Right on track: Towards improving DBS patient selection and care

Geraedts V.J.

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Victor J. Geraedts

Colophon

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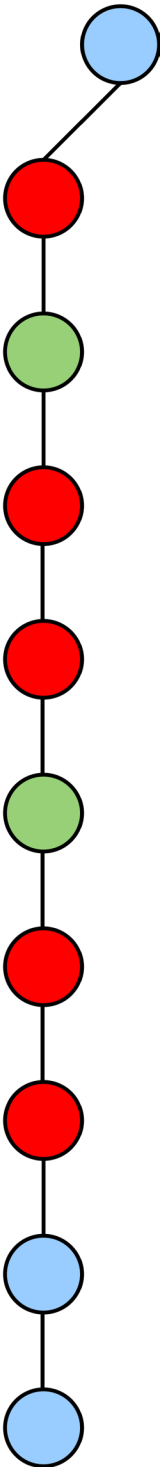
Table of contents

Chapter 1	Introduction	11
Chapter 2	Selecting candidates for Deep Brain Stimulation in Parkinson's Disease: the role of patients' expectations Published in: *Parkinsonism and Related Disorders, July 2019*	25
Chapter 3	What predicts Quality of Life after STN DBS in Parkinson's Disease? A systematic review Published in: *European Journal of Neurology, December 2019*	39
Chapter 4	Intraoperative test stimulation of the subthalamic nucleus aids postoperative programming of chronic stimulation settings in Parkinson's disease Published in: *Parkinsonism and Related Disorders, May 2019*	57
Chapter 5	Stimulation challenge tests after STN DBS improves satisfaction in Parkinson's Disease patients Published in: *Parkinsonism and Related Disorders, October 2019*	71
Chapter 6	Clinical correlations of quantitative EEG in Parkinson's Disease – a systematic review Published in: *Neurology, November 2018*	83
Chapter 7	Quantitative EEG reflects non-dopaminergic disease severity in Parkinson's Disease Published in: *Clinical Neurophysiology, May 2018*	113
Chapter 8	Automated machine Learning for EEG-based classification of cognitive performance during the DBS screening in Parkinson's Disease *Under review, June 2020*	131
Chapter 9	Summary	151
Chapter 10	General discussion	157

Appendices

Abbreviations 172
Nederlandse samenvatting 174
Dankwoord 179
Curriculum Vitae 181
Publications 182



CHAPTER 1

Introduction

Parkinson's Disease (PD) is a progressive neurological disorder, with an estimated prevalence of 0.3% per 100.000 individuals in the population aged over 40 years, which increases up to almost 2% in patients aged over 80 years.[1] In 2016, 6.1 million individuals were diagnosed with PD compared to 2.5 million diagnosed individuals in 1990, making it the fastest growing neurological disorder worldwide.[2] Over the last quarter of a century, increases were seen not only in the prevalence of PD, but also in death rates and rates of disability-adjusted life years. Assuming that the doubling of the prevalence of PD over a course of 25 years is correct (despite objections concerning increased recognition and registration), the worldwide prevalence of PD in 2050 would be estimated at around 12 million people, more than the current population of Belgium.[3] So far, no curative or progression-delaying treatment can be provided. Individually-tailored treatment options are currently our best alternative to relieve this growing disease burden, however the complexity of both the underlying disease mechanism in combination with a heterogeneous clinical presentation impairs the development of consensus criteria on treatment strategies targeting all segments of disease.[4]

Parkinson's Disease

In 1817, exactly 200 years before the initiation of the research detailed in this thesis, James Parkinson wrote his "Essay on the shaking palsy."[5] In this manuscript, the motor symptoms of six patients were described: three patients that were observed within Parkinson's clinic and three individuals encountered on the street. The condition, initially termed Shaking Palsy or Paralysis Agitans, is defined as an 'involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forwards, and to pass from a walking to running pace: the senses and intellects being uninjured'. Much like the suggested explanation, i.e. a 'diseased state of the medulla spinalis', the initial definition has been subject to correction and refinement. In 2015, the International Parkinson and Movement Disorders Society (MDS) delineated criteria for the diagnosis of clinically established PD.[6] First, the presence of parkinsonism should be established: bradykinesia in combination with either rigidity, rest tremor, or both. In the absence of any red flags that could indicate an alternate diagnosis, supportive criteria include amongst others olfactory loss contradicting the initially described uninjured sensory perceptions.

Apart from its characteristic motor symptoms, patients with PD suffer from a wide range of non-motor symptoms, which may manifest several years before the onset of motor symptoms and contribute heavily to disease burden.[7] These non-motor symptoms include amongst others cognitive impairment (including Mild Cognitive Impairment (MCI) and PD Dementia (PDD)), psychotic symptoms (including hallucinations), depression, apathy,

sleep disturbances, postural-instability-and-gait-difficulty and impulse-control disorders.[7-9] A downside of these symptoms is that they typically respond poorly, or not at all, to dopaminergic medication and require elaborate (multidisciplinary) approaches.[10, 11]

Much like the refinement of the diagnosis, the understanding of the underlying disease mechanism of PD has been subject to new insights. It has long been thought that PD was caused by degradation of dopamine-producing neurons in the substantia nigra.[12] However, many of the extrapyramidal symptoms could not be explained by loss of dopaminergic signalling alone. Friedrich Lewy first described intraneuronal inclusions in PD patients in 1912,[13] which were later found to consist of the protein α-synuclein.[14] Although heavily associated with PD, Lewy body inclusions are not specific for PD patients and are found in patients with Dementia with Lewy Bodies (DLB) as well,[15] although it is sometimes argued that both PD and DLB are extreme phenotypes sharing a similar underlying continuum of α-synucleinopathy.[16] Inclusions of α-synuclein have been reported in asymptomatic individuals as well, although previous literature suggests to consider these incident findings as pre-symptomatic PD.[17]

Depositions of α-synuclein, can be found throughout the central, peripheral and autonomic nervous system. The pathological stages of PD have been established by Braak et al,[18, 19] and can be subdivided into roughly three phases: a pre-symptomatic phase prior to the onset of the characteristic motor symptoms, a symptomatic phase including the hallmark PD features, and an advanced stage. According to Braak's hypothesis, during these three stages, the symptomatology can be directly linked to the level of involvement of pathological intraneuronal inclusions within the central nervous system. In the presymptomatic phase, inclusions of Lewy bodies are mainly present in the medulla oblongata and the olfactory bulb. During this stage, patients already demonstrate both autonomic disturbances and hyposmia. During the motor stage, α-synucleinopathy has spread throughout the basal ganglia where it is associated with the characteristic motor features of PD. Some intraneuronal inclusions can be found in the mid- and forebrain, resulting in minor impairments of cortical functions. During the end-stages, α-synuclein depositions have spread out through the cortex, resulting in progressive cognitive decline and psychiatric manifestations (see figure 1.1 for a conceptual drawing).

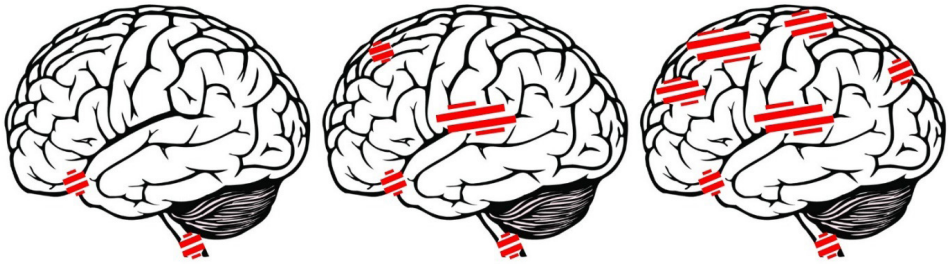


Figure 1.1 Spreading of α-synuclein according to Braak's hypothesis.
In the premotor phase (left), there is α-synucleinopathy (red-shaded areas) limited to the medulla and the olfactory bulb, there causing autonomic symptoms and hyposmia. In the motor phase (middle), the α-synucleinopathy has spread towards the basal ganglia causing the characteristic motor symptoms. Some cortical involvement is already present, causing symptoms of cognitive impairment and confusion. During the advanced stages (right), there is widespread cortical spreading of α-synuclein, causing various non-motor symptoms including cognitive impairment, psychotic symptoms, and sleep disturbances.

Deep Brain Stimulation for Parkinson's Disease

The cornerstone of PD treatment has long since been oral dopaminergic treatment, typically in the form of the dopamine precursor levodopa.[10] In 1960, it was shown that PD patients displayed a marked loss of dopamine in their basal ganglia.[20] Initially isolated from the seeds of the fava bean (Vicia Faba) in 1913,[21] the clinical application of the precursor substance levodopa was demonstrated in 1961 by relieving akinesia in PD patients,[22] and was firmly established in 1967 as the drug-of-choice to target parkinsonism.[23, 24] Other treatment strategies, prior to more advanced therapies, include administration of dopamine-agonists which have been reported efficacious in PD since 1951 (apomorphine).[25]

Despite good initial relief from PD motor symptoms (although limited effects on non-motor symptoms), a third subset of PD symptoms emerges as a consequence of dopaminergic treatment: motor complications. In contrast to the aforementioned motor- and non-motor symptoms, these motor complications are directly attributable to a combination of both the treatment regime and the underlying disease mechanism consisting of presynaptic denervation and increased postsynaptic glutamatergic transmission.[26] Motor complications are typically either in the form of OFF-periods, during which patients are refractory to oral dopaminergic medication, or in the form of dyskinesias characterized by excessive movement. It has been estimated that the majority of PD patients develop medication-related motor complications within 10 years of disease duration (see also figure 1.2).[27]

For those patients suffering from medication-induced motor complications, refractory

to oral treatment, Deep Brain Stimulation (DBS) may be considered. DBS is an invasive surgical procedure which primarily involves motor symptoms and improves quality of life. [28, 29] Motor complications are improved after DBS as a consequence of a reduced need of oral dopaminergic medication. Depending on the patients' primary complaint, DBS may usually target either the ventral intermedius nucleus of the thalamus (VIM), globus pallidum interna (GPi) or subthalamic nucleus (STN), with several studies demonstrating beneficial results of stimulating the zona incerta (ZI) as well.[30, 31] STN DBS is particularly effective in those patients in whom substantial motor improvement is generated by oral dopaminergic treatment.[32] STN DBS typically reduces medication intake by approximately 50%, provides significantly more ON-time and thereby relieves motor complications. [29]

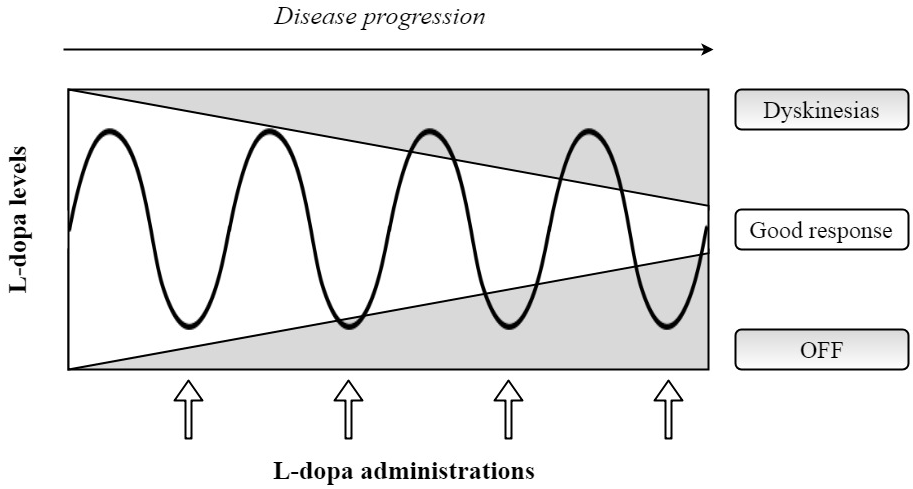


Figure 1.2 Schematic representation of the appearance of motor complications.
Patients with Parkinson's Disease (PD) are initially treated with oral levodopa (L-dopa) (or dopamine-agonists) to relief motor symptoms, causing the levels of L-dopa within the brain to rise and fall in accordance with the timing of the L-dopa administrations. Initially this has a good effect and patients stay within the white-shaded area reflecting good therapeutic control. However, as the disease progresses, patients become refractory to oral dopaminergic treatment and develop motor complications (shaded grey) either in the form of reduced response to treatment (OFF-periods) or excessive movements during the ON-phase (dyskinesias).

Although DBS candidates are generally informed to expect a level of motor functioning comparable to their 'best ON state', studies have shown that stimulated patients may have improved motor functioning compared to their preoperative functioning.[33] Despite these obvious benefits in the motor domain, DBS may have detrimental effects on non-dopaminergic symptoms such as cognitive impairment, psychiatric symptoms, speech intelligibility and postural symptoms.[34-37] It is therefore of paramount importance to not only investigate

whether PD patients may benefit from DBS surgery by improvement of the severity of motor complications, but also screen for those domains at-risk of post-surgical deterioration. It has been estimated that 30% of so-called DBS failures are due to inappropriate referrals.[38, 39] Various screening algorithms have been described to aid in referral practices,[40, 41] but they are either cumbersome or do not cover the entire spectrum of indications / contra-indications for surgery. These algorithms have particularly high sensitivity but very low specificity (STIMULUS tool [41]: sensitivity of 100%, specificity of 12%). Moreover, the initial studies on these algorithms carry inherent selection bias and may have limited external validity.[42] There are no stringent criteria delineating eligibility or ineligibility for DBS surgery.[39, 43] Not only does this result in referral of patients in disease-stages beyond the optimal timing of referral, but it may also lead to patients referred 'too early' in anticipation of long waiting lists or as a result of overinterpretation of the results of the EARLYSTIM trial.[44, 45] Hence, careful assessment of both motor complications and nondopaminergic (mostly non-motor) domains,[46] are crucial in determining DBS eligibility of the optimal candidates for surgery.

The interplay between PD symptoms may limit such an evaluation of symptomatology, particularly the assessment of non-motor symptoms. For example, increasing fatigue or apathy limit the evaluation of cognition or depression due to a lack of motivation. Moreover, differences in personality traits may influence test motivation as well.[47, 48] This indicates the need for biomarkers to complement current measurement instruments, in order to provide a more reliable assessment of DBS eligibility .

EEG Biomarkers in Parkinson's Disease

Our current ability to reflect disease severity or symptomatology within a framework of the underlying disease mechanism is limited. The identification of novel biomarkers within this framework would complement current strategies that evaluate disease severity and provide additional information to be used within the setting of the screening for DBS eligibility.

By definition, a biomarker is objectively measured and evaluated as an indicator of normal biological processes, pathophysiologic processes, or pharmacologic response to a therapeutic intervention.[49] A good biomarker is inexpensive, unsusceptible to bias or misinterpretation, readily available and harmless. Particularly, biomarkers may identify systems-at-risk prior to demonstration of debilitating symptoms.[50] Assuming Braak's hypothesis to be correct and given the association between cortical involvement and non-motor disease severity, a measurement instrument that quantitatively reflects cortical functioning may provide the aforementioned required biomarkers. One such instrument

is quantitative Electroencephalography (qEEG) by measuring cortical functioning directly. qEEG is inexpensive, widely available and non-invasive, making it a highly suitable candidate biomarker to study cortical involvement of an underlying disease mechanism.
The type of qEEG metrics can generally be subdivided into three groups of advancing complexity: spectral measures of cortical rhythms, connectivity measures reflecting synchronized signalling, and graph theory matrices reflecting connectivity-derived functional networks. The number of qEEG metrics is legion: not only is there a vast amount of variables but also assessments at a global, regional, or even electrode-level impair directly comparability.[51, 52] Pros and cons of different qEEG measures, particularly connectivity- and network-metrics, have been previously reported and insight into the different characteristics of the distinct measures is required for accurate interpretation of findings.[53]

Spectral analyses refer to the analysis of signal-speed: i.e. the frequency at which oscillations occur. For each EEG-epoch, a Fast Fourier Transform (FFT) produces a power spectrum for each individual electrode position. This FFT spectrum can then be evaluated by determining the area under the curve (AUC) of each of the frequency bands, commonly 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). The γ band is usually not studied in PD due to its frequent contamination with muscle artifacts. The 'power' (or AUC of the segments of the FFT spectrum) can be seen as absolute values, or as relative values by dividing the absolute bandpower of each frequency band by the absolute power of the total FFT spectrum from the FFT average per electrode position. In order to reflect all spectral information of the FFT spectrum, a spectral slowing ratio can be calculated by dividing the power of the slow frequency bands (i.e δ and θ) by the power of the fast frequency bands (i.e. α1, α2, and β). Lastly, the dominant frequency of the FFT spectrum, seen as the 'FFT peak' (typically somewhere in the θ – α range) reflects the frequency with the highest power in the entire observed spectrum.

Connectivity measures reflect the interdependency between multiple brain regions,[54] whilst the consistency or strength of this interdependency is considered to reflect the underlying synchronization between brain regions.[55] Non-linear phase-based measures, such as the Phase Lag Index,[56] quantify the degree of phase-coupling between two oscillators, such as the time-frequency series derived from EEG channels. A multitude of connectivity metrics exist, each of which has a unique mathematical background and therefore interpretation.[53] The choice of which connectivity metric to study may be based on computational and methodological considerations, but remains in itself arbitrary and therefore may not be the ideal metric to reflect the strongest level of coupling between two signals, as a comparison of all possible connectivity metrics would require more tests than the available sample sizes contains.

Connectivity-derived matrixes may subsequently reflect integration of oscillator-coupling within a compound network, moving beyond the coupling of two time-series towards a more global perspective.[57] Network analyses are a subsidiary of graph theory analysis and visualize the interplay between EEG channels in a compound graph, existing of channels (i.e. 'nodes') and connections between channels (i.e. 'edges'). The dimension of these graphs is still constrained within one (sub)network, e.g. a network of genetic interactions, EEG channels, or the microbiome. Similar to arbitrary choices related to connectivity metrics, networks are subject to choices as well relating to the density of features, underlying connectivity matrix, and choice of network metric.

The use of qEEG to reflect poor cognitive functioning has been described in several studies on PD patients, both in terms of correlation with spectral,[58, 59] connectivity,[60] and network metrics,[61] as well as classification of groups based on cognitive performance.[62] Several studies have linked qEEG biomarkers to prediction of cognitive deterioration in the PD population,[58, 63] although primarily limited to spectral measures. Given that those symptoms that constitute relative contra-indications for DBS are apparent upon cortical involvement of α-synucleinopathy, a measurement instrument that reflects cortical activity may have utility during the screening for DBS eligibility particularly given the difficulty in evaluating cognitive (dys)function. Whereas the use of qEEG in the general PD population has been described in several studies, DBS candidates are a very specific subgroup in the sense that the more 'extreme' patients are not included. Patients with a short disease duration, without motor complications and no cortical symptoms are not yet candidates for surgery, whereas patients with extensive cortical symptoms (i.e. dementia or severe psychotic disturbances) have progressed beyond DBS eligibility. Clinimetric characterisation of qEEG biomarkers in the DBS population is therefore important before the utility as a biomarker of future deterioration can be determined.

Aims and outline

Although STN DBS is a well-established therapy in PD, several of its aspects require further exploration to advance patient selection in care. This thesis therefore consists of two parts: (1) analysis of clinical determinants of DBS treatment success, and (2) exploration of novel neurophysiological biomarkers forscreening of DBS eligibility of PD patients.

Section A: Exploration of current DBS care

In the next three chapters, studies investigating the current approach to DBS care are described. In **Chapter 2**, the reasons for rejection after referral for DBS are described, as well

as patients' expectations prior to surgery, in a large cohort (n=289) of PD patients referred to two university hospitals. In **Chapter 3**, publications on factors predicting Quality of Life changes after STN DBS are systematically reviewed. In **Chapter 4,** a comparison between intraoperative test stimulation and postoperative stimulation settings is drawn, which may benefit the efficiency of finding optimal DBS settings and thereby ultimately reduce patient burden. In **Chapter 5**, the effect of a postoperative stimulator challenge test on patient satisfaction after surgery is reported, as well as the effect of motor- and non-motor symptom changes on patient-reported outcomes.

Section B: Advancing patient selection for DBS through neurophysiological biomarkers
In **Chapter 6**, publications on the correlation of qEEG biomarkers and PD symptoms are systematically reviewed, pertaining to the general PD population. In **Chapter 7**, a qEEG study on DBS candidates is described, which correlated both spectral- and connectivity qEEG biomarkers to non-dopaminergic (non-motor) symptoms in PD to provide evidence for the utility of qEEG during the DBS screening process. In **Chapter 8**, an automated Machine Learning pipeline for automatic classification of cognitive performance (i.e. 'good cognitive performance' vs. 'poor cognitive performance') is described, in order to increase the practical utility of qEEG by limiting both pre-processing efforts and arbitrary choices on qEEG feature selection. The classification-performance of this pipeline is subsequently evaluated on patients with an 'intermediate cognitive performance'. In **Chapters 9 & 10**, a summary of the main conclusions and a general discussion on the results, interpretation, and future perspectives is provided.

