared between the three groups with Kruskal-Wallis H tests for continuous variables and Pearson's $\chi 2$ tests for dichotomous variables. Included and excluded patients

were compared using Mann-Whitney U tests. QEEG parameters were compared across SENS-PD tertiles using Kruskal-Wallis H tests; Mann-Whitney U tests compared the high- and low-disease severity tertiles.

The association between the SENS-PD composite score, SENS-PD subdomains, MDS-UPDRS III score and qEEG parameters was assessed by calculating partial Pearson's r correlation coefficients, with an additional correction for age and usage of psychoactive medication, which may influence EEG parameters. Bias-corrected and accelerated bootstrapping was performed with 7000 samples to normalize the data; further increasing the amount of samples did not improve statistical accuracy.

Given the exploratory nature of our study, to avoid type II errors, no further correction for multiple testing was applied. Missing values were imputed using multiple imputation with five iterations, if no more than 15% of the data was missing.

All analyses were performed using IBM Statistical Package for the Social Sciences 23 Software (SPSS Inc., Chicago, Illinois, USA). Significance was set at the 0.05 level. Graphical visualization of results was performed in either MATLAB R2016A (The MathWorks Inc., Natick, Massachusetts, USA) or GraphPad Prism 7.02 (GraphPad Software Inc., La Jolla, California, USA).

Results

Patient characteristics

Eighty patients underwent DBS screening during the study period. Seventeen patients were excluded due to gross artifacts during EEG recordings (low disease severity: n=8, intermediate severity: n=3, high disease severity: n=6); analysis was thus performed on 63 patients (32% female). There were no significant differences in demographic and clinical variables between included and excluded patients. Mean (SD) age was 62.4 (7.2) years, and disease duration 11.9 (6.3) years (table 7.1). There were no significant differences in age, sex, disease duration, psychoactive drug usage and MDS-UPDRS III score between the three SENS-PD tertiles. By design, both the SENS-PD score and all six subdomains differed significantly between tertiles, with higher scores for the high-disease-severity group.

Spectral analyses

Slower EEG frequency bandpowers (i.e. δ and θ) were higher in the high-disease-severity group, whereas faster frequency bandpowers (i.e. $\alpha 1$, $\alpha 2$ and β) were higher in the low-disease-severity group (figure 7.1).

Table 7.1 Demographic and clinical characteristics

	Overall	Low SENS-PD	Intermediate SENS-PD	High SENS-PD	P
N	63	17	25	21	
EEG data, seconds	516.1	139.3	204.8	172.0	
Age, years	62.4 (7.2)	61.6 (6.4)	62.2 (7.5)	63.3 (7.5)	0.825
Female sex	20 (32)	6 (35)	8 (32)	6 (29.0)	0.906
Disease duration, years	11.9 (6.3)	10.6 (3.0)	12.0 (6.7)	12.9 (7.6)	0.718
Use of psychoactive drugs	15 (31)	3 (18)	5 (20)	7 (33)	0.448
MDS-UPDRS III total score	24.0 (10.1)	20.7 (9.2)	24.3 (11.1)	26.4 (9.1)	0.167
SENS-PD total score	13.1 (4.9)	7.6 (1.8)	12.0 (0.8)	18.8 (2.9)	<0.001[a]
PIGD subscore	1.2 (1.0)	0.7 (0.8)	1.0 (1.0)	1.8 (0.8)	0.001[b, c]
EDS subscore	2.7 (1.8)	1.8 (1.3)	2.1 (1.5)	4.1 (1.6)	<0.001[b, c]
Depression subscore	2.4 (2.0)	1.1 (1.6)	2.1 (1.7)	3.6 (2.1)	0.001[b, c]
Autonomic dysfunction subscore	2.1 (1.2)	1.4 (1.1)	2.0 (1.0)	2.8 (1.2)	0.002[c]
Psychotic symptoms subscore	1.0 (0.9)	0.5 (0.5)	0.9 (0.7)	1.5 (1.1)	<0.001[b, c]
Cognition subscore	4.0 (1.6)	3.0 (1.6)	4.0 (1.2)	4.8 (1.6)	0.002[c]

Results are expressed as mean (SD) for continuous variables, n (%) for categorical variables.
[a] Sig. difference between all three groups. [b] sig. difference between intermediate and high tertiles. [c] sig. difference between low and high tertiles
PIGD: postural instability and gait difficulty; EDS: excessive daytime sleepiness

Mean spectral ratios (supplementary table 7.1) differed significantly between the high and low tertiles, both globally and over the frontal, central, parietal and occipital regions. The high-disease-severity group demonstrated a higher spectral ratio, indicating a greater proportion of slow EEG power.