References

1. Pringsheim T, Jette N, Frolkis A, Steeves TD. The prevalence of Parkinson's disease: a systematic review and meta-analysis. Movement disorders : official journal of the Movement Disorder Society 2014;29:1583-1590.
2. Dorsey ER EA, Nichols E, Abd-Allah F, Abdelalim A, Adsuar JC, Ansha MG, Brayne C, Choi JJ, Collado-Mateo D, Dahodwala N, Do HP, Edessa D, Endres M, Fereshtehnejad SM, Foreman KJ, Gankpe FG, Gupta R, Hankey GJ, Hay SI, Hegazy MI, Hibstu DT, Kasaeian A, Khader Y, Khalil I, Khang YH, Kim YJ, Kokubo Y, Logroscino G, Massano J, Mohamed Ibrahim N, Mohammed MA, Mohammadi A, Moradi-Lakeh M, Naghavi M, Nguyen BT, Nirayo YL, Ogbo FA, Owolabi MO, Pereira DM, Postma MJ, Qorbani M, Rahman MA, Roba KT, Safari H, Safiri S, Satpathy M, Sawhney M, Shafieesabet A, Shiferaw MS, Smith M, Szoeke CEI, Tabarés-Seisdedos R, Truong NT, Ukwaja KN, Venketasubramanian N, Villafaina S, Weldegwergs KG, Westerman R, Wijeratne T, Winkler AS, Xuan BT, Yonemoto N, Feigin VL, Vos T, Murray CJL. Global, regional, and national burden of Parkinson's disease, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. The Lancet Neurology 2018;17:939-953.
3. Laevert CB, P;. Eurostat: your key to European statistics [online]. Available at: https://ec.europa.eu/eurostat/en/web/population-demography-migration-projections/statistics-illustrated.
4. Titova N, Chaudhuri KR. Personalized medicine in Parkinson's disease: Time to be precise. Movement disorders : official journal of the Movement Disorder Society 2017;32:1147-1154.
5. Parkinson J. An essay on the shaking palsy. 1817. J Neuropsychiatry Clin Neurosci 2002;14:223-236; discussion 222.
6. Postuma RB, Berg D, Stern M, et al. MDS clinical diagnostic criteria for Parkinson's disease. Mov Disord 2015;30:1591-1601.
7. Marinus J, Zhu K, Marras C, Aarsland D, van Hilten JJ. Risk factors for non-motor symptoms in Parkinson's disease. Lancet Neurol 2018;17:559-568.
8. van der Heeden JF, Marinus J, Martinez-Martin P, van Hilten JJ. Importance of nondopaminergic features in evaluating disease severity of Parkinson disease. Neurology 2014;82:412-418.
9. 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.
10. Connolly BS, Lang AE. Pharmacological treatment of Parkinson disease: a review. Jama 2014;311:1670-1683.
11. Seppi K, Ray Chaudhuri K, Coelho M, et al. Update on treatments for nonmotor symptoms of Parkinson's disease-an evidence-based medicine review. Movement disorders : official journal of the Movement Disorder Society 2019;34:180-198.
12. Jellinger KA. Neuropathology of sporadic Parkinson's disease: evaluation and changes of concepts. Mov Disord 2012;27:8-30.
13. Rodrigues e Silva AM, Geldsetzer F, Holdorff B, et al. Who was the man who discovered the "Lewy bodies"? Mov Disord 2010;25:1765-1773.
14. Spillantini MG, Schmidt ML, Lee VM, Trojanowski JQ, Jakes R, Goedert M. Alpha-synuclein in Lewy bodies. Nature 1997;388:839-840.
15. McKeith IG, Boeve BF, Dickson DW, et al. Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB Consortium. Neurology 2017;89:88-100.

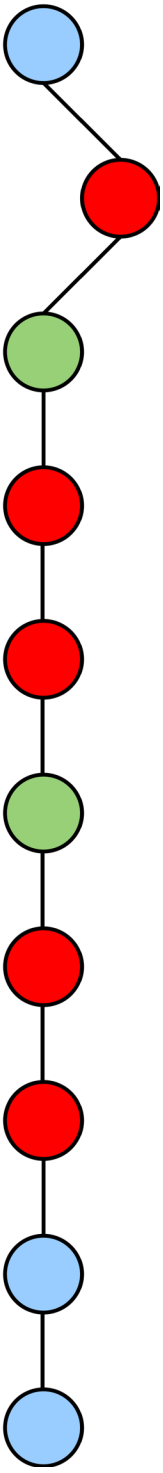
16. Jellinger KA, Korczyn AD. Are dementia with Lewy bodies and Parkinson's disease dementia the same disease? BMC medicine 2018;16:34.
17. Dickson DW, Fujishiro H, DelleDonne A, et al. Evidence that incidental Lewy body disease is pre-symptomatic Parkinson's disease. Acta neuropathologica 2008;115:437-444.
18. Braak H, Del Tredici K. Invited Article: Nervous system pathology in sporadic Parkinson disease. Neurology 2008;70:1916-1925.
19. Goedert M, Spillantini MG, Del Tredici K, Braak H. 100 years of Lewy pathology. Nature reviews Neurology 2013;9:13-24.
20. Ehringer H, Hornykiewicz O. [Distribution of noradrenaline and dopamine (3-hydroxytyramine) in the human brain and their behavior in diseases of the extrapyramidal system]. Klinische Wochenschrift 1960;38:1236-1239.
21. Torquati T. Sulla presenza di una sostanza azotata nei germogli del semi di "vicia faba". Arch Farmacol sper 1913;15:213-223.
22. Birkmayer W, Hornykiewicz O. [The L-3,4-dioxyphenylalanine (DOPA)-effect in Parkinson-akinesia]. Wiener klinische Wochenschrift 1961;73:787-788.
23. Cotzias GC, Papavasiliou PS, Gellene R. Modification of Parkinsonism--chronic treatment with L-dopa. N Engl J Med 1969;280:337-345.
24. Cotzias GC, Van Woert MH, Schiffer LM. Aromatic amino acids and modification of parkinsonism. N Engl J Med 1967;276:374-379.
25. Schwab RS, Amador LV, Lettvin JY. Apomorphine in Parkinson's disease. Transactions of the American Neurological Association 1951;56:251-253.
26. Ahmed I, Bose SK, Pavese N, et al. Glutamate NMDA receptor dysregulation in Parkinson's disease with dyskinesias. Brain : a journal of neurology 2011;134:979-986.
27. Ahlskog JE, Muenter MD. Frequency of levodopa-related dyskinesias and motor fluctuations as estimated from the cumulative literature. Mov Disord 2001;16:448-458.
28. Deuschl G, Agid Y. Subthalamic neurostimulation for Parkinson's disease with early fluctuations: balancing the risks and benefits. Lancet Neurol 2013;12:1025-1034.
29. Deuschl G, Schade-Brittinger C, Krack P, et al. A randomized trial of deep-brain stimulation for Parkinson's disease. N Engl J Med 2006;355:896-908.
30. Blomstedt P, Stenmark Persson R, Hariz GM, et al. Deep brain stimulation in the caudal zona incerta versus best medical treatment in patients with Parkinson's disease: a randomised blinded evaluation. J Neurol Neurosurg Psychiatry 2018;89:710-716.
31. Eisinger RS, Wong J, Almeida L, et al. Ventral Intermediate Nucleus Versus Zona Incerta Region Deep Brain Stimulation in Essential Tremor. Movement disorders clinical practice 2018;5:75-82.
32. 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 regeneration research 2015;10:1018-1022.
33. Okun MS, Gallo BV, Mandybur G, et al. Subthalamic deep brain stimulation with a constant-current device in Parkinson's disease: an open-label randomised controlled trial. Lancet Neurol 2012;11:140-149.
34. Kirsch-Darrow L, Zahodne LB, Marsiske M, Okun MS, Foote KD, Bowers D. The trajectory of apathy after deep

brain stimulation: from pre-surgery to 6 months post-surgery in Parkinson's disease. Parkinsonism Relat Disord 2011;17:182-188.

35. 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.
36. 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.
37. 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.
38. Katz M, Kilbane C, Rosengard J, Alterman RL, Tagliati M. Referring patients for deep brain stimulation: an improving practice. Arch Neurol 2011;68:1027-1032.
39. Okun MS, Tagliati M, Pourfar M, et al. Management of referred deep brain stimulation failures: a retrospective analysis from 2 movement disorders centers. Arch Neurol 2005;62:1250-1255.
40. Okun MS, Fernandez HH, Pedraza O, et al. Development and initial validation of a screening tool for Parkinson disease surgical candidates. Neurology 2004;63:161-163.
41. Moro E, Allert N, Eleopra R, Houeto JL, Phan TM, Stoevelaar H. A decision tool to support appropriate referral for deep brain stimulation in Parkinson's disease. J Neurol 2009;256:83-88.
42. Coleman RR, Kotagal V, Patil PG, Chou KL. Validity and Efficacy of Screening Algorithms for Assessing Deep Brain Stimulation Candidacy in Parkinson Disease. Movement disorders clinical practice 2014;1:342-347.
43. Lang AE, Widner H. Deep brain stimulation for Parkinson's disease: patient selection and evaluation. Mov Disord 2002;17 Suppl 3:S94-101.
44. Schuepbach WM, Rau J, Knudsen K, et al. Neurostimulation for Parkinson's disease with early motor complications. N Engl J Med 2013;368:610-622.
45. Schupbach WM, Rau J, Houeto JL, et al. Myths and facts about the EARLYSTIM study. Mov Disord 2014;29:1742-1750.
46. Almeida L, Deeb W, Spears C, et al. Current Practice and the Future of Deep Brain Stimulation Therapy in Parkinson's Disease. Seminars in neurology 2017;37:205-214.
47. Duckworth AL, Quinn PD, Lynam DR, Loeber R, Stouthamer-Loeber M. Role of test motivation in intelligence testing. Proceedings of the National Academy of Sciences of the United States of America 2011;108:7716-7720.
48. Duckworth AL, Yeager DS. Measurement Matters: Assessing Personal Qualities Other Than Cognitive Ability for Educational Purposes. Educ Res 2015;44:237-251.
49. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Clinical pharmacology and therapeutics 2001;69:89-95.
50. Geraedts VJ, Boon LI, Marinus J, et al. Clinical correlates of quantitative EEG in Parkinson disease: A systematic review. Neurology 2018.
51. Duncan NW, Northoff G. Overview of potential procedural and participant-related confounds for neuroimaging of the resting state. Journal of psychiatry & neuroscience : JPN 2013;38:84-96.
52. Gross J. Analytical methods and experimental approaches for electrophysiological studies of brain oscillations. J Neurosci Methods 2014;228:57-66.
53. van Diessen E, Numan T, van Dellen E, et al. Opportunities and methodological challenges in EEG and MEG resting

state functional brain network research. Clin Neurophysiol 2015;126:1468-1481.

54. Aertsen AM, Gerstein GL, Habib MK, Palm G. Dynamics of neuronal firing correlation: modulation of "effective connectivity". J Neurophysiol 1989;61:900-917.
55. Varela F, Lachaux JP, Rodriguez E, Martinerie J. The brainweb: phase synchronization and large-scale integration. Nat Rev Neurosci 2001;2:229-239.
56. 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. Human brain mapping 2007;28:1178-1193.
57. Stam CJ, van Straaten EC. The organization of physiological brain networks. Clin Neurophysiol 2012;123:1067-1087.
58. Latreille V, Carrier J, Gaudet-Fex B, et al. Electroencephalographic prodromal markers of dementia across conscious states in Parkinson's disease. Brain 2016;139:1189-1199.
59. Morita A, Kamei S, Mizutani T. Relationship between slowing of the EEG and cognitive impairment in Parkinson disease. J Clin Neurophysiol 2011;28:384-387.
60. Hassan M, Chaton L, Benquet P, et al. Functional connectivity disruptions correlate with cognitive phenotypes in Parkinson's disease. NeuroImage Clinical 2017;14:591-601.
61. 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.
62. Cozac VV, Chaturvedi M, Hatz F, Meyer A, Fuhr P, Gschwandtner U. Increase of EEG Spectral Theta Power Indicates Higher Risk of the Development of Severe Cognitive Decline in Parkinson's Disease after 3 Years. Front Aging Neurosci 2016;8:284.
63. 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.



CHAPTER 2

Selecting candidates for Deep Brain Stimulation in Parkinson's Disease: the role of patients' expectations

Geraedts VJ, Kuijf ML, van Hilten JJ, Marinus J, Oosterloo M, Contarino MF
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Abstract

Patients with advanced Parkinson's Disease (PD) may be eligible for Deep Brain Stimulation (DBS) in case of medication-related motor fluctuations or tremor refractory to oral medication. However, several PD symptoms are unresponsive to DBS and constitute relative contra-indications for DBS. Patients referred for DBS undergo an eligibility screening during which motor functioning and contra-indications for surgery are assessed. During this pre-screening the potential benefits and drawbacks of surgery are discussed, together with patients' expectations of the results of DBS. Unrealistic expectations on the benefits of DBS may contribute to reduced patient satisfaction and poor clinical outcomes after surgery. The aim of this multicenter study (289 patients) was to assess the reasons for rejection after an outpatient-based pre-screening visit for DBS referrals, with particular emphasis on the role of patient expectations of DBS. The most frequent reason contributing to rejection was suboptimal oral treatment or satisfying symptom-control with oral medication (50% of rejections). Unrealistic expectations were identified in 38% of rejected patients and were the singular reason for rejection in 4%. Incorporating the assessment of unrealistic expectations increased the accuracy (Area Under the Curve) of determining DBS eligibility from 0.92 ((95% confidence interval (95%CI) 0.88 – 0.97) to 0.97 (95%CI 0.96 – 0.99). Patients' expectations of DBS are easily checked, and better education of patients and treating neurologists with regard to unrealistic expectations of this procedure may improve efficiency of referrals and avoid unnecessary stress and disappointments during screening.

Introduction

Deep brain stimulation (DBS) is considered a highly effective therapy to relieve medication-refractory levodopa-induced motor complications or resistant tremor in Parkinson's disease (PD),[1] generally targeting either the subthalamic nucleus, thalamus or pallidum. The potential benefit of DBS is weighed against possible surgical complications or shortcomings that may compromise its success. Examples of the latter include stimulation-resistant symptoms such as postural instability gait disorder, medication-resistant freezing, speech disturbances, psychiatric and cognitive dysfunction, which do not improve or may even worsen following DBS and therefore constitute relative contra-indications for this treatment. DBS failures are often associated with poor selection of DBS candidates, highlighting the importance of a formal comprehensive screening including brain imaging and formal assessments of motor function, balance, cognition, and psychiatric functioning.[2] However, this extensive screening is stressful, expensive, and time-consuming. Prior to the formal DBS screening, patients are often referred to neurologists experienced in DBS for a 'pre-screening', to assess whether patients are suitable candidates for the full DBS screening procedure. During this pre-screening, patients deemed unsuitable may be rejected at an early stage and thereby avoid participation in the demanding full screening procedure. Several screening algorithms have been proposed to aid in DBS referral, with high sensitivity but low specificity.[3-5] Notably, none of these algorithms considers patients' expectations of DBS. Patients may report various reasons for undergoing DBS which are known to remain unsolved after surgery. Hence, realistic expectations of DBS are considered an important criterion for patients selection,[6] as various studies demonstrated that patients with unrealistic expectations, or with suboptimal education on the benefits of DBS prior to surgery, report lower postoperative satisfaction or QoL.[7-9] Patient-reported expectations of DBS have been scarcely studied;[8-10] the contribution of unrealistic patient expectations to the decision on DBS eligibility is yet unknown.

The aim of our study was to assess the reasons for rejection after an outpatient-based pre-screening visit for DBS referrals, with particular emphasis on the role of patient expectations of DBS in determining eligibility for a full screening for surgical candidacy. Improvement of outpatient-based pre-screening in capturing the patients that are more obviously unsuitable for DBS could contribute to avoid unnecessary participations in a full screening procedure, thereby increasing the efficiency of the screening procedure and reducing overall patient burden. Furthermore, insights on this topic may provide further directions to referring neurologists.

Methods

Study participants

All consecutive PD patients (UK Brain Bank Criteria) referred for DBS between January 2013 and June 2018 to two different Dutch academic DBS centers, the Leiden University Medical Center (LUMC) and the Maastricht University Medical Center (MUMC), were included in the study. Patients already under treatment at the LUMC or MUMC prior to the decision concerning DBS eligibility were excluded. All patients received a formal pre-screening, during which a neurologist experienced in DBS assesses the DBS eligibility based on an extensive patient history and neurological examination during an outpatient visit prior to any formal screening procedure.

Outcome measures

From the electronic patient files, we extracted demographic and clinical variables, as well as indications for DBS (severity of motor fluctuations or presence of refractory tremor) and contra-indications (see table 2.1), as assessed during the initial outpatient visit. At this stage, assessment of outcomes such as motor function and cognition were based on anamnestic data; patients who are selected for the formal pre-operative evaluation would receive the full screening procedures including, among others, cognitive evaluation and levodopa challenge test.

We further extracted expectations of DBS, as reported by the patient after a standardized question. Realistic expectations were defined prior to data-collection as a desire to relief a symptom that is DBS-responsive: 1. Less "OFF"-time, 2. Less dyskinesias, 3. 'Less medication', 4. Relief of therapy-refractory tremor. Unrealistic expectations were defined as a desire to relieve a symptom that is unlikely to be responsive to DBS (e.g. medication-resistant freezing or cognitive symptoms) and was unresponsive to previous adequate dopaminergic therapy exposure.[11] The reasons for rejection for DBS screening were also documented. Patients could be rejected for multiple reasons.

Statistical analysis

Demographic and clinical variables were compared between patients who were accepted and rejected for the DBS eligibility screening with independent Student's T-tests and Pearson $\chi 2$ tests.

A multivariate logistic regression model with a forced entry covariance matrix, including demographic variables, indications, and contraindications for surgery, was used to determine the odds of being accepted for DBS screening (see supplementary table 2.1). A second model

added the factor 'realistic expectations of DBS surgery' to assess its additional contribution in predicting eligibility. The predicted probabilities of both models were plotted on Receiver Operating Characteristic curves to determine the Area Under the Curve (AUC). Significance levels were confirmed using Benjamini Hochberg False Discovery Rate corrections (threshold for significance set at 0.05).

All analyses were performed using IBM Statistical Package for the Social Sciences 23 Software (SPSS Inc., Chicago, Illinois). A formal ethical evaluation of this study was waived by the local medical ethics committees.

Results

Patient characteristics

During the study period, 289 patients were referred to both centers for DBS (LUMC: n=162; MUMC: n=127). Mean (SD) age was 61.0 (8.3) years; mean (SD) disease duration was 9.4 (4.8) years. For 19 patients expectations of DBS were not documented. Further demographic variables are shown in table 2.1.

Table 2.1. Patient characteristics

	Total	Rejected	Accepted	P
N	289	76	213	
% female (n)	90 (31)	23 (30)	67 (31)	0.847
Age in years [a] (mean (SD))	61.0 (8.3)	63.4 (8.4)	60.2 (8.1)	0.003
Disease duration in years [a] (mean (SD))	9.4 (4.8)	8.5 (5.2)	9.7 (4.7)	0.066
Severity "OFF" [b]				
No "OFF"	62 (22)	27 (36)	36 (17)	
1-50% "OFF"	178 (62)	40 (53)	138 (65)	0.003
51-100% "OFF"	48 (17)	9 (12)	39 (18)	
Severity dyskinesias [b]				
No dyskinesias	87 (30)	33 (43)	54 (25)	
1-50% dyskinesias	151 (52)	33 (43)	118 (55)	0.012
51-100% dyskinesias	51 (18)	10 (13)	41 (19)	
Refractory tremor [b]	55 (19)	13 (17)	42 (2)	0.618
Balance impairment or medication-resistant freezing [b]	91 (31)	40 (53)	51 (24)	<0.001
Psychiatric side-effects of dopaminergic medication [b]	105 (36)	33 (43)	72 (34)	0.134
Anamnestic cognitive impairment [b]	97 (34)	39 (51)	58 (27)	<0.001
Sufficient control with current oral treatment or suboptimal treatment [b]	46 (16)	40 (53)	6 (3)	<0.001
Unrealistic expectations [b, c]	62 (23)	54 (67)	28 (8)	<0.001

A higher severity of "OFF", dyskinesias, and refractory tremor were considered good indications for DBS. Balance impairment or freezing during "ON", psychiatric side-effects, cognitive impairment, suboptimal treatment, and unrealistic expectations were considered relative contraindications for surgery.
[a] mean (SD)
[b] valid n (%)
[c] 19 patients missing

Expectations and reasons for undergoing DBS

Several patients reported multiple reasons / expectations. Twenty-three percent of patients (n=63) reported unrealistic expectations of DBS (figure 2.1). There were no differences among referring neurologists and centers in the percentage of referred patients with unrealistic expectations (only LUMC referrals studied).

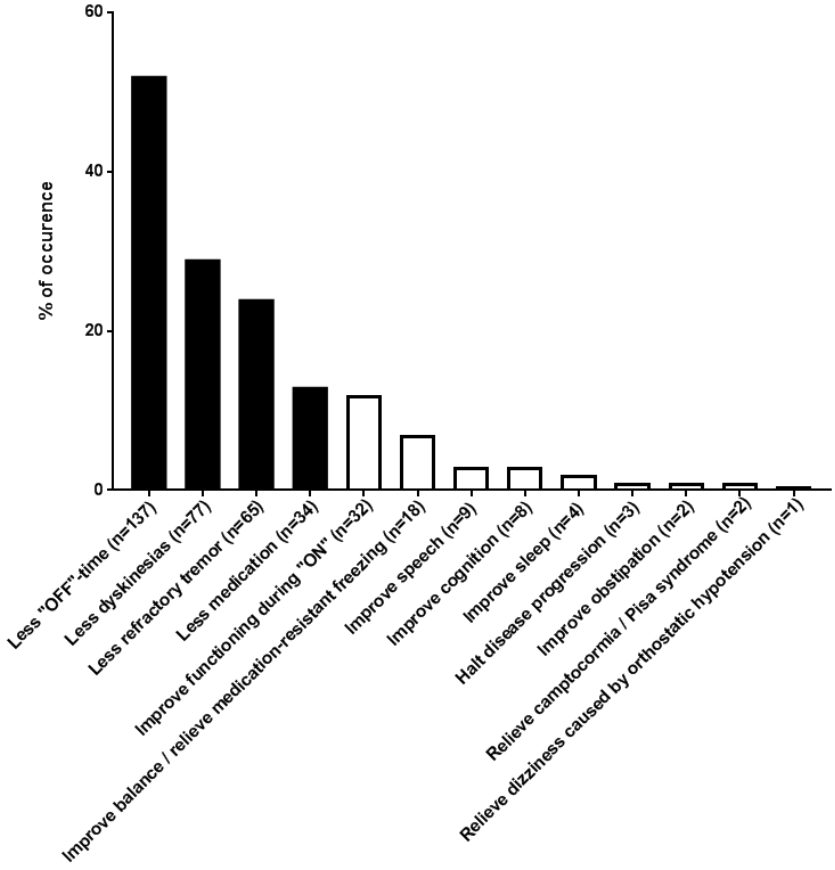

Figure 2.1. Reasons for undergoing DBS
Patient-reported reasons for undergoing DBS, classified as either realistic (black) or unrealistic (white). Data expressed as % of occurence (n). Multiple reasons were possible.

Reasons for rejection

Twenty-six percent of patients (n=76) were rejected for DBS eligibility screening (see supplementary table 2.1). The most-frequent reported reasons that contributed to rejection were sufficient control with oral dopaminergic medication or suboptimal treatment (50%, n=38), unrealistic expectations (38%, n=29), impaired balance or medication-resistant

freezing (36%, n=27), and cognitive impairment (30%, n=23).

Thirty-seven percent of rejections (n=28) were for a single reason. From these, 28% (n=21) was due to sufficient control with oral medication or suboptimal oral treatment, 4% (n=3) due to unrealistic expectations (either improvement of function during "ON", dizziness caused by orthostatic hypotension, or camptocormia), 3% (n=2) due to psychiatric comorbidity (either severe obsessive compulsive disorder prior to PD, or amphetamine-addiction), 1% (n=1) due to severe cognitive impairment, and 1% (n=1) due to medication-resistant freezing.

Contribution of DBS expectations to assessment of eligibility

Analyses were performed on pooled patient data; patients often had several indications or contraindications for surgery. The odds of acceptance for the DBS full screening were significantly reduced (after FDR correction) when balance impairment or medication-resistant freezing (OR=0.06, $p<0.001$), sufficient disease control with oral medication or suboptimal oral treatment (OR<0.01, $p<0.001$), or unrealistic expectations (OR=0.01, $p<0.001$) were present (see supplementary table 2.2). The AUC of the multivariate model without the factor 'realistic expectations of DBS' was 0.92; adding DBS-expectations to the model increased the AUC to 0.97 (see supplementary figure 2.1).

Discussion

In this study we found that the primary reason for rejection was sufficient symptom control with oral medication or suboptimal oral treatment, which contributed in 50% of rejections. Furthermore, 23% of patients referred for DBS surgery had unrealistic expectations of DBS, which was associated with rejection for the DBS screening. Our findings underscore the need to improve what referring health professionals communicate about the effect of DBS. Identification of unrealistic expectations should be an important red flag for referrals to DBS centers.

In 38% of rejections, unrealistic expectations contributed to the decision to reject, although they represented the singular reason in only 4% of rejections, indicating that unrealistic expectations often occur parallel to other contra-indications. Even when patients are good candidates for DBS on medical grounds, unrealistic expectations may result in disappointment with the results of surgery.[6-8] Clinicians should also be aware that patients might be unwilling to reveal their unrealistic expectations in order to favor the selection process, which might result in an underestimation of this issue. Although this factor is not included in current screening algorithms,[4-5] our findings show that it may contribute to better

patient-selection. Patients' needs and wishes concerning DBS-effects can easily be checked in advance and provide an opportunity for patient education and management of expectations prior to referral or screening. In clinical practice, a 'shared decision making' approach in which patients' expectations of treatment are carefully addressed is important, especially when it concerns an invasive and potentially hazardous intervention. Final eligibility is then usually determined based on both clinical grounds and the patients' preferences and desires. Lack of appropriate patient education is often the source of wrong expectations. The results of this study may indeed point to an insufficient or inadequate information procedure done by the treating neurologists. We speculate that two possible scenarios underlie this observation: 1. Patients received suboptimal information on expected outcomes of DBS by their referring neurologists, or 2. Patients received adequate information on DBS but retained unrealistic expectations nonetheless. To what degree unrealistic expectations are retained after proper patient education is unknown and persistent unrealistic desires may still cause postoperative dissatisfaction. Nevertheless, including evaluation of patients' expectations during the pre-screening appears warranted in order to rectify these expectations accordingly during the formal screening. Future studies may investigate whether improved education of both patients and referring neurologists on DBS eligibility improves referring practices, and whether extensive patient education may mitigate previously reported disappointment with DBS surgery.

It is important to notice that all factors were accurately evaluated on an individual basis by movement disorders neurologists experienced with DBS. There may be discussion on which expectations should be considered 'realistic' or 'unrealistic', as, for example, improvement of function during "ON", or improvement of camptocormia may be achieved in some patients, whereas substantial medication reduction is not always achievable.[11] A screening-procedure that is too strict or rigid may lead to withholding patients an effective treatment for at least a subset of their symptoms. Moreover, assessment of treatment-effect was based on anamnestic information rather than formal levodopa-challenge tests, which is suboptimal compared to the full screening procedure. This warrants accurate case-by-case evaluations. Indeed, some of the relative contraindications were also detected in some of the patients who were eventually selected for the full screening. Furthermore, no distinction between DBS targets such as subthalamic, pallidal or thalamic stimulation was made. The decision on DBS targets was made after the initial pre-screening based upon results of the full preoperative evaluation, including a formal levodopa challenge test, neuropsychological evaluation and MRI. For the purpose of this study, we considered improvement of all symptoms unresponsive to dopaminergic treatment (with the exception or tremor) or not directly resulting from medication-related complications to be unrealistic. Only a minority of patients were rejected for a single reason, while in most cases the reason of rejection reflected multiple features

of advanced PD, not expected to respond to DBS. The increase in accuracy of a screening-algorithm after including assessment of expectations provides a minor addition to previously reported algorithms. However, we demonstrate that the error margin of these models can be reduced by more than half and thereby constitutes a relevant addition.

With regard to suboptimal oral treatment, we speculate that patients are often referred at an earlier stage upon their own request, or as an anticipatory strategy on account of the long waiting lists. The positive results of the EARLYSTIM trial [12] may have also prompted neurologists to referring PD patients earlier, although patients without motor complications or with motor complications that can still be controlled by further optimization of medical treatment were not included in that trial. Although it has been speculated that DBS could be beneficial even in the earliest stages of the disease, DBS surgery still bears potentially serious complications, which warrants an adequate patient selection and an accurate weighing of the individual risk/benefit profile.

Strengths of our study include the multicenter design, inclusion of consecutive patients, and near-complete data. Whereas normally a retrospective design constitutes a limitation, in this case this prevented biases by providing an overview of our current clinical practice without opportunity to influence it during data-collection. However, given the retrospective design no exploration of the background of the unrealistic expectations could be performed and the effects of more extensive education on DBS eligibility cannot be estimated. Moreover, both centers reflect Dutch populations and standards of care, and our results require verification in different populations before they can be inferred on a larger scale.

We speculate that our results may contribute to improvement of the DBS referral procedure by providing practical indications for referring neurologists. We suggest incorporating assessment of DBS expectations in the screening for DBS eligibility to verify whether further patient education on the effect of DBS is required. Patients associations and neurological associations might play a role in improving information concerning DBS indications and effects among patients and their treating neurologists.

Acknowledgements
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References

1. Benabid AL, Chabardes S, Mitrofanis J, Pollak P. Deep brain stimulation of the subthalamic nucleus for the treatment of Parkinson's disease. Lancet Neurol 2009;8:67-81.
2. Martinez-Ramirez D, Okun MS. Rationale and clinical pearls for primary care doctors referring patients for deep brain stimulation. Gerontology 2014;60:38-48.
3. Coleman RR, Kotagal V, Patil PG, Chou KL. Validity and Efficacy of Screening Algorithms for Assessing Deep Brain Stimulation Candidacy in Parkinson Disease. Movement disorders clinical practice 2014;1:342-347.
4. Moro E, Schupbach M, Wachter T, et al. Referring Parkinson's disease patients for deep brain stimulation: a RAND/UCLA appropriateness study. J Neurol 2016;263:112-119.
5. Okun MS, Fernandez HH, Pedraza O, et al. Development and initial validation of a screening tool for Parkinson disease surgical candidates. Neurology 2004;63:161-163.
6. Hariz M. Fulfillment of patients' expectations is the ultimate goal of deep brain stimulation for Parkinson disease. World neurosurgery 2014;82:1037-1039.
7. Agid Y, Schupbach M, Gargiulo M, et al. Neurosurgery in Parkinson's disease: the doctor is happy, the patient less so? Journal of neural transmission Supplementum 2006:409-414.
8. Hasegawa H, Samuel M, Douiri A, Ashkan K. Patients' expectations in subthalamic nucleus deep brain stimulation surgery for Parkinson disease. World neurosurgery 2014;82:1295-1299.e1292.
9. Maier F, Lewis CJ, Horstkoetter N, et al. Patients' expectations of deep brain stimulation, and subjective perceived outcome related to clinical measures in Parkinson's disease: a mixed-method approach. J Neurol Neurosurg Psychiatry 2013;84:1273-1281.
10. Reddy P, Martinez-Martin P, Brown RG, et al. Perceptions of symptoms and expectations of advanced therapy for Parkinson's disease: preliminary report of a Patient-Reported Outcome tool for Advanced Parkinson's disease (PRO-APD). Health and quality of life outcomes 2014;12:11.
11. Almeida L, Deeb W, Spears C, et al. Current Practice and the Future of Deep Brain Stimulation Therapy in Parkinson's Disease. Seminars in neurology 2017;37:205-214.
12. Schuepbach WM, Rau J, Knudsen K, et al. Neurostimulation for Parkinson's disease with early motor complications. N Engl J Med 2013;368:610-622.

Supplementary material

Supplementary table 2.1. Reasons for rejection

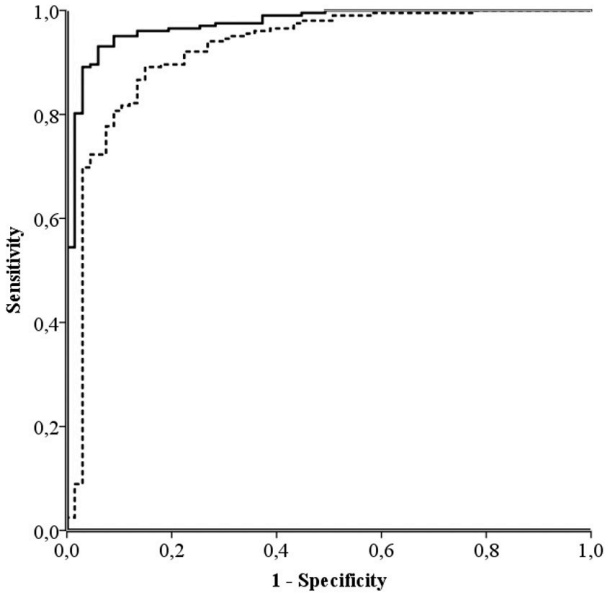
N	76
Sufficient control or suboptimal oral treatment	38 (50)
Unrealistic expectations	29 (38)
Impaired balance / freezing during on	27 (36)
Impaired cognition	23 (30)
Soft speech	14 (18)
Advanced age	10 (13)
Declined	8 (11)
Psychiatric comorbidity	7 (9)
Psychiatric side-effects	4 (5)

Data expressed as valid n (%)
Multiple reasons were possible.

Supplementary table 2.2. Likelihood of acceptance for DBS screening: multivariate analyses

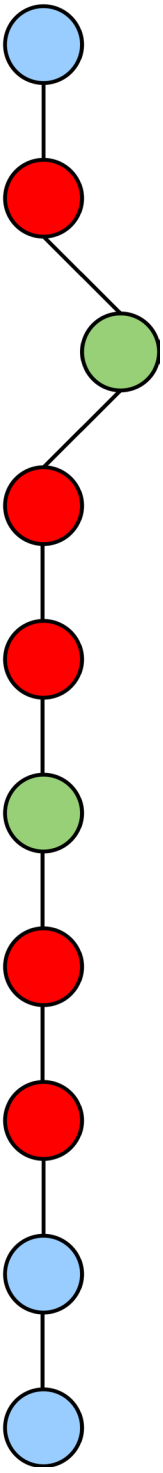
	OR[a]	95%CI	P [b]	ΔR^2 [c]	P
Age	1.02	0.95 – 1.11	0.562	0.06	0.04
Disease duration	1.13	1.01 – 1.27	0.040		
1 – 50% "OFF" [d]	0.69	0.13 – 3.57	0.656	0.13	<0.001
51 – 100% "OFF" [d]	2.71	0.35 – 20.71	0.337		
1 – 50% dyskinesias [e]	1.24	0.27 – 5.77	0.786		
51 – 100% dyskinesias [e]	3.52	0.51 – 24.38	0.202		
Refractory tremor	0.88	0.16 - 4.49	0.881		
Balance impairment / freezing during "ON"	0.06	0.02 – 0.28	<0.001	0.44	<0.001
Nonmotor side-effects	0.41	0.13 – 1.34	0.140		
Cognitive impairment	0.25	0.07 – 0.87	0.029		
Further treatment options possible	0.00	0.00 – 0.01	<0.001		
Unrealistic expectations	0.01	0.00 – 0.04	<0.001	0.17	<0.001

[a] OR to be accepted for screening
[b] Bold values indicate that significance remained after False Discovery Rate correction
[c] Nagelkerkes R^2, [d] significance of ΔR^2
[d] Relative to 'no "OFF"-time'
[e] Relative to 'no dyskinesias'
OR: Odds Ratio; 95%CI: 95% Confidence Intervals



Supplementary figure 2.1. Inclusion of DBS-expectations increases the accuracy of predicting the likelihood of acceptance for DBS screening

Dashed line: AUC model without 'realistic expectations': 0.92 (95%CI 0.88 – 0.97). Continuous line: AUC model including 'realistic expectations': 0.97 (95%CI 0.96 – 0.99). AUC: Area Under the Curve.



CHAPTER 3

What predicts Quality of Life after STN DBS in Parkinson's Disease? A systematic review

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Abstract

Background and purpose

Subthalamic deep brain stimulation (STN DBS) is an effective therapy against medication-refractory motor complications in patients with Parkinson's disease. However, it remains difficult to predict which baseline patient characteristics are associated with quality of life (QoL) after surgery. The objective was to identify preoperative factors associated with QoL after STN DBS by systematically reviewing publications of sufficient methodological quality.

Methods

Main databases were systematically searched up to March 2019 to identify studies that investigated factors associated with QoL after STN DBS in patients with idiopathic Parkinson's disease.

Results

In all, 869 studies were identified, of which 18 fulfilled the inclusion criteria. Higher QoL after DBS appears to be associated with a large preoperative difference between ON and OFF motor function in some studies, although there was no clear association of severity of motor function or motor complications with postoperative QoL. Four studies suggested that older age at surgery is associated with a lower improvement, although six other studies reported no association. No or limited evidence was found for cognitive impairment or psychiatric dysfunction.

Conclusion

Various relative contraindications for STN DBS such as cognitive impairment and psychiatric dysfunction appear to be unrelated to postoperative QoL. Lower severity of dyskinesias was associated with greater postoperative QoL improvement but has been insufficiently studied. Higher baseline QoL was suggestive of higher postoperative QoL. However, the lack of clear correlations with disease-related variables suggests that QoL may be individually influenced by other factors, indicating that an ideal preoperative patient profile with regard to QoL improvement cannot be readily provided.

Introduction

Parkinson's disease (PD) is a multisystem neurodegenerative disorder characterized by motor and non-motor symptoms that collectively contribute to decreased quality of life (QoL). Medication-related motor complications [1] occur in most patients within 10 years of medication use.[2] Subthalamic deep brain stimulation (STN DBS) is an effective therapy for patients with motor complications refractory to oral medication adjustments. STN DBS was demonstrated to be superior to best medical treatment in improving QoL.[3,4]

Traditionally, the primary outcome after STN DBS has been the improvement of motor symptoms.[5] However, motor improvement does not necessarily mirror improvement of QoL after DBS,[6,7] and some patients report dissatisfaction after surgery despite improvement of motor function.[8,9] This suggests that postoperative patient management should address other aspects that may influence individual well-being beyond motor improvement alone.[8] To date, it remains difficult to predict before surgery which patient characteristics are associated with benefit in terms of QoL improvement after STN DBS.

In order to further improve post-surgery satisfaction and QoL, and to tune the expectations of surgical candidates, more insight is needed into factors influencing postoperative QoL. Identification of such factors may help to improve patient management and provide additional information that could aid during the decision-making process for DBS eligibility.

In this systematic review, studies of sufficient methodological quality were analysed with the aim of identifying preoperative factors associated with QoL after STN DBS, and their potential utility in improving DBS screening is discussed.

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed. Eight relevant databases were systematically searched for potentially eligible studies up to 1 March 2019.

Study selection

Studies were screened on title and abstract for the following inclusion criteria: (1) separate cohorts with idiopathic PD, (2) intervention STN DBS, (3) outcome QoL scale, (4) association between preoperative factors and postoperative QoL reported, (5) follow-up duration post-DBS ≥6 months, (6) original peer-reviewed article, (7) $n \geq 10$, (8) article in English. Studies

pooling the results of STN DBS and other targets were excluded. A minimum of 6 months was chosen as the follow-up duration to account for the time involved in achieving optimal stimulation parameter settings.[10,11] Both change in QoL from baseline and postoperative QoL scores if corrected for baseline QoL were accepted as outcomes. For clarity, results from different QoL scales were pooled together unless there was a discrepancy between separate QoL scales within the same study.

Data extraction

The initial screening (title and abstract) was performed by two independent reviewers (VJG and SF); full-text screening was decided upon after mutual agreement. Risk of bias was assessed using an in-house checklist (supplementary table 3.1; range 0–21, higher scores reflecting better quality). Items from a previous standard checklist [12] were adapted to fit the specific objectives of the present review. The quality threshold for inclusion was set at 11 points; low-quality studies were excluded. Included studies were classified as medium quality (quality index (QI) 11–13), high quality (QI 14–16) and very high quality (QI ≥ 17).