The SENS-PD composite score showed a significant positive correlation with the spectral ratio: a higher ratio, reflecting a greater proportion of slow EEG power, correlated with more severe non-dopaminergic impairment, across all brain regions. The subdomains cognition and psychotic symptoms showed significant correlations for all regions, whilst the subdomains PIGD and depression showed a non-significant positive trend. The subdomains EDS, autonomic dysfunction and the MDS-UPDRS III score did not correlate with EEG parameters (figure 7.2).

Functional connectivity

Global PLI in the α2 band was significantly different between the three tertiles, while differences in the other frequency bands were non-significant (supplementary table 7.2). Regional mean α2 PLI values (supplementary table 7.3) differed significantly between the tertile groups over the frontal, central, temporal and occipital regions. Patients in the high-disease-severity group had a lower connectivity density, i.e. number of connections per threshold PLI value, than patients in the low-disease-severity group (figure 7.3), indicating that higher disease severity was associated with lower functional connectivity.

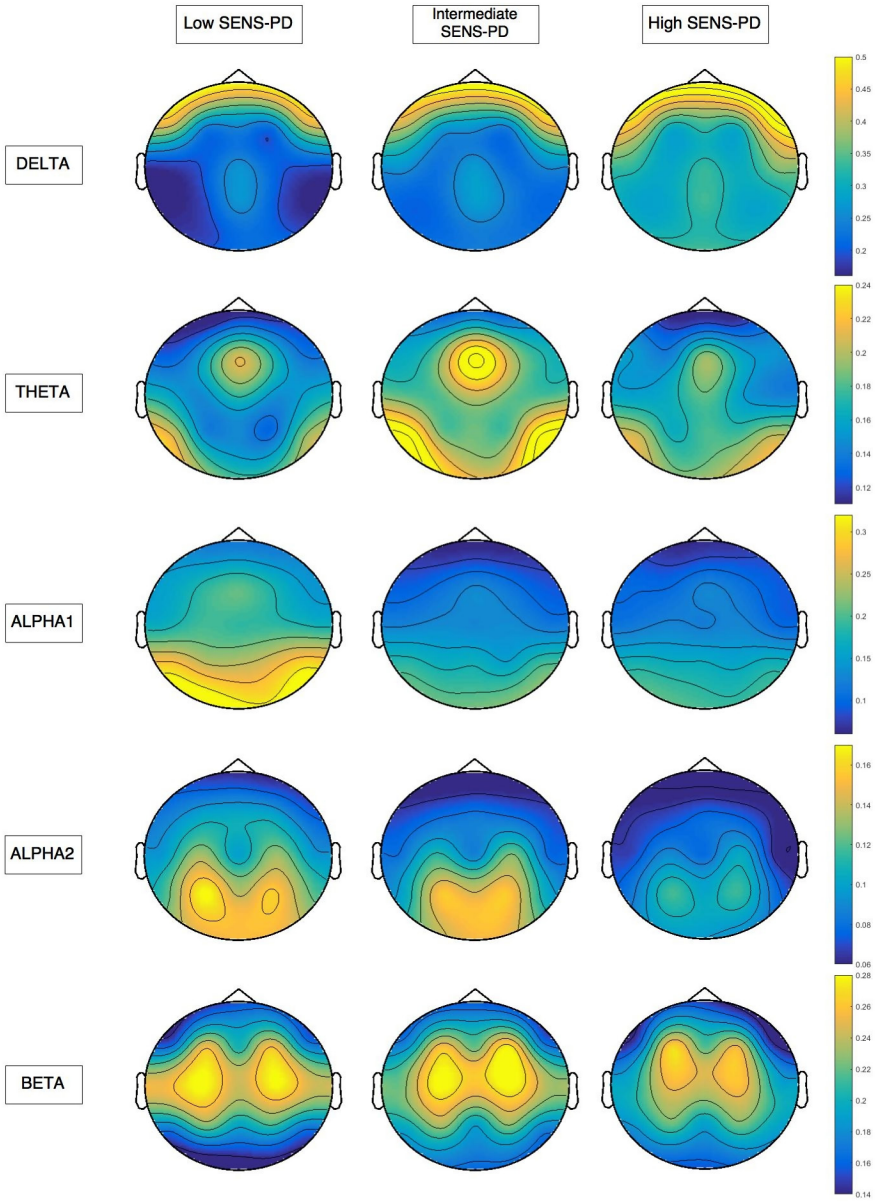

Figure 7.1. Distribution of the mean spectral powers per tertile of disease severity
The high SENS-PD group demonstrated higher power in the slow EEG frequency bands (i.e. δ and θ); the low SENS-PD group demonstrated higher power in the faster EEG frequency bands (i.e. α1, α2 and β), indicating a global slowing of EEG frequency with increasing disease severity (yellow: high power, blue: low power).

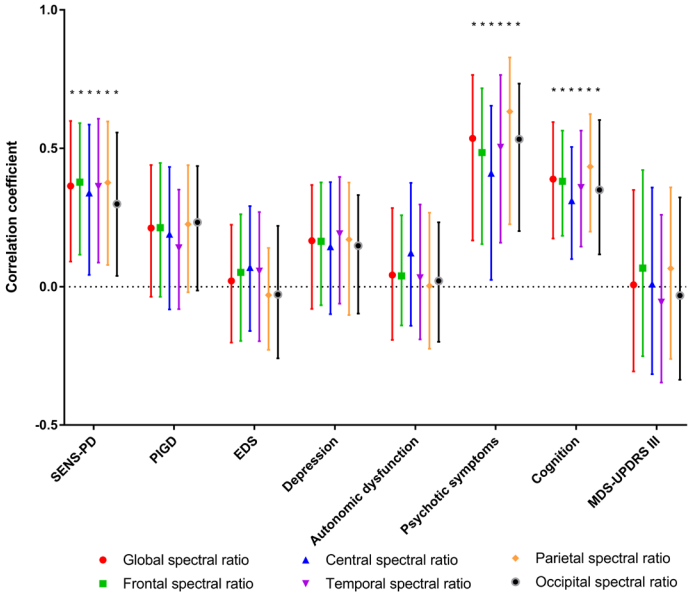

Figure 7.2. Correlation of slow-over-fast spectral ratio and disease severity
Asterisks indicate significant correlations. A spectral ratio of slow-over-fast EEG power correlated significantly with the SENS-PD composite score (i.e. more slow EEG power correlated with increased non-dopaminergic disease severity). The subdomains psychotic symptoms and cognition correlated significantly with the spectral ratio, whilst a trend could be observed for the subdomains PIGD and depression. Error bars reflect 95% confidence intervals.

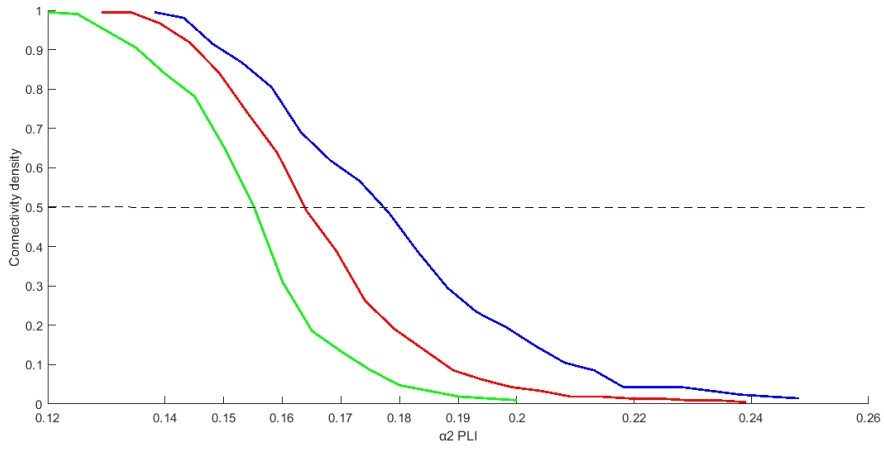

Figure 7.3A. Connectivity density per tertile of non-dopaminergic disease severity (SENS-PD)
Blue: low SENS-PD group, red: intermediate SENS-PD group, green: high SENS-PD group. The high SENS-PD group demonstrated lower α2 PLI density than the low SENS-PD group, indicating a reduction of functional connectivity with increasing disease severity. Network maps of the mean PLI at three thresholds, i.e. PLI=0.13, 0.15 and 0.17 are shown in figure 3B.