Results

The search performed on 1 March 2019 yielded 869 studies. After screening of title and abstract 150 studies remained for full-text screening; 18 studies were ultimately included (figure 3.1). Interrater agreement regarding eligibility (Cohen's κ) was 0.82. All included studies are detailed in table 3.1. Studies were subdivided by follow-up to account for differences in the time course of QoL following DBS: short-term follow-up (6 months), intermediate follow-up (6 months to 5 years) and long-term follow-up (>5 years). Most studies reported an improvement in QoL, although only on a subscale level in some studies.[13-21] One study reported no change in QoL.[22]

Sociodemographic variables

One study found that higher age was associated with lower Parkinson's Disease Questionnaire 39 (PDQ39) summary index (SI) improvement at 1-year follow-up,[19] and three other studies reported negative correlations of higher age and PDQ39 subscore stigma,[15] activities of daily living (ADL),[15,17,23] mobility,[15,17] cognition,[15,17] and communication [15] in the intermediate follow-up. Six different studies found no association between age and postoperative QoL, regardless of follow-up (0.5–6 years).[13,14,18,21,24,25]

Sex [18,19,21,24,26] and education [24] were not significantly associated with postoperative QoL (0.5–6 years' follow-up) (figure 3.2).

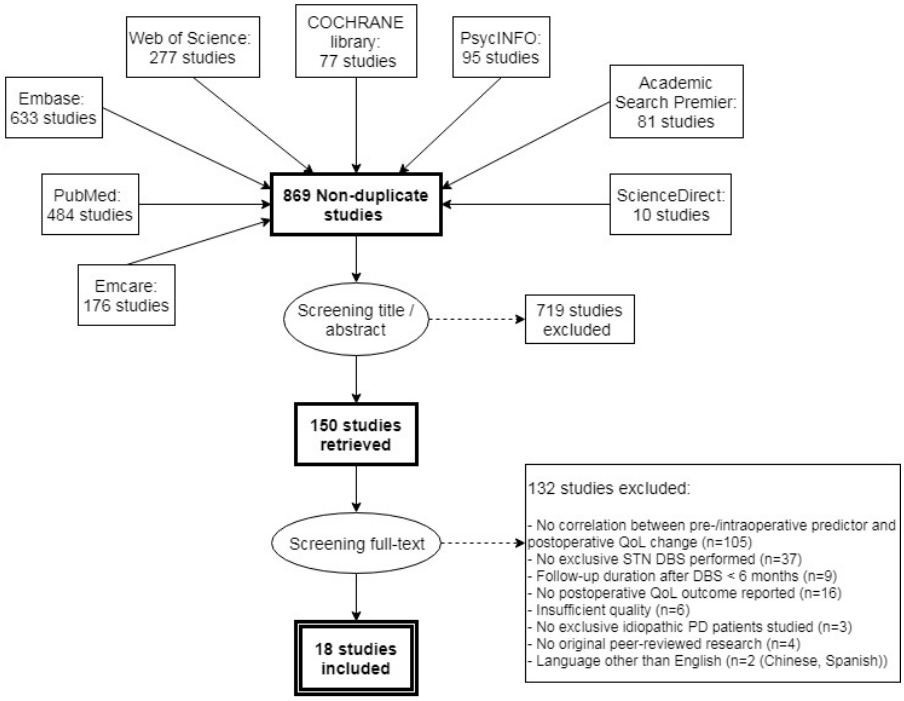

Figure 3.1. PRISMA flow diagram of selected studies
Several studies had multiple reasons for exclusion.

Clinical variables

The amount of Unified Parkinson's Disease Rating Scale Part III (UPDRS III) improvement after a dopamine challenge test correlated positively with the PD QoL scale (PDQL) improvement (1-year follow-up),[27] although this effect was not observed on the PDQ39 and Short Form 36 (SF36) scales in three different studies (0.5–2 years' follow-up).[14,24,25] A higher Hoehn and Yahr (HY) stage was associated with greater QoL improvement at 1-year follow-up,[24] whereas UPDRS III scores (either ON or OFF) were not associated with postoperative QoL change in four studies with 1–6 years' follow-up.[14,18,24,25]

Lower baseline dyskinesia scores (UPDRS IV) were associated with greater improvement in SF36 Physical Health (PH) scores at 0.5 years' follow-up but not with PDQ39 SI and SF36 Mental Health (MH) scores.[14] At 6 years' follow-up, lower baseline dyskinesia scores were associated with greater PDQ39 SI improvement.[18] In contrast, cumulative daily OFF time before surgery correlated positively with improvement in PDQ39 SI (but not with SF36 scores),[14] and severity of motor complications in general was not associated with QoL change at 2–6 years' follow-up.[18,25]

Table 3.1. Selected studies

Reference	N (PD)	Mean Age (years)	Follow-up (years)	Electrode placement	Outcome	Type of outcome	QoL improved?	QI	Comments
Bargiotas 2017 et al [30]	74	62.2	1	STN (unspecified)	PDQ39, SF36 MH / PH	Change from baseline	Yes	**	
Chandran 2014 et al [26]	51	55.3	1	Bilat. STN	PDQL[a]	Change from baseline	Yes	*	
Dafsari 2018 et al [13]	120	62.1	0.5	Bilat. STN	PDQ8	Change from baseline	Partly	***	Improvement of PDQ8 subscales depended on age
Daniels 2011 et al [14]	60	59.7	0.5	STN (unspecified)	PDQ39, SF36 MH / PH	Change from baseline	Partly	**	57% of patients reached the threshold for PDQ39-improvement (at least 10.9 points).
Derost 2007 et al [15]	57	61.9	0.5 / 1 / 2	Bilat. STN	PDQ39[a]	Change from baseline	Partly	**	QoL only improved in 'young' patients; stabilization or worsening of QoL in 'old' patients
Erola 2005 et al [23]	29	59.5	1	Bilat. STN	PDQ39[a]	Change from baseline	Yes	*	
Floden 2015 et al [29]	106	62.4	0.5	Uni- and bilat. STN	PDQ39	Change from baseline	Yes	*	
Frizon 2018 et al [21]	67	62.8	0.75	Uni- and bilat. STN	PDQ39	Change from baseline	Partly	**	Some, but not all, patients were classified as 'improvers' in terms of QoL
Hasegawa 2014 et al [28]	19	59.8	0.5	Bilat. STN	PDQ39	Change from baseline	Yes	**	
Katz 2015 et al [22]	108	?	2	Bilat. STN	PDQ39	Change from baseline	No	***	
Lezcano 2016 et al [16]	69	61.3	5	Bilat. STN	PDQ39	Absolute scores	Partly	***	Several, but not all, PDQ39 subscales improved.
Liu 2018 et al [24]	45	61.8	1	Bilat. STN	PDQ39	Change from baseline	Yes	**	
Ory-Magne 2007 et al [17]	45	60.1	1 / 2	Bilat. STN	PDQ39	Change from baseline	Partly	**	Several, but not all, PDQ39 subscales improved.
Schüpbach 2019 et al [25]	124	52.9	2	Bilat. STN	PDQ39	Change from baseline	Not reported	**	This article did not report whether QoL improved; however a different paper on the same cohort reported improved QoL after DBS STN.[4]
Siderowf 2006 et al [18]	18	57.3	0.5 / 6	Bilat. STN	PDQ39[a]	Change from baseline	Partly	**	Several, but not all, PDQ39 subscales improved.

Table 3.1. continued

Reference	N (PD)	Mean Age (years)	Follow-up (years)	Electrode placement	Outcome	Type of outcome	QoL improved?	QI	Comments
Smeding 2011 et al [27]	105	58.4	1	Bilat. STN	PDQL	Change from baseline	Yes	**	
Soulas 2011 et al [19]	41	62	0.5 / 1	STN (unspecified)	PDQ39, SF36 MH / PH	Absolute scores	Partly	**	Improvement of PDQ39 and SF36 PH, but not SF36 MH.
Witt 2011 et al [20]	60	60	0.5	STN (unspecified)	PDQ39[a]	Change from baseline	Partly	*	Improvement of QoL depended on cognition

[a] Including subdomains.
QI (quality index): *** ≥ 17; ** QI 14-16; * QI ≤ 11-13
PDQ39 / 8: Parkinson's Disease Questionnaire 39 / 8; PDQL: Parkinson's Disease Quality of Life questionnaire; SF36: Short Form 36 health form; MH: mental health component; PH: physical health component;
Bilat.: bilateral electrode placement; STN: Subthalamic Nucleus; QoL: Quality of Life; Unilat.: unilateral electrode placement.

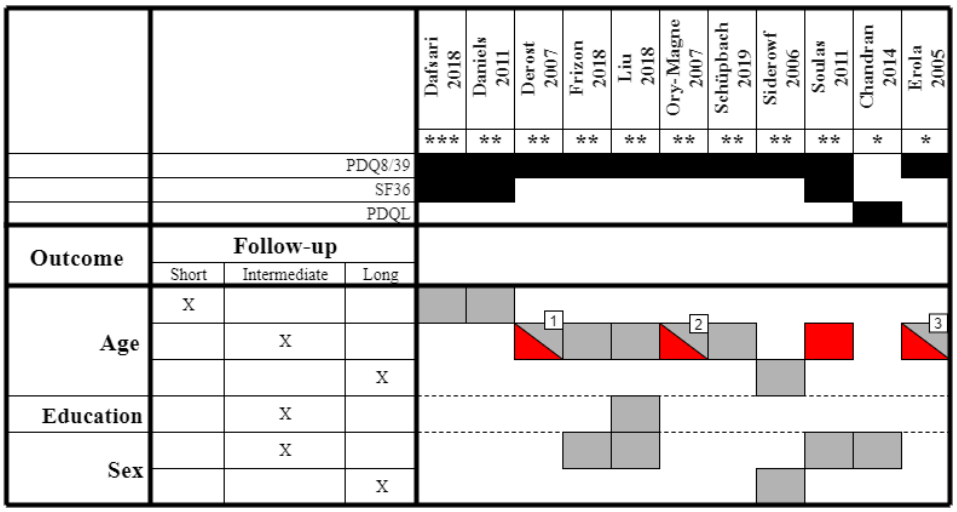

Figure 3.2. Demographic factors associated with QoL after DBS

Red box: significant negative association with QoL. Grey box: no significant association. Dual-shaded boxes indicate discrepancy between different (sub)scales used in the study.

[1] Significant negative association between age and subscales stigma, ADL, mobility, and cognition, but not with other PDQ39 subscales.

[2] Significant negative association between age and ADL, mobility, and cognition, but not with other PDQ39 subscales.

[3] Significant negative association between age and ADL, but not with other PDQ39 subscales.

Short-term follow-up (FU): 6 months; intermediate follow-up: 6 months – 5 years; long-term follow-up: > 5 years. Asterisks indicated quality index (QI): * medium quality (QI 11-13), ** high quality (QI 14-16), *** very high quality (QI ≥ 17). Studies are sorted based on their QI (highest quality on the left). Scales used to determine QoL are denoted below the studies. Factors are sorted in alphabetical order.

PDQ8/39: Parkinson's Disease Questionnaire 8/39; PDQL: Parkinson's Disease Quality of Life questionnaire; SF36: Short Form 36 health form.

Preoperative use of dopaminergic medication yielded contrasting results, with one study demonstrating that higher levodopa equivalent dosage (LED) was associated with a higher odds of being a 'responder' in terms of higher postoperative PDQ39 scores [21] contrasted by a different study with a similar follow-up duration (approximately 1 year) and similar LED that reported a negative association of LED with QoL improvement.[24] Two studies found no association of baseline medication use and QoL change, regardless of follow-up (0.5–6 years).[14,18] Other treatment variables and disease characteristics were not associated with QoL change (figure 3.3).

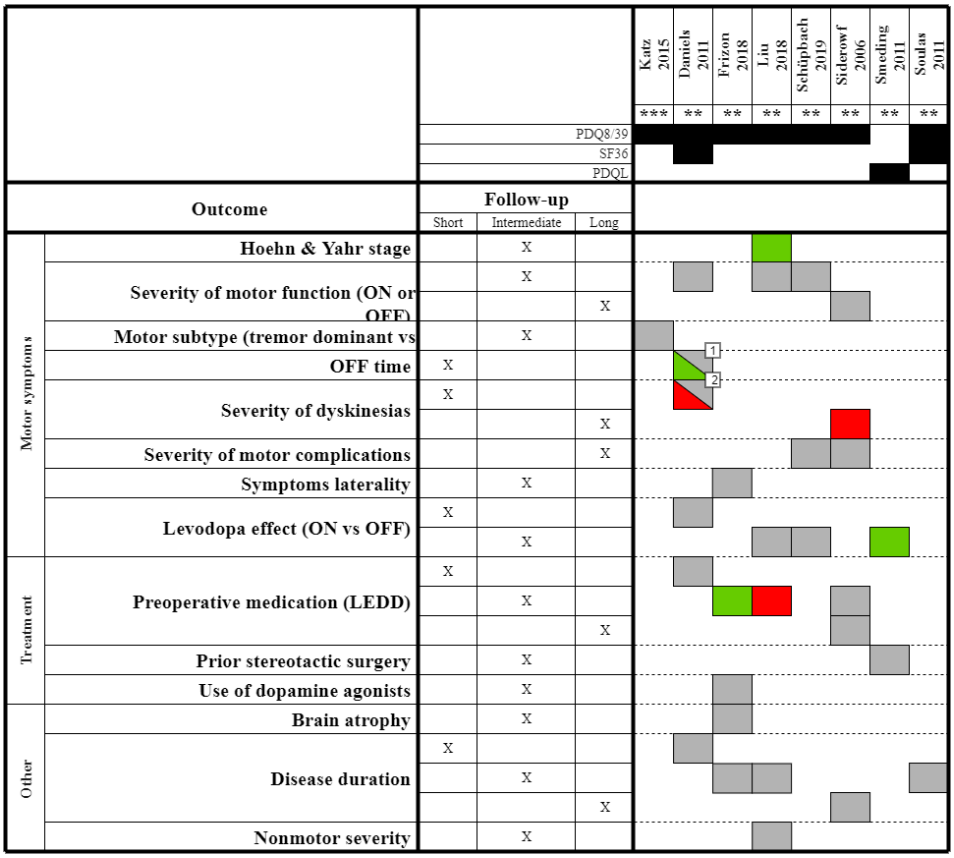

Figure 3.3. Preoperative clinical factors associated with QoL after DBS

Green box: significant positive association with Quality of Life (QoL) (either improvement of QoL or higher postoperative score). Red box: significant negative association with QoL. Grey box: no significant association. Dual-shaded boxes indicate discrepancy on between different (sub)scales used in the study.

[1] Significant positive association between cumulative daily OFF time and PDQ39, but not with SF36 mental health or physical health scores.

[2] Significant negative association between severity of dyskinesias and SF36 physical health, but not with PDQ39 or SF36 mental health.

Short-term follow-up (FU): 6 months; intermediate follow-up: 6 months – 5 years; long-term follow-up: > 5 years. Asterisks indicated quality index (QI): ** high quality (QI 14-16), *** very high quality (QI ≥ 17). Studies are sorted based on their QI (highest quality on the left). Scales used to determine QoL are denoted below the studies. Factors are sorted in alphabetical order.

LEDD: levodopa equivalent dose; PDQ8/39: Parkinson's Disease Questionnaire 8/39; PDQL: Parkinson's Disease Quality of Life questionnaire; PIGD: Postural-Instability-and-Gait-Difficulty; SF36: Short Form 36 health form

Psychosocial variables

Baseline QoL scores were positively correlated with PDQ39 improvement in three studies (1- to 5-year follow-up),[16,24,25] whereas one study with 1-year follow-up found that patients with worse baseline QoL had a higher odds of becoming a 'responder' in terms of PDQ39

improvement after STN DBS.[21] At 6 years' follow-up, baseline QoL was not significantly associated with postoperative PDQ39 SI change.[18] The preoperatively self-reported expected improvement in QoL (i.e. expected change in PDQ39 SI) correlated positively with actual improvement in PDQ39 SI at 0.5 years' follow-up.[28]

Cognition, usually assessed with the Mattis Dementia Rating Scale (MDRS) (one study used the Mini-Mental State Examination),[24] was only associated with QoL change at 0.5 years' follow-up in one study: the lowest quartile (MDRS 130–137, i.e. greater cognitive impairment) had significantly lower improvement of PDQ39 scores after 6 months compared to the three higher quartiles.[20] Six studies found no association of cognition and QoL change, regardless of follow-up duration (0.5–2 years).[14,19,24,25,27,29]

Psychiatric dysfunction, such as anxiety (Becks Anxiety Inventory or State-Trait Anxiety Inventory),[14,19] apathy (Starkstein Apathy Scale),[30] and depression (Becks Depression Inventory),[14,19,21,24,25] was not associated with QoL change in any study regardless of follow-up duration (0.5–2 years).

One study found that the extent to which a coping strategy focused on social support was used (Ways of Coping Checklist Revised) was negatively correlated with SF36 MH at 1 year (a focus on social support resulted in lower QoL) but not with PDQ39 SI or SF36 PH. No correlation was found for other coping strategies.[19] Various aspects of sleep metrics (Fatigue Severity Scale, Epworth Sleepiness Scale and sleep efficiency as part of the Multiple Sleep Latency Test) were not predictive of QoL outcomes at 1-year follow-up (figure 3.4).[30]

Discussion

The present systematic review included 18 studies of sufficient methodological quality that examined factors associated with QoL after STN DBS.

There is no evidence to support using sociodemographic factors to predict QoL after DBS. Four studies suggested that older age at surgery is associated with a lower improvement of QoL after intermediate follow-up, although six other studies reported no association. The inconsistency of the results points against the use of calendar age as a predictor of postoperative QoL.

A good preoperative response to levodopa is considered indicative of postoperative motor improvement,[31] and indeed a larger preoperative difference in motor scores between ON

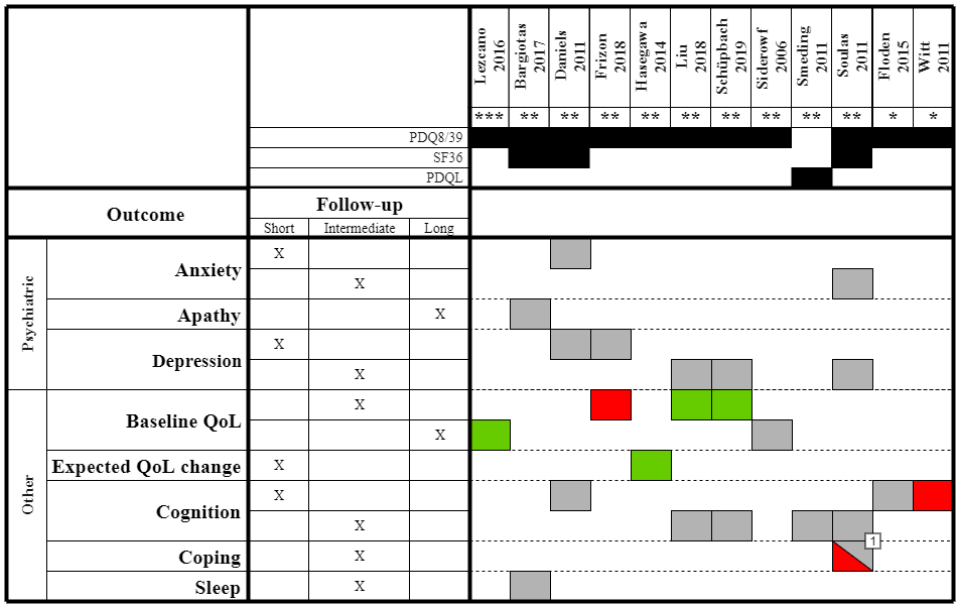

Figure 3.4. Preoperative psychosocial factors associated with QoL after DBS
Green box: significant positive association with Quality of Life (QoL) (either improvement of QoL or higher postoperative score). Red box: significant negative association with QoL. Grey box: no significant association. Dual-shaded boxes indicate discrepancy on between different (sub)scales used in the study.
[1] Significant negative association between a coping strategy focussed on social support and SF36 mental health, but not with PDQ39 or SF36 physical health.
Short-term follow-up (FU): 6 months; intermediate follow-up: 6 months – 5 years; long-term follow-up: > 5 years. Asterisks indicated quality index (QI): * medium quality (QI 11-13), ** high quality (QI 14-16), *** very high quality (QI ≥ 17). Studies are sorted based on their QI (highest quality on the left). Scales used to determine QoL are denoted below the studies. Factors are sorted in alphabetical order.
PDQ8/39: Parkinson's Disease Questionnaire 8/39; PDQL: Parkinson's Disease Quality of Life questionnaire; SF36: Short Form 36 health form.

and OFF states was significantly associated with better postoperative QoL in one large study ($n = 105$).[27] However, this finding was not confirmed in three other studies (of comparable size and quality). A possible explanation for this discrepancy is that Smeding *et al.*[27] used the PDQL scale to assess QoL, whereas the three studies that found no significant association used the PDQ39. The PDQL scale places greater emphasis on the motor aspects of QoL and is therefore more likely to pick up correlations with motor alterations following DBS, in contrast to the PDQ39 which focuses least on motor items. The actual level of motor severity was not associated with QoL, independent of follow-up.[14,18,22,24,25] The association of motor fluctuations with postoperative QoL remains unclear. More OFF time at baseline influenced several QoL subscales positively at short-term follow-up,[14] but severity of motor fluctuations in general was not associated with postoperative QoL at 6 years' follow-up.[18] This suggests that an initial

beneficial effect of improvements in motor fluctuations on QoL (i.e. a sudden gain in ON time increases short-term postoperative QoL) is lost in the long term, when other factors may be more relevant in determining QoL. Patients with greater severity of dyskinesias at baseline demonstrated smaller improvements on several QoL subscales at short-term follow-up [14] and with QoL after 6 years.[18] Whilst dyskinesias may be a source of stigma,[1] growing evidence shows that patients are less bothered by dyskinesias than by other symptoms as they are often unaware of the extent of their dyskinesias.[32] A potential limitation of all included studies is the use of the UPDRS to quantify dyskinesias, whereas the Unified Dyskinesia Rating Scale may be more appropriate. This might have led to an underestimation of the role of dyskinesias in determining QoL. Careful examination of the association between QoL and detailed assessments of dyskinesias is a potential target for future studies.