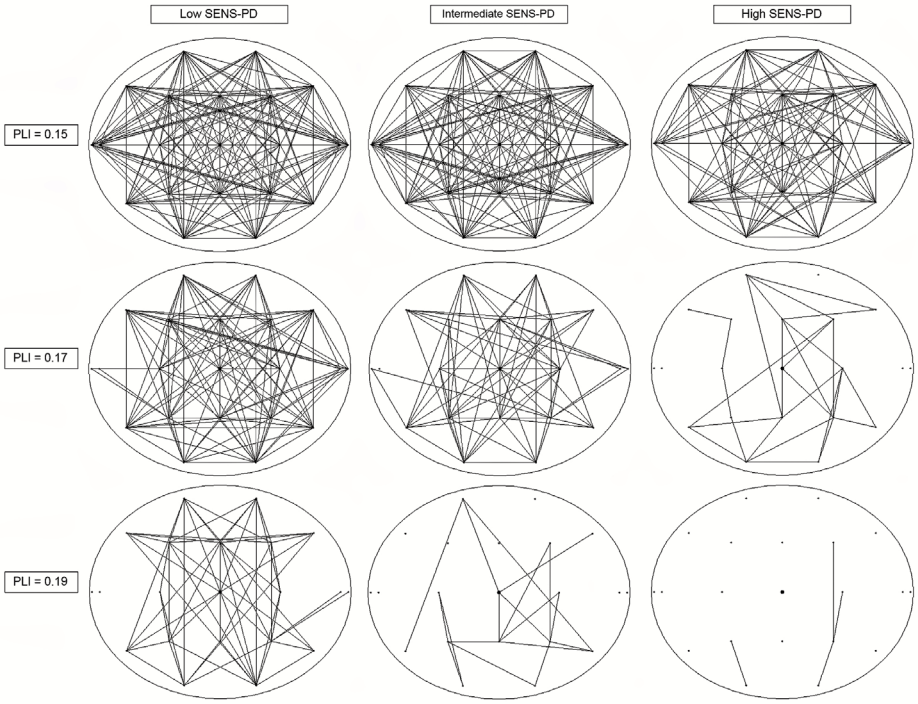

Figure 7.3B. Average network maps of the mean PLI in the α2 band per tertile of disease severity
The α2 PLI network maps are plotted at three thresholds: PLI =0.15, 0.17 and 0.19. A line indicates a level of functional connectivity of at least the threshold-value. With higher SENS-PD scores, the threshold for functional connectivity is lowered, indicating a greater degree of cortical desynchronization with increased disease severity.

Global, frontal, central, parietal and occipital PLI in the α2 band was significantly negatively associated with the SENS-PD composite score and with the cognitive subdomain (supplementary figures 7.1 and 7.2). The subdomain 'psychotic symptoms' showed a significant negative correlation over the central electrodes and a negative trend over all brain regions. In all instances, reduced functional connectivity correlated with higher disease severity.

Discussion

Several qEEG parameters were found to have potential as neurophysiological determinants of advanced non-dopaminergic disease severity in PD. As high non-dopaminergic disease severity is a relative contra-indication for DBS, qEEG analysis may ultimately complement clinimetric evaluations to optimize the screening process of DBS candidates.

Slower EEG oscillatory activity was associated with more advanced non-dopaminergic disease severity measured by the SENS-PD score and, in particular, with the subdomains cognition and psychotic symptoms, with a trend towards a correlation with PIGD and depressive symptoms. Conversely, the subdomains EDS and autonomic dysfunction did not show a clear pattern of correlation. Motor impairment did not significantly correlate with spectral parameters.

Previous literature confirms the association between cortical slowing and cognitive impairment in PD.[11] The consistent EEG slowing both on a global level and across all the different brain areas indicates diffuse dysfunction. It has been previously suggested that diffuse cortical slowing in PD reflects a degeneration of a non-dopaminergic system with ascending cortical projections,[21] which seems compatible with the observed correlation between clinical measures of non-dopaminergic disease severity and EEG slowing.

Cortical slowing has been associated with severity of psychiatric symptoms also in other conditions. In schizophrenic patients, auditory hallucinations were associated with task-related θ slowing [22] and in cases with a delirium, visual hallucinations were associated with θ-δ slowing.[23] Although results of these studies based on other diseases may not be directly comparable with PD, we speculate that these findings suggest a more general cortical desynchronization, rather than network alterations that are specific to PD.

Reduced functional connectivity in the α2 band significantly correlated with higher non-dopaminergic disease severity, particularly with cognition, with a similar trend for the subdomains psychotic symptoms, depression, PIGD and EDS. Motor impairment did not correlate with functional connectivity. Only one EEG-study previously investigated PLI in PD, reporting reduced α1 PLI values in demented PD patients relative to cognitively normal PD patients. α1 PLI likewise correlated with the MMSE scale.[15] Reduced α1 PLI values were also found to correlate with increased severity in Alzheimer's Disease (AD).[24] Our results indicate a non-significant trend for α1 PLI, whereas we found α2 PLI to be significantly reduced. This discrepancy can be explained by a difference in population, as previous studies investigated patients with more advanced cognitive deterioration while our population did not include demented PD patients, being this a contra-indication for the DBS screening procedure. However, these findings suggest that desynchronization of a similar α-band (either α1 or α2) network might underlie cognitive deterioration in both PD and AD.

The described qEEG parameters, both oscillatory slowing and functional connectivity, demonstrate discriminative ability at a group-level and may be further investigated to determine their potential as biomarkers at an individual level.

Strengths of our study are the large sample size of consecutively included patients, standardized examinations and use of a novel and validated clinimetric scale (SENS-PD). A limitation of the SENS-PD scale is that the different subdomains may reflect different systems-at-risk, indicating that similar scores between patients may reflect altogether different phenotypes, although this holds true for any multidimensional scale including the MDS-UPDRS III. From a clinical perspective, not all symptoms may be equally important, therefore the correlations with the SENS-PD scale were studied both for the composite scores and its subdomains. Our study population consisted of potential candidates for DBS. Typically, these patients had severe motor symptoms without obvious clinical signs of cognitive dysfunction or psychotic symptoms. This homogeneity constitutes both a limitation and a strength: although it is currently unknown whether our results can be generalised to all PD patients, we show that qEEG is capable of quantifying subtle differences in patients with cognitive and psychiatric symptoms that might go unnoticed in a global clinical impression. Investigations in a wider range of PD patients at different disease stages are likely to show even more pronounced correlations. Consequently, QEEG biomarkers for non-dopaminergic disease severity at different disease-stages could have clinical applicability beyond DBS screening, such as monitoring of disease progression.

The two applied methods of qEEG analysis do not show identical correlations with non-dopaminergic domains, suggesting that they address different functional aspects. The negative association of cortical connectivity in the α2 band with cognitive impairment but the lack of correlation with the other non-motor domains may reflect the subcortical nature of the latter. Whereas α-band connectivity is associated with cognition, it is not specifically limited to cognition as evidenced by a non-significant trend in the domain 'psychotic symptoms.' Although subcortical networks influence cortical processes,[25] the exact subcortical alterations are not properly visualized by EEG which accounts for the different results. Likewise, the lack of correlation between motor functioning and EEG slowing provides further evidence that severity of motor impairment as assessed by the MDS-UPDRS III is not reflected by cortical slowing.[14] Indeed, oscillatory alterations in the (subcortical) basal ganglia, which correlate with motor dysfunction,[26] cannot be captured by EEG. Magnetoencephalography (MEG) could investigate these subcortical networks,[25] however MEG is not widely available and is less applicable for routine DBS screening purposes. Previous longitudinal studies using MEG have identified slowing of oscillatory brain activities to be correlated with global disease progression in PD.[21]

A limitation of the applicability of EEG as a biomarker is the proportion of excluded patients due to EEG artifacts. These artifacts are partly inherent to the disease itself, such as altered muscle tone, increased ocular movements, tremor, dyskinesias, and sleepiness. As baseline

characteristics, both motor and non-motor severity, did not differ between included and excluded patients, we expect that the incidence of artifacts is not associated with disease severity. This is also confirmed by the fact that in our cohort the number of recordings excluded because of artefacts was comparable in the low disease severity group and high disease severity group.

Several factors might influence EEG activity, such as aging or use of psychoactive medication. For this reason we corrected our results for both factors. Careful consideration of normal age-related alterations cannot be neglected when assessing individual EEGs.

Changes of spectral- and connectivity parameters have also been found in epilepsy,[27] AD,[24] and schizophrenia [28] but it remains unclear whether these disorders have a common cortical denominator or whether there are different disease-specific network alterations.

EEG is available in every hospital, readily accessible and cheaper than other functional neuroimaging measures such as MEG, fMRI, PET or SPECT.[29] Moreover, source referencing amplified the spatial resolution, overcoming criticism of EEG's limited resolution.[30] Whereas the 21-channel EEG setup could be enhanced by using a high-density setup, we demonstrated that conventional routine EEG is sufficient to provide parameters of non-dopaminergic disease severity. Advanced setups do not seem necessary to achieve sufficient discriminative ability on a group-level. In this study we demonstrate that disease severity is accurately reflected by both functional connectivity and simpler EEG spectral measures, which are calculated with relative ease by neurophysiologists. Future research could focus on validation in larger and more heterogeneous cohorts to investigate whether qEEG may serve as biomarkers at an individual level, and determine its accuracy in estimating disease severity. The use of EEG parameters to aid the selection process of DBS candidates should also be further investigated.