As preoperative dyskinesias may be associated with high LED, the positive psychotropic effects generated by LED may be substantially reduced following STN DBS resulting in lower responses on QoL scales. However, this effect can only explain the negative correlation in the short-term follow-up but not at 6 years' follow-up. Additionally, only one study showed a negative correlation between LED and change in QoL after surgery whereas three other studies found either no association or a positive correlation of change in LED and change in QoL after surgery.[14,18,24] Given that motor complications constitute an important reason to perform STN DBS,[34] the association of these factors with postoperative QoL needs to be further elucidated.

The only factors positively correlated with postoperative QoL improvement were preoperative expected QoL change and baseline QoL, although the latter was not consistent throughout all studies. Several hypotheses may underlie these observations, such as dispositional optimism (i.e. a higher baseline QoL may suggest better social functioning and a more active approach towards social reintegration) or an easier compliance to postoperative changes in ADL. One study reported an association between a greater likelihood of being a 'responder' in terms of postoperative QoL and lower baseline QoL,[21] which is possibly caused by a regression-to-the-mean phenomenon.

Although cognitive dysfunction and psychiatric disturbances are considered relative contraindications for DBS surgery,[31] the available literature demonstrates that these factors are not related to postoperative QoL. Only one study suggested a negative association of MDRS scores at group level with QoL improvement (i.e. the lowest quartile had less QoL improvement),[20] contrasted by results from a different study with a similar MDRS group composition that found no association, although the within-group composition of the lowest quartile in particular may have differed.[29] In the first study, there were significant differences

in other cognitive tests between the MDRS quartiles at baseline, whereas these differences were not observed in the latter study, indicating that other cognitive tests may have better potential for predicting postoperative QoL than MDRS. Moreover, no linear correlation was found between MDRS scores and either QoL scores or QoL improvement.[14,24,25] The limited variability in cognitive scores may explain the absence of a linear trend, suggesting that the MDRS may not be appropriate to predict QoL post-DBS. Likewise, preoperative psychiatric disturbances such as depression and anxiety were not associated with postoperative QoL.[14,19,21,24,25] As no results are available on more severe cognitive or psychiatric dysfunction, it is emphasized that these findings should not be extrapolated to patients with clinically significant cognitive deterioration or psychosocial disturbances.

Strengths include the use of the PRISMA guidelines, a systematic literature search and assessment of methodological quality. Due to the scarcity of relevant studies, differences in QoL instruments were disregarded, despite variations in content and responsiveness of individual instruments.[33] Furthermore, several studies were excluded due to a follow-up duration of less than 6 months or not exclusively examining QoL after STN DBS. A brief examination of the results of these studies revealed no new insights.

The association between preoperative predictors and QoL may differ per QoL subscale, which limits comparability between studies. Several included studies indeed suggested that outcomes were dependent on the type of QoL metric.[14,30] Both the PDQ39/8 and PDQL have been developed and validated specifically for PD patients, whereas the generic SF36 scale allows for comparability with other diseases. Given that the emphasis within the respective scales lies on different domains, caution is advised when comparing results between different scales, although most studies included in this review using SF36 also used PDQ39/8.

Most studies reported correlation coefficients whereas two studies addressed clinically relevant differences.[16,21] As the minimal clinically important difference for PDQ39 SI has been previously established,[34] it is recommended that future study designs incorporate this. Moreover, most studies applied univariate analyses. Although potentially useful for the identification of relevant variables, multivariate models are required to accurately model QoL improvements, particularly given the multidimensional nature of QoL assessments.

Should one or more factors consistently be related to postoperative QoL, it would be worth evaluating them in the screening stage for DBS and discussing them with DBS candidates. Unfortunately, none of the findings has been replicated in multiple studies with at least intermediate follow-up, and thus the available data are currently insufficient to suggest changes in clinical practice.

The lack of consensus between studies and the ambiguity of the mechanism behind the observations suggests that QoL may be influenced more by other (yet unstudied) factors. Although social adjustment is frequently associated with QoL in the general PD population and plays an important role during the pre- and post-surgical management of DBS patients,[8] this factor is not studied in depth so far and should be considered in terms of the prediction of postoperative QoL. Moreover, whether preoperative expectations of DBS surgery were met postoperatively [35] has never been studied with regard to QoL change. This review further demonstrates that QoL may be highly heterogeneous and individually determined, as well as scale dependent. An ideal preoperative patient profile with regard to postoperative QoL cannot be readily provided yet. Future studies may identify novel factors that contribute more to modelling the prediction of postoperative QoL.

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References

1. Chapuis S, Ouchchane L, Metz O, et al. Impact of the motor complications of Parkinson's disease on the quality of life. Mov Disord 2005; 20: 224–230.
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, Schade-Brittinger C, Krack P, et al. A randomized trial of deep-brain stimulation for Parkinson's disease. N Engl J Med 2006; 355: 896–908.
4. Schüpbach WM, Rau J, Knudsen K, et al. Neurostimulation for Parkinson's disease with early motor complications. N Engl J Med 2013; 368: 610–622.
5. Charles PD, Van Blercom N, Krack P, et al. Predictors of effective bilateral subthalamic nucleus stimulation for PD. Neurology 2002; 59: 932–934.
6. Floden D, Cooper SE, Griffith SD, et al. Predicting quality of life outcomes after subthalamic nucleus deep brain stimulation. Neurology 2014; 83: 1627–1633.
7. Agid Y, Schüpbach M, Gargiulo M, et al. Neurosurgery in Parkinson's disease: the doctor is happy, the patient less so? J Neural Transm Suppl 2006; 409–414.
8. Schüpbach M, Gargiulo M, Welter ML, et al. Neurosurgery in Parkinson disease: a distressed mind in a repaired body? Neurology 2006; 66: 1811–1816.
9. Geraedts VJ, van Hilten JJ, Marinus J, et al. Stimulation challenge test after STN DBS improves satisfaction in Parkinson's disease patients. Parkinsonism Relat Disord 2019; 69: 30–33.
10. Pourfar MH, Mogilner AY, Farris S, et al. Model-based deep brain stimulation programming for Parkinson's disease: the GUIDE Pilot Study. Stereotact Funct Neurosurg 2015; 93: 231–239.
11. Morishita T, Inoue T. Need for multiple biomarkers to adjust parameters of closed-loop deep brain stimulation for Parkinson's disease. Neural Regen Res 2017; 12: 747–748.
12. Marinus J, Zhu K, Marras C, et al. Risk factors for non-motor symptoms in Parkinson's disease. Lancet Neurol 2018; 17: 559–568.
13. Dafsari HS, Reker P, Stalinski L, et al. Quality of life outcome after subthalamic stimulation in Parkinson's disease depends on age. Mov Disord 2018; 33: 99–107.
14. Daniels C, Krack P, Volkmann J, et al. Is improvement in the quality of life after subthalamic nucleus stimulation in Parkinson's disease predictable? Mov Disord 2011; 26: 2516–2521.
15. Derost PP, Ouchchane L, Morand D, et al. Is DBS-STN appropriate to treat severe Parkinson disease in an elderly population? Neurology 2007; 68: 1345–1355.
16. Lezcano E, Gomez-Esteban JC, Tijero B, et al. Long-term impact on quality of life of subthalamic nucleus stimulation in Parkinson's disease. J Neurol 2016; 263: 895–905.
17. Ory-Magne F, Brefel-Courbon C, Simonetta-Moreau M, et al. Does ageing influence deep brain stimulation outcomes in Parkinson's disease? Mov Disord 2007; 22: 1457–1463.
18. Siderowf A, Jaggi JL, Xie SX, et al. Long-term effects of bilateral subthalamic nucleus stimulation on health-related quality of life in advanced Parkinson's disease. Mov Disord 2006; 21: 746–753.

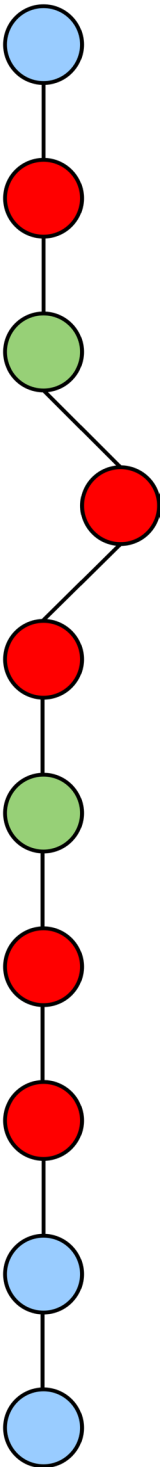
19. Soulas T, Sultan S, Gurruchaga JM, et al. Depression and coping as predictors of change after deep brain stimulation in Parkinson's disease. World Neurosurg 2011; 75: 525–532.
20. Witt K, Daniels C, Krack P, et al. Negative impact of borderline global cognitive scores on quality of life after subthalamic nucleus stimulation in Parkinson's disease. J Neurol Sci 2011; 310: 261–266.
21. Frizon LA, Hogue O, Achey R, et al. Quality of life improvement following deep brain Parkinson's disease: development of a prognostic model. Neurosurgery 2018.
22. Katz M, Luciano MS, Carlson K, et al. Differential effects of deep brain stimulation target on motor subtypes in Parkinson's disease. Ann Neurol 2015; 77: 710–719.
23. Erola T, Karinen P, Heikkinen E, et al. Bilateral subthalamic nucleus stimulation improves health-related quality of life in parkinsonian patients. Parkinsonism Relat Disord 2005; 11: 89–94.
24. Liu FT, Lang LQ, Yang YJ, et al. Predictors to quality of life improvements after subthalamic stimulation in Parkinson's disease. Acta Neurol Scand 2018;139:346-352.
25. Schüpbach WMM, Tonder L, Schnitzler A, et al. Quality of life predicts outcome of deep brain stimulation in early Parkinson disease. Neurology 2019; 92: e1109–e1120.
26. Chandran S, Krishnan S, Rao RM, et al. Gender influence on selection and outcome of deep brain stimulation for Parkinson's disease. Ann Indian Acad Neurol 2014; 17: 66–70.
27. Smeding HM, Speelman JD, Huizenga HM, et al. Predictors of cognitive and psychosocial outcome after STN DBS in Parkinson's disease. J Neurol Neurosurg Psychiatry 2011; 82: 754–760.
28. Hasegawa H, Samuel M, Douiri A, et al. Patients' expectations in subthalamic nucleus deep brain stimulation surgery for Parkinson disease. World Neurosurg 2014; 82: 1295–1299.e2.
29. Floden D, Busch RM, Cooper SE, et al. Global cognitive scores do not predict outcome after subthalamic nucleus deep brain stimulation. Mov Disord 2015; 30: 1279–1283.
30. Bargiotas P, Eugster L, Oberholzer M, et al. Sleep–wake functions and quality of life in patients with subthalamic deep brain stimulation for Parkinson's disease. PLoS One 2017; 12: e0190027.
31. Lang AE, Houeto JL, Krack P, et al. Deep brain stimulation: preoperative issues. Mov Disord 2006; 21(Suppl 14): S171–96.
32. Chaudhuri KR, Jenner P, Antonini A. Should there be less emphasis on levodopa-induced dyskinesia in Parkinson's disease? Mov Disord 2019; 34: 816–819.
33. Marinus J, Ramaker C, van Hilten JJ, et al. Health related quality of life in Parkinson's disease: a systematic review of disease specific instruments. J Neurol Neurosurg Psychiatry 2002; 72: 241–248.
34. Horvath K, Aschermann Z, Kovacs M, et al. Changes in quality of life in Parkinson's disease: how large must they be to be relevant? Neuroepidemiology 2017; 48: 1–8.
35. Geraedts VJ, Kuijf ML, van Hilten JJ, et al. Selecting candidates for deep brain stimulation in Parkinson's disease: the role of patients' expectations. Parkinsonism Relat Disord 2019; 66: 207–211.

Supplementary material

Supplementary table 3.1 Risk of bias assessment

No.	Criteria	Requirements	Score
1	Study objectives	0. The objectives are not clearly stated. 1. The objectives are clearly stated.	
2	Study design	0. The study design is not clearly stated. 1. The study design is clearly stated.	
3	Characteristics of studied population	0. The studied population's characteristics are not clearly described. 1. Gender, age, disease duration, UPDRS (or equivalent CISI-PD) or H&Y are described. 2. Gender, age, disease duration UPDRS (or equivalent CISI-PD) and H&Y are described.	
4	Characteristics of the non-responders, excluded ones or responders with missing data	0. The characteristics of the non-responders or excluded ones are not described. 1. Gender and age of the non-responders or excluded ones are described. 2. Gender, age and disease duration of the non-responders or excluded ones are described.	
5	Sampling method for recruitment of study population	0. The sampling method for recruitment of the study population is not appropriately described. 1. The location(s) and the type of institution where study population is recruited are mentioned. 2. The location(s), type of institution, and amount of approached individuals are mentioned.	
6	Sample size	0. < 50 PD patients. 1. 50-100 PD patients. 2. > 100 PD patients.	
7	Choice of the instrument to assess the concerned domain is justified.	0. No justification of the choice of the instrument is given. 1. The choice of instrument is justified or the instrument is validated to assess the domain in PD. 2. The choice of instrument is justified and instrument is validated to assess the domain in PD.	
8	Selection of independent variables justified	0. The choice of < 50% of the independent variables is clearly justified. 1. The choice of 50- 70% of the independent variables is clearly justified. 2. The choice of 70-100% of the independent variables is clearly justified.	
9	Comprehensible statistical methods	0. The statistical methods applied are not comprehensible. 1. The statistical methods applied are comprehensible.	
10	Main factors associated with the concerned domain	0. Main factors associated with the concerned domain are not clearly stated. 1. The main factors associated with concerned domain are clearly stated. 2. The main factors associated with concerned domain are clearly stated and quantified, and described with a quantitative associated value (e.g. R^2).	
11	Agreement / disagreement with other studies	0. Agreements of findings from previous studies are not clearly described. 1. Agreements or discrepancies of findings from previous studies are clearly described. 2. Agreements and discrepancies of findings from previous studies are clearly described.	
12	Strengths / limitations	0. The limitations of the study are not clearly described. 1. The strengths or limitations of the study are clearly described. 2. The strengths and limitations of the study are clearly described.	
		Total quality score	

Modified from: Marinus J, Zhu K, Marras C, Aarsland D, van Hilten JJ. Risk factors for non-motor symptoms in Parkinson's disease. Lancet Neurol 2018;17:559-568.



CHAPTER 4

Intraoperative test stimulation of the subthalamic nucleus aids postoperative programming of chronic stimulation settings in Parkinson's disease

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Abstract

Background

It is unknown whether intraoperative testing during awake Deep Brain Stimulation (DBS) of the subthalamic nucleus (STN) can be used to postoperatively identify the best settings for chronic stimulation.

Objective

To determine whether intraoperative test stimulation is indicative of postoperative stimulation results.

Methods

Records of consecutive Parkinson's Disease patients who received STN DBS between September 2012 and December 2017 were retrospectively analyzed. The best depth identified after intraoperative stimulation via the microelectrode's stimulation tip was compared with the depth of the contact selected for chronic stimulation after a standard monopolar contact review. Moreover, thresholds for induction of clinical effects (optimal improvement of rigidity and induction of side-effects) were compared between stimulation at the postoperatively selected contact and at the corresponding intraoperative depth.

Results

Records of 119 patients were analyzed (mean (SD) age 60.5 (6.5) years, 31.9% female, 238 STNs). In 75% of cases, the postoperatively selected contact corresponded with the intraoperative depth with the largest therapeutic window or was immediately dorsal to it. Higher stimulation intensities were required postoperatively than intraoperatively to relieve rigidity ($p=0.002$) and induce capsular side-effects ($p=0.016$).

Conclusion

In the majority of cases, the postoperative contact for chronic stimulation was at a similar level or immediately dorsal with respect to the identified best intraoperative depth. Postoperatively, relief of rigidity and induction of capsular side-effects occur at higher stimulation intensities than during intraoperative test stimulation.

Introduction

Deep Brain Stimulation (DBS) of the subthalamic nucleus (STN) is an effective treatment to improve Parkinson's Disease (PD) symptoms and quality of life.[1-3] Optimal placement of DBS leads is required to induce maximal motor improvement at low stimulation intensities, with high thresholds for stimulation-induced side-effects.[4] During surgery, simultaneous microelectrode recording (MER) tracks may optimize target localization by identifying typical STN electrical activity.[5-6] Moreover, test stimulation with the microelectrode tip can help identifying the best location for the definitive lead by assessing both motor improvements and stimulation-induced side-effects.[7]

During the early postoperative period, a monopolar contact review is generally performed to identify the best contact for chronic stimulation.[8] This time-consuming procedure is in our experience often poorly tolerated by patients.

It is unknown if the results of intraoperative testing are indicative of postoperative stimulation settings. The aim of this study was to investigate how the results of intraoperative testing compare to results of the postoperative contact review. This knowledge could ultimately make postoperative testing more efficient and less burdensome to patients.

Methods

All consecutive PD patients who received STN DBS at the Haga Teaching Hospital / Leiden University Medical Center between September 2012 and December 2017, with available records of intraoperative and postoperative test stimulation procedures, were retrospectively analyzed. The local Medical Ethics Committee waived formal evaluation of this study.

Surgical procedure

Surgery was performed with standard techniques (see supplementary material).[2, 9] Stereotactic frame-based 3D MRI was used for visually-adjusted targeting. Surgery was performed bilaterally, with patients awake, withdrawn from dopaminergic medication and sedatives. Two to four microelectrodes were inserted simultaneously ("Ben Gun"). Intraoperative stimulation was performed from the cannula tip. Permanent leads were implanted and centered along the best trajectory and depth, with the deepest contact not below the substantia nigra.

Intraoperative stimulation

Test stimulation with 60 µs and 130 Hz was performed with constant current at several depths with at least 2-mm distance along selected trajectories inside the STN. Mostly, 3 data-points per track were collected within the STN. Baseline symptom-severity was scored with the Unified Parkinson's Disease Rating Scale (UPDRS) items 20-22-23 prior to MER electrodes placement. Intensity was increased stepwise starting at 1 mA with 0.5 mA steps until debilitating side-effects appeared. Improvement of rigidity, tremor, and bradykinesia was recorded on standardized forms; only rigidity was used to reflect clinical improvement for purposes of accuracy and reliability. All persistent and debilitating side-effects were classified as either capsular (muscle twitching, dysarthria, gaze paresis) or non-capsular (diplopia, paresthesias, nausea, general discomfort), and dyskinesias. Other side-effects were transient (including paresthesias) or considered non-debilitating.

Aiming at maximum clinical benefit and enhancing comparability, the therapeutic window was defined as the difference between the required amplitude for obtaining maximal improvement of rigidity (UPDRS 0/1) and the threshold for inducing debilitating side-effects. When 'stun effects' relieved PD symptoms making scoring unreliable, or if no side-effects up to ≥4 mA, no therapeutic window was defined. If insufficient improvement, the therapeutic window was set at 0.

Postoperative macrostimulation

Postoperative monopolar contact review was performed by the same neurologist who performed the intraoperative examination, ±10 days after surgery when the device was switched on for the first time. Although unblinded, data from intraoperative stimulation was not used during the postoperative contact review. When directional leads were implanted, a standard omnidirectional monopolar contact review was performed at all levels. The procedure of the postoperative contact review was similar to the intraoperative test stimulation, except that conjugated eye movements were not systematically tested. The definitive contact for chronic stimulation was chosen based on the lowest threshold for optimal benefit or on the largest therapeutic window, at the physician's discretion.

Outcome measures

The postoperatively selected contacts and the contacts used at one-year follow-up were matched to corresponding intraoperative microstimulation depths, as previously described elsewhere.[2] In case of bipolar settings, the cathode was selected; in case of double monopolar settings, the middle was selected.

The best intraoperative depth was defined in two ways: the depth with the largest therapeutic

window, or with the lowest threshold for relieving rigidity. Additionally, all thresholds for clinical effects and therapeutic window sizes were compared between postoperatively selected contact points and stimulation at corresponding intraoperative depths, irrespective of whether these were the best intraoperative depths.

Statistical analysis

Differences in symptom-severity, and therapeutic window sizes were compared using non-parametric Wilcoxon's signed rank tests. Symptom-severity was compared at each of the postoperatively selected contact points using non-parametric Kruskal-Wallis H-tests. To compare differences between intraoperative and postoperative thresholds, Gehan-Breslow-Wilcoxon survival analyses were performed. As chronic stimulation intensities commonly do not exceed 4.5 mA, results obtained at intensities >4,5mA were excluded. Analyses were performed using IBM SPSS 23 or GraphPad Prism 7.02.

Results

A total of 145 PD patients underwent bilateral STN DBS in the selected period; 26 patients had missing records. We therefore included 119 consecutive patients (238 leads, 224 Medtronic 3389, 7 Vercise Cartesia) (table 4.1). For seven STNs, bipolar settings were chosen postoperatively; in all other STNs monopolar settings were used.

Table 4.1. Patient characteristics

N	119
Age at surgery (years)	60.5 (6.5)
Female sex (%)	31.9 (n=38)
Preoperative UPDRS III rigidity score [a]	2.8 (1.0)
Postoperative UPDRS III rigidity score [b]	1.9 (1.3)
Preoperative UPDRS III bradykinesia score [a]	2.7 (1.0)
Postoperative UPDRS III bradykinesia score [b]	2.0 (1.2)
Preoperative UPDRS III tremor score [a]	1.2 (1.3)
Postoperative UPDRS III tremor score [b]	1.1 (1.3)

Due to the limited range of the scores for symptom-severity, data is expressed as mean (standard deviation) for purposes of clarity.
[a] As scored during surgery, off medication, before starting of the procedure.
[b] As scored during the postoperative contact review, off medication.

Postoperative stimulation site

The postoperatively selected contact was the most dorsal in 54 cases (23%), the second-most dorsal in 126 cases (54%), the second-most ventral in 46 cases (20%), and most ventral in seven cases (3%) (missing n=5).

In 34% of cases, the contact selected for chronic stimulation coincided with the intraoperative depth with the best therapeutic window and in 41% cases was immediately dorsal to it. In 38% of cases, the selected contact coincided with the intraoperative depth with the lowest threshold for rigidity improvement, and in 34% was immediately dorsal to it (figure 4.1).

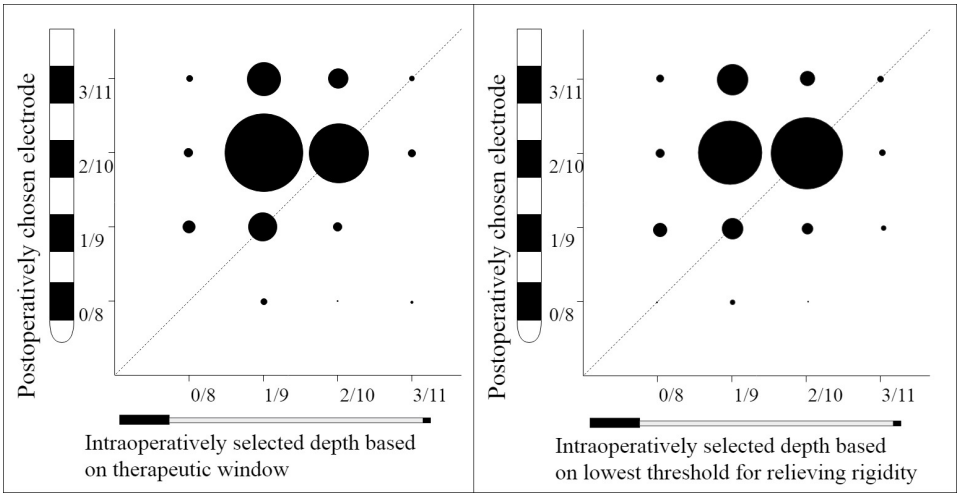

Figure 4.1. Postoperative selected contact compared to intraoperatively selected depth.
Depth selected for chronic stimulation, compared to the depth which intraoperatively yielded the largest therapeutic window (A), or the lowest threshold for rigidity (B). Dashed lines indicate perfect correlations. Circle-sizes reflect the number of sides.

After one-year follow-up, the contact point initially selected was maintained as monopolar, double monopolar or in bipolar configuration in 76% of leads (n=157/206).

There was no difference in the percentage of contacts that corresponded with the best intraoperative depth (or was immediately dorsal to it) at one year follow-up with respect to immediately after surgery.

Induction of benefit and side-effects

Intraoperatively (prior to MER insertion), UPDRS rigidity-scores were higher than during postoperative assessments ($Z=-7.47$, $p<0.001$, table 4.1), as were bradykinesia scores ($Z=-6.85$, $p<0.001$). Tremor was not different between assessments ($Z=-0.44$, $p=0.658$). There were no differences between the postoperatively selected contact points concerning baseline levels of rigidity ($X_2=3.57$, $p=0.312$), bradykinesia ($X_2=1.55$, $p=0.670$), or tremor ($X_2=0.60$, $p=0.898$).

A "stun effect" was observed intraoperatively in 4 sides and postoperatively in 22. There was no different trend for the finally chosen contact in these sides (middle two contact points selected in 75%).

During intraoperative stimulation, relief of rigidity (i.e. improvement to UPDRS 0/1) was observed in 97% of cases (n=186). For six sides debilitating side-effects occurred before rigidity relief. In 58% of cases, capsular side-effects were observed (n=125), non-capsular side-effects were observed in 13% of cases (n=27).

During postoperative stimulation, rigidity was relieved in 100% of cases (n=144). Capsular side-effects occurred in 60% of cases (n=117); non-capsular side-effects occurred in 16% (n=35). Intraoperatively, thresholds for relieving rigidity were lower than during postoperative stimulation at corresponding levels (intraoperative mean: 1.94 (0.80) mA vs. postoperative mean: 2.13 (0.83) mA, $X2=9.43$, $p=0.002$) (figure 4.2A), as were thresholds for inducing capsular side-effects (intraoperative mean: 3.15 (0.78) mA vs. postoperative mean: 3.34 (0.75) mA, $X2=5.69$, $p=0.017$) (figure 4.2B), whereas thresholds for inducing non-capsular side-effects were not different (intraoperative mean: 3.02 (0.96) mA vs. postoperative mean: 3.67 (0.91) mA, $X2=0.44$, $p=0.507$).

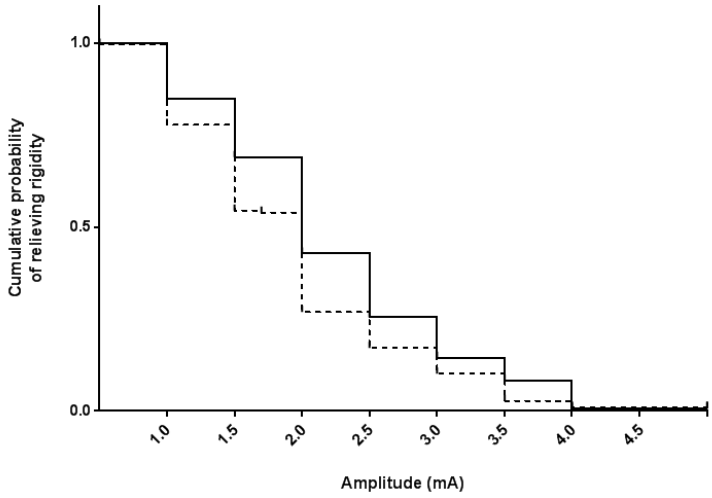

Figure 4.2A. Intraoperative vs. postoperative stimulation intensity for relieving rigidity.
Available intraoperative records: n=192, available postoperative records: n=144 (144 paired assessments. Dashed line: intraoperative assessment, continuous line: postoperative assessment. Vertical ticks indicates censoring. An event was characterized as relief of rigidity. When debilitating side-effects occurred at a certain threshold before rigidity was relieved, cases were censored at the threshold for side-effects (P=0.002).

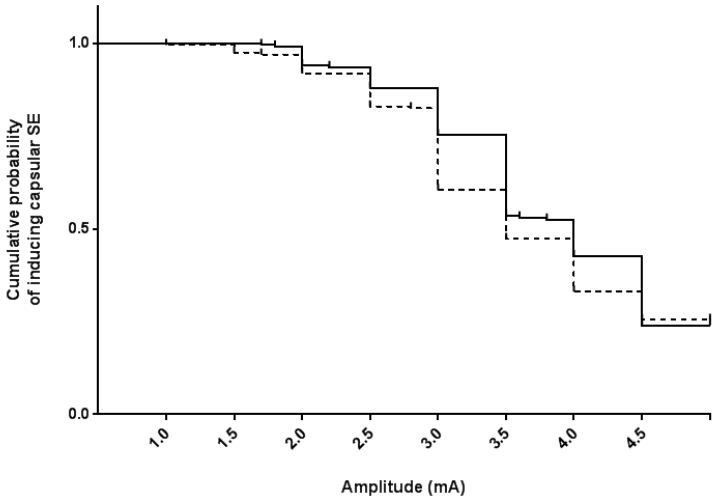

Figure 4.2B. Intraoperative vs. postoperative stimulation intensity for inducing capsular side-effects. Available intraoperative records: n=214, available postoperative records: n=195 (195 paired assessments. Dashed line: intraoperative assessment, continuous line: postoperative assessment. Vertical ticks indicates censoring. An event was characterized as occurrence of capsular side-effects (excluding gaze paresis). If no side-effects occurred, a case was censored at the highest tested level (p=0.016). SE = side-effect.

Widths of the therapeutic windows were not different between intra- and postoperative measurements (90 paired assessments, intraoperative mean: 1.36 (0.95) mA vs. postoperative mean: 1.42 (0.88) mA, Z=-0.20, p=0.844).

Discussion

We investigated differences between intraoperative test stimulation and postoperative contact review. The majority of contacts selected for chronic stimulation corresponded to the intraoperative depth with the largest therapeutic window (or with the lowest threshold for relieving rigidity) or was immediately dorsal to it.

These results indicate that intraoperative testing can reduce the postoperative search space and improve efficiency by pointing to the two contacts with the highest chance of selection. This becomes even more important when directional leads (more stimulation options) are implanted. We recommend to initially focus on the two most promising contacts based on intraoperative testing, and test the other contacts only in case of unsatisfactory results. The selection of a more dorsal contact for chronic stimulation probably stems from the beneficial effects of stimulating the upper part of the STN, or the dorsally located zona incerta.[10-11]

The threshold for inducing non-capsular side-effects was not different between assessments, likely because of the small number of observations. However, both the thresholds for relieving rigidity and inducing capsular side-effects were lower intraoperatively than during the postoperative contact review. This should be considered during intraoperative decision-making. Various factors may have contributed to this, such as differences in 'volume of tissue activated' (VTA) between stimulation through electrodes with different designs, shape and position of the stimulating field, or differences in tissue impedance. At similar stimulation intensities, the VTA generated by MER electrodes is considerably larger than that generated by the definitive contact, which may partly explain our observations.[12] Furthermore, the macrostimulation tip [12-13] produces spherical VTAs [12] while the DBS electrodes produce a torus-shaped VTA [14] with an altered current vector, which may influence clinical effects (figure 4.3).[15, 16]

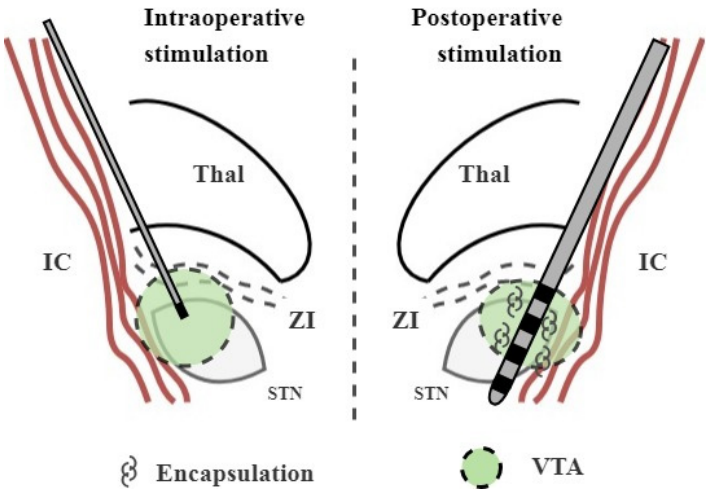

Figure 4.3. Differences in electric fields between intraoperative and postoperative assessments.
During intraoperative stimulation (left), the generated current is directed within a spherical VTA (green-shaded area), causing an outward current directionality that is similar in all directions.[12, 14] As the MER macrostimulation tip is newly introduced and relatively thin, there is no encapsulation yet. During the postoperative stimulation, the VTA is torus-shaped, resulting in a different current vector which is more perpendicular to the IC anisotropy, causing lower degree of activation.[15, 16] As a result of the increased encapsulation, the impedance surrounding the DBS lead is increased [25-27] which causes a different propagation of the electric current around the DBS lead, as well as a smaller VTA [12] with less current spreading over the STN, ZI and IC.
This figure is solely for schematic purposes; the drawn structures may not reflect the actual anatomic proportions.
IC: internal capsule; STN: subthalamic nucleus, Thal: thalamus; VTA: volume of tissue activated; ZI: zona incerta.

The lower baseline levels of rigidity during postoperative testing may partly be explained by persistent stun effects, generated after definitive lead insertion.[17-18] Even though stun effects

are predictive of the ultimate effectiveness of DBS,[19] they might impair or even preclude optimization of DBS settings at early stages.[20] Performing the postoperative review later might result in less stun effects. Moreover, our patients underwent complete dopaminergic medication withdrawal before surgery, and only an overnight medication withdrawal before postoperative contact review; carryover effects of medication cannot be excluded. However, whereas this could explain differences in thresholds for relieving rigidity, it does not explain differences in inducing side-effects.

Our observation of lower intraoperative than postoperative thresholds for relieving rigidity is supported by previous literature,[2] although the threshold for side-effects in that study was lower during postoperative stimulation, which lead to significant differences in the therapeutic windows as opposed to our findings. A possible reason for this discrepancy is that this study performed the postoperative stimulation using a constant-voltage mode, whereas intraoperative stimulation was performed with constant current mode.[21, 22]

A study investigating 12 dystonia patients (GPi DBS) found a small trend towards lower postoperative thresholds for capsular side-effects,[23] which increased after 6-17 months. Intraoperative evaluation was performed under general anesthesia, which might account for increased thresholds for capsular side-effects. Moreover, thresholds of self-reported side-effects or dysarthria cannot be recorded under anesthesia.[24]

Strengths of this study include the large sample size, standardized procedures, and standardized reporting of clinical effects. Possible limitations include the retrospective design and inherent missing data. Although the assessment order differed (intraoperatively dorsal-to-ventral; postoperatively ventral-to-dorsal), a carryover effect was likely limited due to sufficient waiting time and return to baseline symptom-levels.

Future studies may apply prospective designs to minimize missing data. Additionally, replication of these results in other targets may confirm whether they are specific for the STN and surrounding anatomical structures.

To what extent these results may ultimately aid in improving the efficiency of postoperative contact review remains to be explored.

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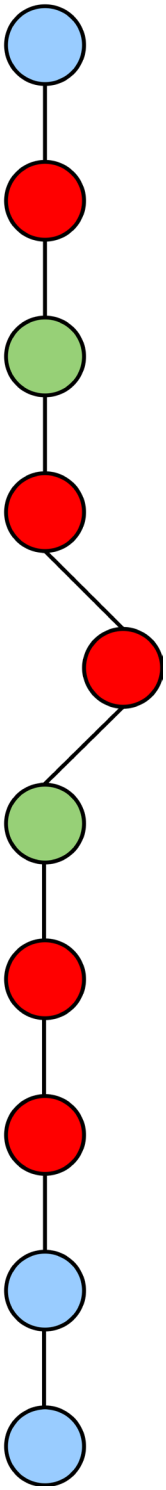
References

1. Deuschl G, Agid Y. Subthalamic neurostimulation for Parkinson's disease with early fluctuations: balancing the risks and benefits. Lancet Neurol 2013;12:1025-1034.
2. Blume J, Schlaier J, Rothenfusser E, et al. Intraoperative clinical testing overestimates the therapeutic window of the permanent DBS electrode in the subthalamic nucleus. Acta Neurochir (Wien) 2017.
3. Deuschl G, Schade-Brittinger C, Krack P, et al. A randomized trial of deep-brain stimulation for Parkinson's disease. N Engl J Med 2006;355:896-908.
4. Mehanna R, Machado AG, Connett JE, Alsaloum F, Cooper SE. Intraoperative Microstimulation Predicts Outcome of Postoperative Macrostimulation in Subthalamic Nucleus Deep Brain Stimulation for Parkinson's Disease. Neuromodulation : journal of the International Neuromodulation Society 2017;20:456-463.
5. Machado AG, Deogaonkar M, Cooper S. Deep brain stimulation for movement disorders: patient selection and technical options. Cleve Clin J Med 2012;79 Suppl 2:S19-24.
6. Bour LJ, Contarino MF, Foncke EM, et al. Long-term experience with intraoperative microrecording during DBS neurosurgery in STN and GPi. Acta Neurochir (Wien) 2010;152:2069-2077.
7. Priori A, Egidi M, Pesenti A, et al. Do intraoperative microrecordings improve subthalamic nucleus targeting in stereotactic neurosurgery for Parkinson's disease? J Neurosurg Sci 2003;47:56-60.
8. Wagle Shukla A, Zeilman P, Fernandez H, Bajwa JA, Mehanna R. DBS Programming: An Evolving Approach for Patients with Parkinson's Disease. Parkinsons Dis 2017;2017:8492619.
9. Bot M, Bour L, de Bie RM, Contarino MF, Schuurman PR, van den Munckhof P. Can We Rely on Susceptibility-Weighted Imaging for Subthalamic Nucleus Identification in Deep Brain Stimulation Surgery? Neurosurgery 2016;78:353-360.
10. Lanotte MM, Rizzone M, Bergamasco B, Faccani G, Melcarne A, Lopiano L. Deep brain stimulation of the subthalamic nucleus: anatomical, neurophysiological, and outcome correlations with the effects of stimulation. J Neurol Neurosurg Psychiatry 2002;72:53-58.
11. Maks CB, Butson CR, Walter BL, Vitek JL, McIntyre CC. Deep brain stimulation activation volumes and their association with neurophysiological mapping and therapeutic outcomes. J Neurol Neurosurg Psychiatry 2009;80:659-666.
12. Alonso F, Vogel D, Johansson J, Wardell K, Hemm S. Electric Field Comparison between Microelectrode Recording and Deep Brain Stimulation Systems-A Simulation Study. Brain sciences 2018;8.
13. Hemm S, Pison D, Alonso F, et al. Patient-Specific Electric Field Simulations and Acceleration Measurements for Objective Analysis of Intraoperative Stimulation Tests in the Thalamus. Frontiers in Human Neuroscience 2016;10.
14. Madler B, Coenen VA. Explaining clinical effects of deep brain stimulation through simplified target-specific modeling of the volume of activated tissue. AJNR Am J Neuroradiol 2012;33:1072-1080.
15. Chaturvedi A, Butson CR, Lempka SF, Cooper SE, McIntyre CC. Patient-specific models of deep brain stimulation: influence of field model complexity on neural activation predictions. Brain Stimul 2010;3:65-67.
16. Esler TB, Kerr RR, Tahayori B, Grayden DB, Meffin H, Burkitt AN. Minimizing activation of overlying axons with epiretinal stimulation: The role of fiber orientation and electrode configuration. PLoS One 2018;13:e0193598.