In conclusion, we have demonstrated that both EEG slowing and reduced functional connectivity in the α2 band are associated with increased non-dopaminergic disease severity in PD, particularly with cognitive impairment and psychotic symptoms. These EEG alterations were apparent both globally and over separate brain regions. The studied qEEG parameters may have the potential to ultimately serve as complementary biomarkers of non-dopaminergic disease severity in PD.

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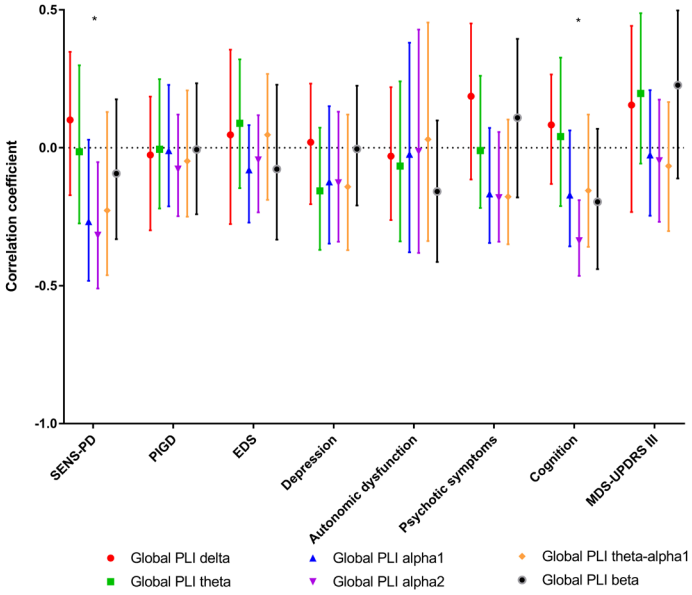
References

1. Jellinger KA. Neuropathology of sporadic Parkinson's disease: evaluation and changes of concepts. Mov Disord 2012;27:8-30.
2. Ahlskog JE, Muenter MD. Frequency of levodopa-related dyskinesias and motor fluctuations as estimated from the cumulative literature. Mov Disord 2001;16:448-458.
3. Deuschl G, Agid Y. Subthalamic neurostimulation for Parkinson's disease with early fluctuations: balancing the risks and benefits. Lancet Neurol 2013;12:1025-1034.
4. Moldovan AS, Groiss SJ, Elben S, Sudmeyer M, Schnitzler A, Wojtecki L. The treatment of Parkinson's disease with deep brain stimulation: current issues. Neural Regen Res 2015;10:1018-1022.
5. Contarino MF, Daniele A, Sibilia AH, et al. Cognitive outcome 5 years after bilateral chronic stimulation of subthalamic nucleus in patients with Parkinson's disease. J Neurol Neurosurg Psychiatry 2007;78:248-252.
6. Weaver FM, Follett K, Stern M, et al. Bilateral Deep Brain Stimulation vs Best Medical Therapy for Patients With Advanced Parkinson Disease A Randomized Controlled Trial. Jama-J Am Med Assoc 2009;301:63-73.
7. Tripoliti E, Zrinzo L, Martinez-Torres I, et al. Effects of subthalamic stimulation on speech of consecutive patients with Parkinson disease. Neurology 2011;76:80-86.
8. Russmann H, Ghika J, Villemure JG, et al. Subthalamic nucleus deep brain stimulation in Parkinson disease patients over age 70 years. Neurology 2004;63:1952-1954.
9. Duncan JS. Conventional and clinimetric approahces to individualization of antiepileptic drug therapy. In: Meinardi HC, J. A.; Baker, G. A.; da Silva A. M., ed. Quantitative assessment in epilepsy care. Porto, Portugal: Springer Science+Business Media, LLC, 1993.
10. Duckworth AL, Yeager DS. Measurement Matters: Assessing Personal Qualities Other Than Cognitive Ability for Educational Purposes. Educ Res 2015;44:237-251.
11. Caviness JN, Hentz JG, Belden CM, et al. Longitudinal EEG changes correlate with cognitive measure deterioration in Parkinson's disease. J Parkinsons Dis 2015;5:117-124.
12. Cozac VV, Gschwandtner U, Hatz F, Hardmeier M, Ruegg S, Fuhr P. Quantitative EEG and Cognitive Decline in Parkinson's Disease. Parkinsons Dis 2016;2016:9060649.
13. George JS, Strunk J, Mak-McCully R, Houser M, Poizner H, Aron AR. Dopaminergic therapy in Parkinson's disease decreases cortical beta band coherence in the resting state and increases cortical beta band power during executive control. NeuroImage Clinical 2013;3:261-270.
14. Babiloni C, De Pandis MF, Vecchio F, et al. Cortical sources of resting state electroencephalographic rhythms in Parkinson's disease related dementia and Alzheimer's disease. Clinical Neurophysiology 2011;122:2355-2364.
15. Utianski RL, Caviness JN, van Straaten ECW, et al. Graph theory network function in parkinson's disease assessed with electroencephalography. Clinical Neurophysiology 2016;127:2228-2236.
16. Postuma RB, Berg D, Stern M, et al. MDS clinical diagnostic criteria for Parkinson's disease. Mov Disord 2015;30:1591-1601.
17. Goetz CG, Fahn S, Martinez-Martin P, et al. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): Process, format, and clinimetric testing plan. Mov Disord