17. Mestre TA, Lang AE, Okun MS. Factors influencing the outcome of deep brain stimulation: Placebo, nocebo, lessebo, and lesion effects. Mov Disord 2016;31:290-296.
18. Chen CC, Pogosyan A, Zrinzo LU, et al. Intra-operative recordings of local field potentials can help localize the subthalamic nucleus in Parkinson's disease surgery. Experimental neurology 2006;198:214-221.
19. Tykocki T, Nauman P, Koziara H, Mandat T. Microlesion effect as a predictor of the effectiveness of subthalamic deep brain stimulation for Parkinson's disease. Stereotact Funct Neurosurg 2013;91:12-17.
20. Meidahl AC, Tinkhauser G, Herz DM, Cagnan H, Debarros J, Brown P. Adaptive Deep Brain Stimulation for Movement Disorders: The Long Road to Clinical Therapy. Mov Disord 2017;32:810-819.
21. Schlaier JR, Habermeyer C, Janzen A, et al. The influence of intraoperative microelectrode recordings and clinical testing on the location of final stimulation sites in deep brain stimulation for Parkinson's disease. Acta Neurochir (Wien) 2013;155:357-366.
22. Pollo C, Kaelin-Lang A, Oertel MF, et al. Directional deep brain stimulation: an intraoperative double-blind pilot study. Brain : a journal of neurology 2014;137:2015-2026.
23. Reese R, Reich MM, Falk D, Deuschl G, Mehdorn HM, Volkmann J. Intraoperative Thresholds for Capsular Stimulation Are Reliable for Chronic Pallidal Deep Brain Stimulation in Dystonia. Stereotact Funct Neurosurg 2017;95:79-85.
24. Ho AL, Ali R, Connolly ID, et al. Awake versus asleep deep brain stimulation for Parkinson's disease: a critical comparison and meta-analysis. J Neurol Neurosurg Psychiatry 2018;89:687-691.

Supplementary material

For target localization, stereotactic frame-based 3D magnetic resonance imaging (MRI) and StealthStation™ planning software (Medtronic, Minneapolis, Minnesota, USA) were used. The STN was generally localized at 12 mm lateral, 2 mm posterior and 4 mm inferior to the midcommissural point; individual adjustments were made after visual inspection of T2-weighted MRI scans. Path planning started just in front of the coronal suture and with 20-30° lateral angulation to the midline, with individual adjustments made to avoid blood vessels, sulci, and ventricles. Lead-implantation was performed with patients awake, withdrawn from dopaminergic medication and sedatives. Dopamine agonists were gradually reduced and stopped at least 3 days prior to surgery; levodopa was stopped at least 24 hours prior to surgery. Procedures were performed bilaterally. MERs were obtained by inserting 2 to 4 parallel cannulas and microelectrodes simultaneously (FHC, Bowdoin, Maine, USA) in a 2 mm interspace "Ben Gun" array. Intraoperative stimulation was performed using the microelectrode stimulation tip (semi-microstimulation). The permanent leads (model 3389, Medtronic, Minneapolis, Minnesota, USA; or model Vercise Cartesia™, Boston Scientific, Marlborough, Massachusetts, USA) were subsequently implanted along the best trajectory. After MER and intraoperative test stimulation, permanent leads were usually positioned with the middle two contacts placed at the level with best stimulation effect, provided that the deepest contact was not below the substantia nigra. The pulse generator was placed under general anesthesia during the same surgical session and connected to the permanent leads.



CHAPTER 5

Stimulation challenge test after STN DBS improves satisfaction in Parkinson's Disease patients

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Abstract

Objective

Although subthalamic Deep Brain Stimulation (STN DBS) is proven effective in improving symptoms of Parkinson's Disease (PD), previous literature demonstrates a discrepancy between objective improvement and patients' perception thereof. We aimed to examine whether postoperative stimulation challenge tests (SCT) alters patients' satisfaction after STN DBS for PD.

Methods

Fifty-four PD patients underwent preoperative levodopa challenge tests and were routinely invited for SCT 1-2 years postoperatively. SEverity of predominantly Nondopaminergic Symptoms in PD (SENS-PD) scores quantified non-dopaminergic disease severity. Motor functioning was quantified using Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) III scores; a ratio between conditions ON and OFF (preoperative Med-ON vs. Med-OFF, and postoperative Med-ON/Stim-ON vs. Med-OFF/Stim-OFF) reflected treatment benefit. 'Global Impression of Change' (GIC) and 'Global Satisfaction with Surgery' (GSS) Likert scales were filled out before and immediately after SCT.

Results

Postoperative Med-ON/Stim-ON severity was lower than preoperative ON severity. Disease severity scores were not different between assessments. GIC and GSS scores were higher after SCT versus before (GIC: Z=-3.80, r=0.37, subjects indicating maximum scores before SCT: 32.1%, after SCT: 57.1%; GSS: Z=-3.69, r=0.35, maximum scores before SCT: 25.0%, after SCT: 46.4%). Higher non-dopaminergic disease severity was associated with lower GIC and GSS scores (GIC: OR 1.2 (95%CI 1.0 – 1.3); GSS: OR 1.2 (95%CI 1.1 – 1.3), while motor-scores and magnitude of DBS-effects were not.

Conclusion

SCT improves patients' satisfaction and is recommended especially in case of suboptimal subjective valuations. This information should be considered in clinical practice and in the context of clinical trials.

Introduction

Subthalamic Deep Brain Stimulation (STN DBS) is an effective treatment for patients with Parkinson's Disease (PD) with motor complications refractory to medication. STN DBS yields an average motor improvement of approximately 40%, and reduces medication requirements by approximately 50%.[1] However, previous literature demonstrates a discrepancy between objective improvement and patients' perception thereof,[2] with several patients reporting mixed or negative valuations in terms of postoperative satisfaction.[2, 3]

Many centres perform a stimulation challenge test (SCT) during DBS follow-up to evaluate the benefit of either STN DBS alone or combined with medication, compared to the benefit provided by medication alone. This procedure is considered a standard quality check to verify efficacy of STN DBS against the benchmark of levodopa response, and identify poor responders.[4, 5] However, this test is time-consuming and bothersome for some patients. Hence, SCTs are sometimes performed only when clinically indicated, in case of suboptimal responses or complex side-effects.

We hypothesized that, in addition to the above-mentioned benefits, switching the stimulator OFF after overnight withdrawal from dopaminergic medication makes patients more aware of the severity of their motor symptoms in a practically defined OFF-state and allows them to compare this directly to their motor functioning during the ON-state afterwards.

The aim of this study was to examine whether postoperative ON-OFF testing alters patients' perceived impression of DBS effects and improves satisfaction after surgery.

Methods

Study participants

Seventy-four consecutive patients who underwent STN DBS surgery between September 2015 and April 2019 at the Leiden University Medical Centre / HAGA Teaching Hospital received routine preoperative levodopa challenge tests and were invited for a SCT 1-2 years postoperatively in the context of routine follow-up examinations. A formal ethical evaluation was waived by the local medical ethics committee as all data originated from standard clinical procedures.

Outcome measures

PD patients were examined after overnight withdrawal from dopaminergic medication in the following sequence: (1) Stimulation 'ON' (Stim-ON) / Medication 'OFF' (Med-OFF), (2) Stim-

OFF/Med-OFF, (3) Stim-ON/Med-ON, (4) Stim-OFF/Med-ON. After the Med-OFF conditions, patients were given a supra-threshold dosage (dispersible Levodopa/Benserazide) of 120% of the morning levodopa equivalent dose. Between conditions (1) and (2), and between (3) and (4), 15 minutes were provided to adjust to the altered settings; 60 minutes were required between conditions (2) and (3) to ensure maximum medication benefit.

The Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) III scores were used to quantify motor functioning.[6] A ratio between conditions ON and OFF (i.e. preoperative Med-ON vs. Med-OFF, and postoperative Med-ON/Stim-ON vs. Med-OFF/Stim-OFF) was used to reflect treatment benefit. The SEverity of predominantly Nondopaminergic Symptoms in PD (SENS-PD) scale [7] was used to assess nondopaminergic disease severity during Stim-ON/Med-ON. The SENS-PD scale is a composite score comprising six predominantly non-dopaminergic domains: postural instability and gait difficulty (PIGD), psychotic symptoms, excessive daytime sleepiness, autonomic dysfunction, cognitive impairment, and depressive symptoms. This scale, validated for PD patients, includes symptoms typically unresponsive to dopaminergic medication and may more accurately reflect progression of an underlying disease-mechanism than dopamine-sensitive measures,[8] particularly in PD patients sensitive to motor-fluctuations such as the DBS population. Higher scores on all scales indicate greater impairment.

Four weeks prior to testing, patients filled out two 7-point Likert scales at home: 'Global impression of change' (GIC) ranging from 'symptoms worsened a lot' to 'symptoms improved a lot', and 'Global satisfaction with surgery' (GSS) ranging from 'very dissatisfied' to 'very satisfied'. Both Likert scales were filled out again immediately after the SCT.

Statistical analysis

Symptom severity scores before and after DBS were compared using Repeated Measures General Linear Models. Responses in GIC and GSS were compared before and after SCT using Wilcoxon signed rank tests. Wilcoxon test statistics were approximated towards a standard normal distribution to give a standardized Z statistic, which was subsequently divided by the square root of the sample size to provide an effect size. The critical cut-off for Z statistics for α=0.05 is 1.96, and for α=0.01 is 2.58. The effect of symptom severity (either MDS-UPDRS III or SENS-PD scores) on GIC and GSS response was assessed using ordinal regression (Polytomous Universal Models); responses were pooled on three levels for analytic purposes (0=very satisfied / a lot improved (i.e. optimal responses), 1=satisfied / improved, 2=slightly satisfied / slightly improved or lower scores). The assumption of proportional odds was confirmed by checking the individual multinomial logistic regression coefficients. All analyses were performed using IBM SPSS 25 Software (SPSS Inc., Chicago, Illinois, USA). De-identified data may be shared upon request.

Results

Fifty-four patients (32% female, mean ± SD age 62.7 ± 7.8 years) were included. Reasons for exclusion were: refusal of the SCT (n=15), forgotten to withdraw dopaminergic medication (n=1), patient moved (n=1), previous SCT elsewhere (n=1), severe comorbidity unrelated to this study (n=1, malignancy, not invited to participate), and language barrier (n=1). Excluded patients were not demographically different.

Postoperative (mean (SD)) Med-ON/Stim-ON scores (17.5 (7.8)) were lower than preoperative ON-scores (20.5 (9.3)). DBS markedly reduced MDS-UPDRS-III scores postoperatively (mean (SD) Med-OFF/Stim-ON 25.7 (9.1), Med-OFF/Stim-OFF 47.9 (9.6)). MDS-UPDRS-III OFF-severity was not different before and after surgery, neither was non-dopaminergic disease severity (table 5.1). Both GIC (optimal response (i.e. 'my symptoms improved a lot') before SCT: 32%, after SCT: 57%) and GSS scores (optimal response (i.e. 'very satisfied with surgery) before SCT: 25%, after SCT: 46%) were higher after SCT (GIC: Z=3.80, r=0.37; GSS: Z=3.69, r=0.35) (figure 5.1), demonstrating a medium-to-large effect according to Cohen's Criteria.

Greater postoperative non-dopaminergic severity was associated with lower GIC and GSS scores (GIC: OR (95%CI) 1.2 (1.0 – 1.3); GSS: OR (95%CI) 1.2 (1.1 – 1.3)). Motor severity, either Med-OFF/Stim-OFF, Med-ON/Stim-ON, or a ratio reflecting motor improvement produced by combined stimulation and medication with respect to postoperative OFF, were not associated with GIC and GSS responses after SCT (supplementary table 5.1).

Table 5.1. Clinical characteristics

	Preoperative	Postoperative	95%CI of difference [c]
N		54	
Female sex (% (n))		32 (18)	
Age (years) [a]		62.7 (7.8)	
Follow-up (months) [a]		16.7 (5.5) (range 11-28)	
MDS-UPDRS-III Med-ON [a] (Med-ON / Stim-ON) [b]	20.5 (9.3)	17.5 (7.8)	0.2 – 5.7
MDS-UPDRS-III Med-OFF [a] (Med-OFF / Stim-OFF)	45.1 (12.7)	47.9 (9.6)	-6.6 – 0.9
MDS-UPDRS-III Med-OFF / Stim-ON [a]		25.7 (9.1)	15.5 – 23.2 [d]
Ratio MDS-UPDRS-III ON over OFF (Med-ON / Stim-ON over Med-OFF / Stim-OFF) [a, b]	0.45 (0.15)	0.37 (0.15)	0.04 – 0.14
SENS-PD [a]	11.4 (4.6)	12.1 (5.6)	-2.3 – 0.7

[a] mean (SD), [b] three patients used no medication after DBS, MDS-UPDRS-III scores in the Med-OFF/Stim-ON condition were then used. [c] computed using generalized linear models (repeated measures), [d] relative to preoperative MDS-UPDRS III Med-ON

SENS-PD: SEverity of predominantly Nondopaminergic Symptoms in PD; MDS-UPDRS: Movement Disorders Society Unified Parkinson's Disease Rating Scale

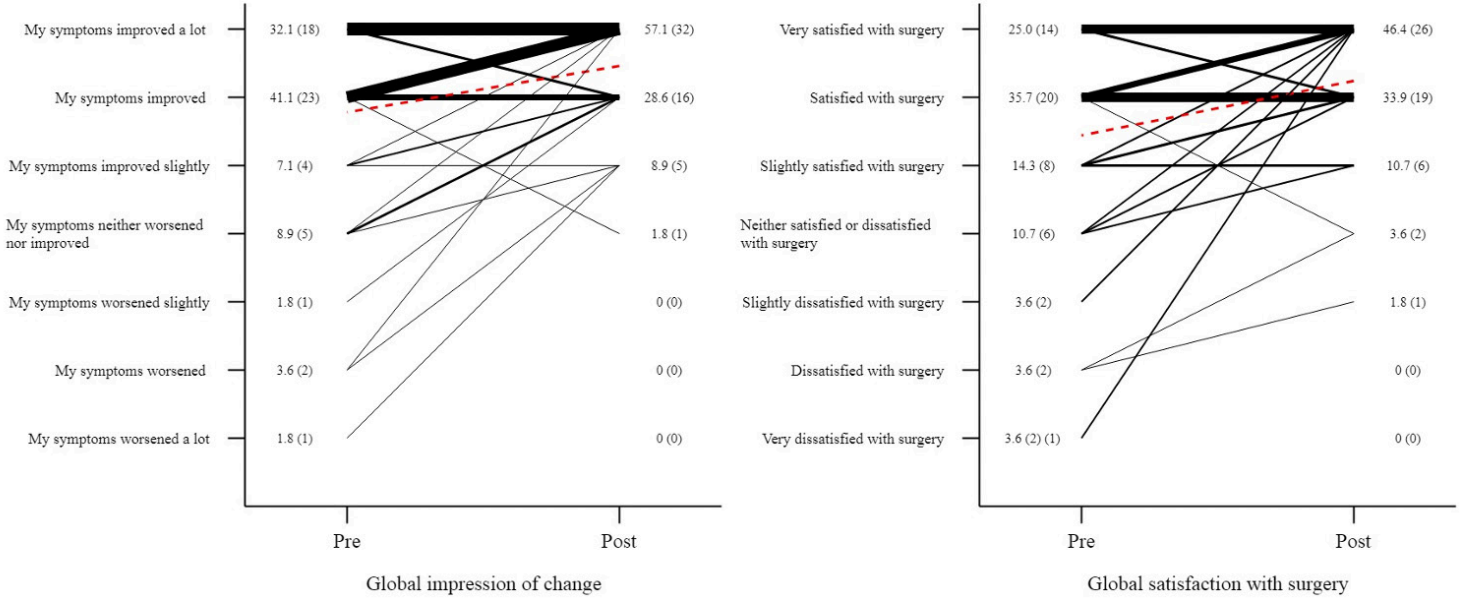

Figure 5.1. Global Impression of Change and Global Satisfaction with Surgery before and after stimulation challenge tests
Seven-point Likert-scales shown on the Y-axes, before and after stimulation challenge tests. The thickness of the lines reflects the number of patients. The red dashed lines reflect the pre- and postoperative averages (Global Impression of change: Z=-3.800, Global Satisfaction with Surgery: Z==-3.685). The proportions per response option are denoted next to the lines, responses are shown as % (n).

Discussion

In this study we show that patients are generally satisfied after STN DBS and that satisfaction and subjective perception of benefit after surgery increase after a postoperative SCT. These results could be driven by a tendency to forget the experienced preoperative motor severity, since patients generally no longer experience motor fluctuations to the same degree as before surgery. In a previous study, where PD patients were asked to recall their preoperative QoL scores six months after surgery, they substantially overestimated their preoperative functioning,[9] indicating impaired perception of the postoperative improvement due to recall bias. Experiencing the OFF condition during the SCT confronts patients with their actual motor severity and provides a more accurate perception of their disease severity and the relief that DBS has brought. These results may have clinical utility to improve patient awareness and thus satisfaction, particularly for patients who consider themselves dissatisfied with the results of DBS. Our analyses included patients who reported optimal satisfaction and could by definition either remain optimally satisfied after SCT, or regress towards a lower level of satisfaction, whereas including only suboptimally satisfied patients would have provided even larger effect sizes.

In the Netherlands, performing SCTs at least once postoperatively (typically around 1-year follow-up) is considered routine clinical practice to estimate the magnitude of stimulation-induced motor benefits and accordingly optimize treatment when needed.[10] Our study demonstrates clear patient benefits in terms of improved postoperative satisfaction as well, and provides further arguments in favour of postoperative SCTs.

Strikingly, the magnitude of motor improvement due to DBS was not correlated to either GIC or GSS, indicating that the exact amount of improvement does not influence perception of change or satisfaction. This is in line with previous studies [2,3] that demonstrated no correlation between subjective perception of outcome and objective motor improvement. We speculate that patients may have different, possibly unrealistic, expectations of DBS surgery, which may contribute to perceiving the overall post-operative situation as less satisfactory.[3,11] On the opposite, we found that greater non-dopaminergic disease severity correlated with lower GSS and GIC scores. Previous literature indicated that non-dopaminergic disease severity is mostly unaffected by DBS,[12] which is confirmed by our results, and that non-motor symptoms are important determinants of quality of life in PD.[13] We speculate that the stimulation-induced relief of severe motor fluctuations shifts patients' focus to those aspects of the disease that are unresponsive to STN DBS. Although this was not systematically investigated, several patients indeed reported non-dopaminergic symptoms such as cognitive impairment and balance impairments to be more prominent post-surgery.

In this study we show, for the first time, that use of a SCT can improve postoperative satisfaction in a cohort of consecutive patients. A four-week interval was considered sufficient to ensure that patients would not exactly recall their initial responses to GIC and GSS questionnaires. Limitations include the substantial number of patients that refused participation (20%, n=15). Reasons for refusal were not systematically documented, but included unavailability, difficulty to reach the centre, and anxiety at the idea of switching the stimulator off. Another consideration is the possibility of 'participant reactivity' - where patients may be prone to please the investigator by providing more favourable responses after personal contact compared to the situation prior to the SCT, especially after prolonged patient-caregiver relationships. This factor was likely limited in our study, as the treating neurologist was not involved in the ON-OFF testing.

A SCT provides a reliable method to quantify motor improvement after DBS, but is also useful to increase patients' postoperative satisfaction. In addition, this information should be taken into account when designing clinical trials with patients' satisfaction as outcome. We recommend to use the SCT as part of the routine follow-up after DBS, especially in case of suboptimal postoperative satisfaction. Future research should identify whether increases in GIC and GSS after a SCT are sustained or whether this fades over time.