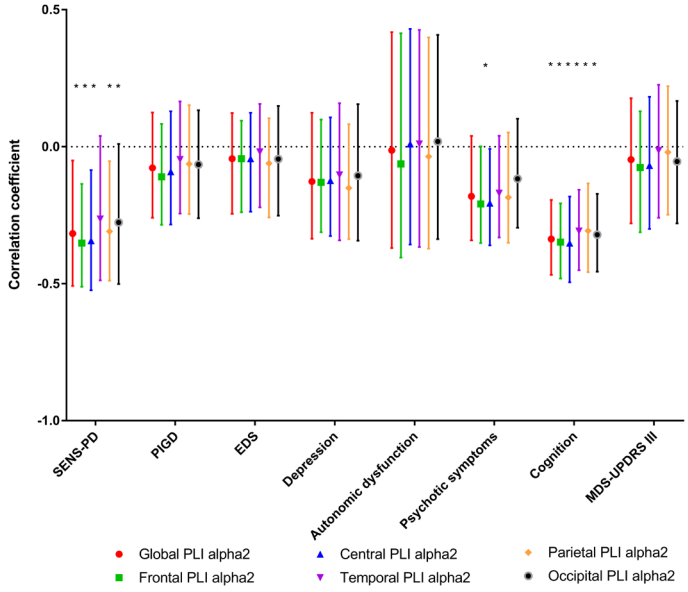
2007;22:41-47.

18. van der Heeden JF, Marinus J, Martinez-Martin P, van Hilten JJ. Evaluation of severity of predominantly non-dopaminergic symptoms in Parkinson's disease: The SENS-PD scale. Parkinsonism Relat Disord 2016;25:39-44.
19. Hjorth B. Source derivation simplifies topographical EEG interpretation. American Journal of EEG Technology 1980;20:121-132.
20. Stam CJ, Nolte G, Daffertshofer A. Phase lag index: assessment of functional connectivity from multi channel EEG and MEG with diminished bias from common sources. Hum Brain Mapp 2007;28:1178-1193.
21. Olde Dubbelink KT, Stoffers D, Deijen JB, Twisk JW, Stam CJ, Berendse HW. Cognitive decline in Parkinson's disease is associated with slowing of resting-state brain activity: a longitudinal study. Neurobiol Aging 2013;34:408-418.
22. Zheng L, Chai H, Yu S, Xu Y, Chen W, Wang W. EEG theta power and coherence to octave illusion in first-episode paranoid schizophrenia with auditory hallucinations. Psychopathology 2015;48:36-46.
23. Teeple RC, Caplan JP, Stern TA. Visual hallucinations: differential diagnosis and treatment. Prim Care Companion J Clin Psychiatry 2009;11:26-32.
24. Engels MM, Stam CJ, van der Flier WM, Scheltens P, de Waal H, van Straaten EC. Declining functional connectivity and changing hub locations in Alzheimer's disease: an EEG study. BMC Neurol 2015;15:145.
25. Boon LI, Hillebrand A, Olde Dubbelink KTE, Stam CJ, Berendse HW. Changes in resting-state directed connectivity in cortico-subcortical networks correlate with cognitive function in Parkinson's disease. Clin Neurophysiol 2017;128:1319-1326.
26. Brittain JS, Brown P. Oscillations and the basal ganglia: motor control and beyond. Neuroimage 2014;85 Pt 2:637-647.
27. Liang SF, Wang HC, Chang WL. Combination of EEG Complexity and Spectral Analysis for Epilepsy Diagnosis and Seizure Detection. Eurasip J Adv Sig Pr 2010.
28. John JP, Rangaswamy M, Thennarasu K, et al. EEG power spectra differentiate positive and negative subgroups in neuroleptic-naive schizophrenia patients. The Journal of neuropsychiatry and clinical neurosciences 2009;21:160-172.
29. Lystad RP, Pollard H. Functional neuroimaging: a brief overview and feasibility for use in chiropractic research. The Journal of the Canadian Chiropractic Association 2009;53:59-72.
30. Burle B, Spieser L, Roger C, Casini L, Hasbroucq T, Vidal F. Spatial and temporal resolutions of EEG: Is it really black and white? A scalp current density view. Int J Psychophysiol 2015;97:210-220.

Supplementary material



Supplementary 7.1 Correlation of global PLI and disease severity



Supplementary figure 7.2 Correlation of alpha2 PLI and disease severity

Supplementary table 7.1 Spectral ratios

	Overall	Low SENS-PD	Intermediate SENS-PD	High SENS-PD	p[a]	p[b]
Global spectral ratio	1.23 (1.10)	0.75 (0.38)	1.18 (0.96)	1.69 (0.45)	0.075	0.040
Frontal spectral ratio	1.52 (1.10)	1.03 (0.45)	1.49 (0.86)	1.96 (1.52)	0.069	0.031
Central spectral ratio	1.08 (0.94)	0.67 (0.34)	1.05 (0.78)	1.46 (1.21)	0.078	0.031
Temporal spectral ratio	1.27 (1.16)	0.75 (0.39)	1.28 (1.00)	1.69 (1.56)	0.088	0.059
Parietal spectral ratio	1.19 (1.27)	0.69 (0.48)	1.08 (0.97)	1.72 (1.78)	0.102	0.042
Occipital spectral ratio	1.40 (1.68)	0.77 (0.57)	1.33 (1.75)	2.01 (2.03)	0.102	0.022

Results are expressed as mean (SD)
[a] P-values computed using Kruskal-Wallis tests; [b] P-values for the comparison between high and low tertiles (Mann-Whitney U-tests)

Supplementary table 7.2 Global PLI

	Overall	Low SENS-PD	Intermediate SENS-PD	High SENS-PD	p[a]	p[b]
Global PLI δ band	0.15 (0.03)	0.15 (0.02)	0.16 (0.03)	0.15 (0.03)	0.104	0.977
Global PLI θ band	0.15 (0.04)	0.16 (0.05)	0.16 (0.04)	0.15 (0.03)	0.301	0.886
Global PLI α1 band	0.22 (0.07)	0.26 (0.09)	0.210 (0.04)	0.21 (0.05)	0.096	0.060
Global PLI α2 band	0.17 (0.06)	0.20 (0.09)	0.16 (0.04)	0.15 (0.05)	0.011	0.001
Global PLI β band	0.09 (0.03)	0.09 (0.03)	0.09 (0.03)	0.09 (0.02)	0.611	0.356

Results are expressed as mean (SD)
[a] P-values computed using Kruskal-Wallis tests; [b] P-values for the comparison between high and low tertiles (Mann-Whitney U-tests)

Supplementary table 7.3 PLI α2 band

	Overall	Low SENS-PD	Intermediate SENS-PD	High SENS-PD	p[a]	p[b]
Global PLI α2 band	0.17 (0.06)	0.20 (0.09)	0.16 (0.04)	0.15 (0.045)	0.010	0.002
Frontal PLI α2 band	0.17 (0.07)	0.210 (0.10)	0.15 (0.04)	0.15 (0.04)	0.009	0.002
Central PLI α2 band	0.16 (0.06)	0.20 (0.08)	0.16 (0.04)	0.15 (0.04)	0.022	0.003
Temporal PLI α2 band	0.16 (0.06)	0.19 (0.09)	0.15 (0.03)	0.15 (0.06)	0.033	0.014
Parietal PLI α2 band	0.17 (0.01)	0.210 (0.10)	0.17 (0.05)	0.16 (0.04)	0.113	0.033
Occipital PLI α2 band	0.18 (0.07)	0.22 (0.10)	0.16 (0.04)	0.16 (0.06)	0.038	0.012

Results are expressed as mean (SD)
[a] P-values computed using Kruskal-Wallis tests; [b] P-values for the comparison between high and low tertiles (Mann-Whitney U-tests)