Acknowledgements
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References

1. Deuschl G, Schade-Brittinger C, Krack P, et al. A randomized trial of deep-brain stimulation for Parkinson's disease. N Engl J Med 2006;355:896-908.
2. Maier F, Lewis CJ, Horstkoetter N, et al. Subjective perceived outcome of subthalamic deep brain stimulation in Parkinson's disease one year after surgery. Parkinsonism Relat Disord 2016;24:41-47.
3. Maier F, Lewis CJ, Horstkoetter N, et al. Patients' expectations of deep brain stimulation, and subjective perceived outcome related to clinical measures in Parkinson's disease: a mixed-method approach. J Neurol Neurosurg Psychiatry 2013;84:1273-1281.
4. Hartmann CJ, Wojtecki L, Vesper J, et al. Long-term evaluation of impedance levels and clinical development in subthalamic deep brain stimulation for Parkinson's disease. Parkinsonism Relat Disord 2015;21:1247-1250.
5. Chou KL, Taylor JL, Patil PG. The MDS-UPDRS tracks motor and non-motor improvement due to subthalamic nucleus deep brain stimulation in Parkinson disease. Parkinsonism Relat Disord 2013;19:966-969.
6. Goetz CG, Tilley BC, Shaftman SR, et al. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. Mov Disord 2008;23:2129-2170.
7. 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.
8. Geraedts VJ, Marinus J, Gouw AA, et al. Quantitative EEG reflects non-dopaminergic disease severity in Parkinson's disease. Clin Neurophysiol 2018.
9. Gronchi-Perrin A, Viollier S, Ghika J, et al. Does subthalamic nucleus deep brain stimulation really improve quality of life in Parkinson's disease? Mov Disord 2006;21:1465-1468.
10. Temel Y, Leentjens AF, de Bie RMA. Handboek diepe hersenstimulatie bij neurologische en psychiatrische aandoeningen. Houten: Springer Nature 2016.
11. Geraedts VJ, Kuijf ML, van Hilten JJ, Marinus J, Oosterloo M, Contarino MF. Selecting candidates for Deep Brain Stimulation in Parkinson's disease: the role of patients' expectations. Parkinsonism & Related Disorders.
12. Almeida L, Deeb W, Spears C, et al. Current Practice and the Future of Deep Brain Stimulation Therapy in Parkinson's Disease. Seminars in neurology 2017;37:205-214.
13. Prakash KM, Nadkarni NV, Lye WK, Yong MH, Tan EK. The impact of non-motor symptoms on the quality of life of Parkinson's disease patients: a longitudinal study. Eur J Neurol 2016;23:854-860.

Supplementary material

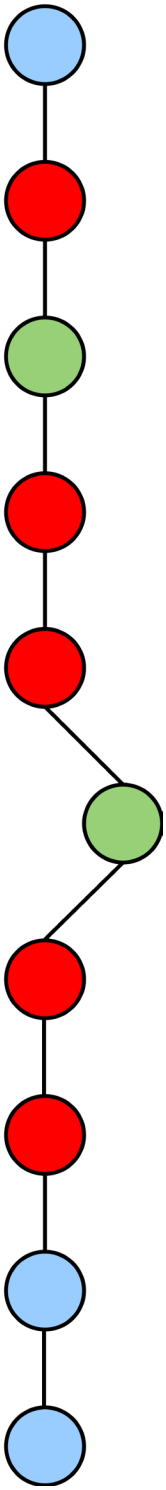
Supplementary table 5.1. Correlation with motor function and non-dopaminergic disease severity

	GIC		GSS	
	OR [a]	95%CI	OR [a]	95%CI
Postoperative SENS-PD	1.168	1.043 – 1.309	1.185	1.059 – 1.327
Postoperative MDS-UPDRS-III ratio ON-ON / OFF-OFF [b]	2.299	0.066 – 80.153	7.4	0.236 – 231.659
Postoperative MDS-UPDRS-III ON-ON [b]	0.991	0.925 – 1.062	1.008	0.944 – 1.076
Postoperative MDS-UPDRS III OFF-OFF	0.962	0.908 – 1.019	0.954	0.902 – 1.009

[a] ORs computed using ordinal regression on three levels (0 = very satisfied / a lot improved; 1 = satisfied / improved, 2 = slightly satisfied / slightly improved or lower scores). ORs > 1 indicate that higher symptom severity indicates lower postoperative satisfaction / subjective improvement. Separate analyses were carried out due to multicollinearity.

[b] Three patients used no medication after DBS: for these patients MDS-UPDRS-III scores in the Med-OFF / Stim-ON condition were used.

GIC: global impression of change; GSS: global satisfaction with surgery; SENS-PD: SEverity of predominantly Nondopaminergic Symptoms in PD, Cog: subscale cognition, Psy: subscale psychotic symptoms, PIGD: subscale postural-instability-and-gait-difficulty, Aut: subscale autonomic symptoms, Sleep: subscale sleep problems, Dep: subscale depression; MDS-UPDRS: Movement Disorders Society Unified Parkinson's Disease Rating Scale.



CHAPTER 6

Clinical correlates of quantitative EEG in Parkinson Disease – a systematic review

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Abstract

Objective

To assess the relevance of Quantitative electroencephalography (qEEG) measures as outcomes of disease severity and progression in PD.

Methods

Main databases were systematically searched (January 2018) for studies of sufficient methodological quality that examined correlations between clinical symptoms of idiopathic PD and cortical (surface) qEEG metrics.

Results

Thirty-six out of 605 identified studied were included. Results were classified into four domains: cognition (23 studies), motor function (13 studies), responsiveness to interventions (7 studies), and other (10 studies). In cross-sectional studies, EEG slowing correlated with global cognitive impairment and with diffuse deterioration in other domains. In longitudinal studies, decreased dominant frequency and increased θ power, reflecting EEG slowing, were biomarkers of cognitive deterioration at an individual level. Results on motor dysfunction and treatment yielded contrasting findings. Studies on functional connectivity at an individual level, longitudinal studies on other domains or on connectivity measures, were lacking.

Conclusion

QEEG parameters reflecting EEG slowing, particularly decreased dominant frequency and increased θ power, correlate with cognitive impairment and predict future cognitive deterioration. QEEG could provide reliable and widely available biomarkers for non-motor disease severity and progression in PD, potentially promoting early diagnosis of non-motor symptoms and an objective monitoring of progression. More studies are needed to clarify the role of functional connectivity and network analyses.

Introduction

Parkinson's disease (PD) is a complex multisystem neurodegenerative disease characterized by motor features and non-motor symptoms [1] such as cognitive impairment, neuropsychiatric disturbances and sleep abnormalities.[2] Non-motor symptoms can present early in the disease course, worsen with advancing disease, and largely do not improve on dopaminergic treatment, suggesting that they may more accurately reflect severity and progression of the underlying disease.[3] To date, there are no reliable objective biomarkers for disease progression in PD.

By definition, a biomarker is objectively measured and evaluated as an indicator of normal biological processes, pathophysiological processes, or pharmacologic response to a therapeutic intervention.[4] Quantitative biomarkers may identify systems at-risk before overt expression of the disorder. Ideally, biomarkers are cheap, unsusceptible to bias, widely available and non-invasive. Electroencephalography (EEG) combines these aspects [5] and provides insight into cortical dysfunction by measuring brain activity directly.[6] Quantitative analyses of brain rhythms measured by EEG (qEEG) provide not only spectral information of cortical rhythms, but also additional data on regional or whole-brain synchronization ("connectivity") of brain activity. Connectivity-derived graph-theory matrices quantify the efficiency of such functional networks (figure 6.1).[7] If detectable, early signs of cortical dysfunction may serve as prognostic markers of future clinical deterioration, thereby reducing diagnostic delay and improving patient management.

Previous studies explored correlations of qEEG features with domains such as motor impairment [8, 9] or cognition [10-12] in PD patients. However, there is a wide variety in EEG acquisition-methodology, processing and analysis, and patient population. Moreover, most studies focus primarily on reporting results rather than emphasizing methodological quality and reproducibility. The relationship between qEEG and its clinical correlates remains unclear; there is no complete overview of associations between cortical EEG rhythms and clinical symptoms of PD. In this systematic review, we aim to present a comprehensive overview of studies of sufficient methodological quality on clinical correlates of resting-state qEEG in PD. Particularly, we evaluate the relevance of this method to characterize brain function and connectivity as reliable and easy utilizable outcomes of PD severity and progression.

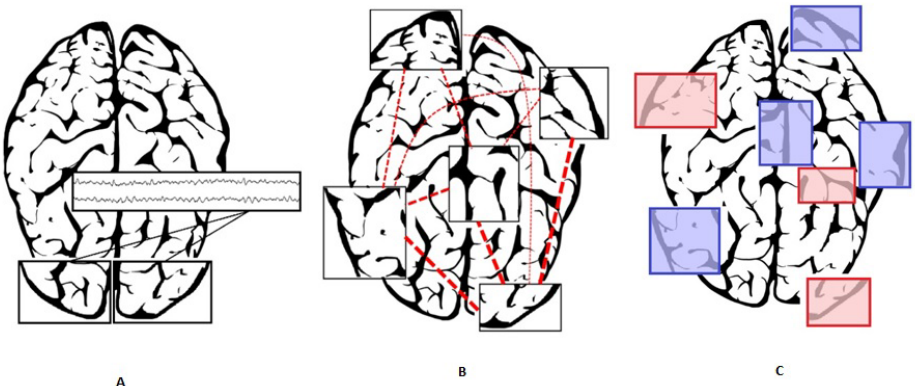


Figure 6.1. Principles of quantitative EEG analyses

A. *Spectral analyses:* an estimation of the amount of oscillations at given frequencies via a Fast Fourier Transformation (FFT), generally expressed as either power per frequency-band (i.e. δ 0.5–4.0 Hz, θ 4.0–8.0 Hz, α 8.0–13.0 Hz, β 13.0–30.0 Hz), or as a dominant frequency (i.e. FFT peak).

B. *Connectivity analyses:* an assessment of the strength of functional connections between individual electrodes / brain regions (red dashed lines) throughout the brain to quantify brain synchronization. Connectivity-strength can be low (i.e. thin dashed line) compared to high connectivity (e.g. occipital regions (thicker lines)). Functional connectivity is typically assessed within separate frequency-bands.

C. *Network analyses:* whole-brain networks derived from connectivity analyses are reflected in a coherent 'graph' which accounts for hierarchy and can therefore identify which brain regions are most important, i.e. 'hub-nodes' (red), or less important, i.e. 'non-hub-nodes' (blue).

Methods

In this systematic review we adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (http://www.prisma-statement.org/) (checklist available from Dryad).

Data sources and search

PubMed, Embase, Web of Science, COCHRANE Library, Emcare, Academic Search Premier and Sciencedirect were systematically searched for potentially relevant studies up to January 2, 2018 (date of search), using appropriate keywords (data available from Dryad).

Study selection

Eligibility was initially assessed by screening titles and abstracts, based on the following inclusion criteria: (1) data available on cohorts with idiopathic PD of at least 10 patients; (2) original research; (3) quantitative cortical (surface) EEG measures analyzed; (4) article in English or German; (5) qEEG data on correlations with clinical symptoms. A clinical correlate was defined as a correlation with an important clinical symptom, therapy or disease-specific characteristic relevant to PD. Two exclusion criteria were used: (1) no resting state EEG; (2) analysis focusing exclusively on local

field potentials (LFP). Task-based methodology was excluded because it is difficult to standardize, often semi-quantitative and thereby subject to observer-bias. LFPs recordings measure activity from subcortical structures rather than cortical. The use of implantable electrodes makes them invasive and thereby less attractive as a biomarker.

Data extraction and risk of bias assessment

Screening of titles and abstracts was performed by two independent reviewers (VJG and LIB). Data extraction was performed using piloted forms (forms available from Dryad). Inclusion for full-text screening was decided after discussion of discrepancies and re-reading of the pertinent sections until mutual agreement was reached. Cohen's kappa for interrater agreement was calculated.

Results were categorized in the following domains: cognition, motor function, responsiveness to interventions, and 'other'. For purposes of clarity, terms like 'Background Rhythm Frequency', 'peak frequency', 'mean frequency' and 'median frequency' have been designated as 'dominant frequency' in this review.

Risk of bias was assessed using the Checklist for Case Series developed by the Joanna Briggs Institute (JBI),[13] extended with an item addressing clear reporting of EEG acquisition conditions allowing for reproducibility (data available from Dryad (supplementary material 6.1)). The quality threshold for inclusion was set at six or more 'yes' responses in total, provided that at least one 'yes' response was obtained for items 1-3, at least two 'yes' responses for items 4-8, and a 'yes' for the item on EEG acquisition.

Results

Search results and study characteristics

The initial search yielded 605 studies; 123 of these studies were examined in detail, after which 36 remained for final inclusion (figure 6.2). Interrater agreement κ was 0.713. Reasons for exclusion were: no resting-state EEG (n=26); no correlation of EEG measures to clinical symptoms of PD (n=21); insufficient methodological quality (n=15); no separate measures of cortical activity (e.g. only coupling with EMG) (n=10); no separate idiopathic PD cohorts of more than 10 patients (n=7); no original research (n=4); and LFP-focused analysis (n=4).

The selected studies are detailed in table 1. Nine studies were classified as medium quality studies (JBI=6), 21 as high quality (JBI 7-8) and six as very high quality (JBI 9-10). Seventeen articles were case-control studies, 13 case-series, and six longitudinal follow-up (FU) studies (table 6.1).

Table 6.1. Selected studies

Reference	Region, Country	Study type	N (PD)	Psy. active drugs	Age (years)	Classic bandpower definitions	EEG in ON or OFF	Quality	Comments
Cozac et al [33]	Basel, Switzerland	FU	37		67		?	**	High-density EEG (256 electrodes).
Cozac et al [43]	"	CC	54	?	68		?	**	High-density EEG (214 electrodes).
Eichelberger et al [29]	"	CS	57	?	67	No	?	**	High-density EEG (256 electrodes).
Hatz et al [40]	"	CS	40	?	68		ON	**	High-density EEG (256 electrodes).
Filipovic et al [39]	Belgrade, Yugoslavia	CS	24		50	No	OFF	**	
Pozzi et al [25]	Buenos Aires, Argentina	CC	47		65		ON	**	
Fonseca et al [23]	Campinas, Brazil	CC	32		67	No	ON	**	
Fonseca et al [42]	"	CC	32		68	No	ON	*	
Babiloni et al [34]	Cassino, Italy	CC	13	?	72		ON	*	
Mostile et al [19]	Catania, Italy	CC	34	?	66		Both	*	L-dopa naïve patients.
Bonanni et al [10]	Chieti, Italy	FU	35		70		ON	**	
Arnaldi et al [32]	Genoa, Italy	FU	54	?	69	?	?	**	
He et al [21]	Guangzhou, China	CC	135	Yes	60		?	**	
He et al [37]	"	CC	52	Yes	46		ON	**	Early-onset PD patients.
Helkala et al [16]	Kuopio, Finland	CC	18	Yes	68	No	?	**	
Soikkeli et al [26]	"	CC	36	Yes	72	No	?	*	
Gagnon et al [41]	Montreal, Canada	CC	15		64		Both	***	Low-density EEG (2 electrodes).
Latreille et al [12]	"	FU	68	?	65		OFF	**	Low-density EEG (12 electrodes).
Moisello et al [9]	New York, USA	CC	15	?	61		ON	*	High-density EEG (256 electrodes).
Jech et al [8]	Prague, Czech Republic	CS	12	?	57	No	Both	*	
Hassan et al [28]	Rennes, France	CS	124	?	66		ON	**	High-density EEG (128 electrodes).
Melgari et al [35]	Rome, Italy	CS	24		73		Both	**	
Stanzione et al [20]	"	CC	19		64	No	OFF	**	
George et al [38]	San Diego, USA	CC	16	?	63	?	Both	**	
Swann et al [48]	"	CC	15	?	63		Both	**	Low-density EEG (2 electrodes).
Caviness et al [14]	Scottsdale, USA	CS	66		76		ON	**	
Caviness et al [11]	"	FU	71		74		ON	***	
Caviness et al [22]	"	CS	134		76		ON	***	
Klassen et al [31]	"	FU	106		76		ON	***	
Utianski et al [30]	"	CS	88		76		ON	*	

Table 6.1 continued

Reference	Region, Country	Study type	N (PD)	Psy. active drugs	Age (years)	Classic bandpower definitions	EEG in ON or OFF	Quality	Comments
Neufeld et al [24]	Tel-Aviv, Israel	CS	20		72	No	OFF	*	
Guner et al [15]	Tepecik, Turkey	CC	45		67		ON	**	
Kamei et al [17]	Tokyo, Japan	CS	32	?	70	No	?	**	
Morita et al [36]	"	CS	106	?	68	No	?	***	
Morita et al [18]	"	CS	100		68	No	?	***	
Tanaka et al [27]	Zürich, Switzerland	CC	29		66	No	ON	*	

*CC: Case Control, CS: Case series, FU: follow-up; HC: healthy controls; *: JBI=6; **: JBI=7-8; ***: JBI=9-10.*
Classic bandpower ranges was defined as: δ: ± 0.5-4 Hz, θ: 4-8 Hz, α 8-13 Hz, β: 13- ±30 Hz

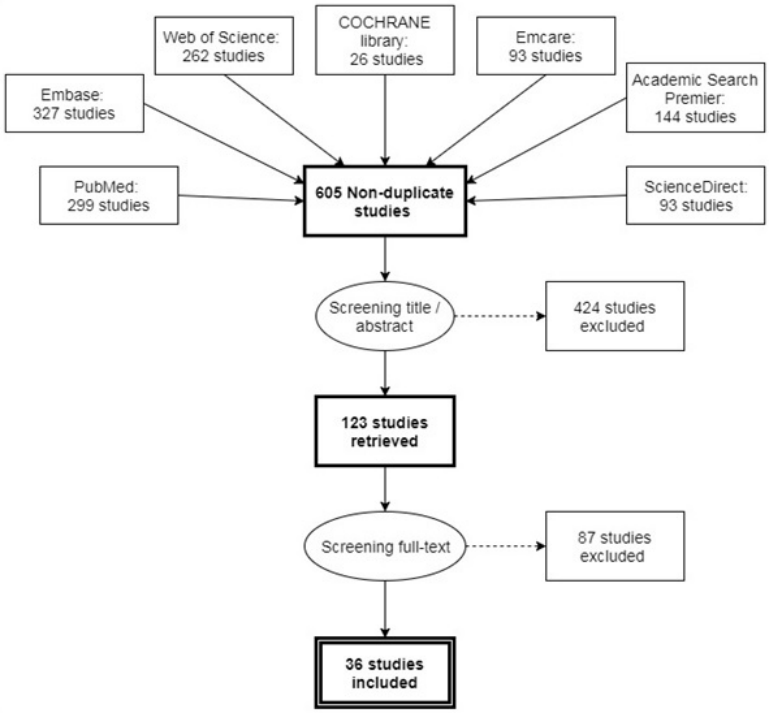


Figure 6.2. PRISMA flow diagram of selected studies.

Results were categorized into 'cognition' (n=23), 'motor function' (n=13), 'responsiveness to interventions' (n=7), and 'other' (not otherwise specified) (n=10). The studied qEEG measures are defined in table 6.2.

Table 6.2. Definition of qEEG metrics

Spectral analyses	*Bandpower*	Reflects the amount of oscillations within a given frequency band, typically assessed with a Fast Fourier Transformation (FFT). Power can be absolute, or relative (as a fraction of total power).
	Dominant frequency	The frequency with the most oscillations (dominant peak in the FFT spectrum), typically between 4 and 13 Hz.
Connectivity	*Index of lateralization (IL)*	Reflects EEG asymmetry by calculating power-differences between homologous pairs of EEG-electrodes.
	Phase Lag Index (PLI)	Assesses differences in relative phase distribution around 0 phase difference between brain regions.
	Phase Locking Value (PLV)	Absolute value of phase differences between brain regions.
	Coherence	The level of consistency between brain regions for relative amplitude and phase.

Table 6.2 continued,

Network	*Edge-Wise Connectivity Index (EWCI)*		$EWCI = \sum_i^n \mathrm{Wi} \times 100$, in which N is the number of edges in the subnetwork and W_i is the weight of edge i in the network. Defines the sum of weights of the (significant) subnetwork.
	Weighted Network (WN)	γ	Normalized weighted clustering coefficient (all weights divided by the maximum weight): functional connectivity between neighbouring nodes.
		λ	Normalized characteristic path length (all weights divided by the maximum weight): average weight of shortest paths between any two nodes within the network.
		K_w	Weighted degree divergence: reflects the broadness of weighted degree distribution.
		Modularity	Ratio of inter-group connections over total number of edges.
	Minimum Spanning Tree	*Betweenness Centrality*	Number of paths between all other nodes in the MST crossing the node of interest, divided by the total number of paths in the MST.
		Diameter	Longest distance between any two nodes in the MST network.
		Eccentricity	Maximum distance between a node and any other node in the MST.
		Leaf fraction	Ratio between number of leaf nodes (only one edge) divided by the total number of nodes within the MST.
		Tree hierarchy	T_h = leaf number / (2m B_{max}), in which m is the number of edges and B_{max} is the hightest betweenness centrality of any node in the tree. Defines hierarchy of the MST organization (optimal topology.
		Degree	Number of edges for each node divided by maximum number of possible edges.

Cognition

Nineteen cross-sectional studies investigated cognitive function. Increased EEG slowing correlated with severity of cognitive impairment, defined as lower scores on global cognitive tests or tests evaluating separate cognitive domains,[11, 12, 14-21] or with the patients cognitive state (either cognitively normal (NCOG), Mild Cognitive Impairment (MCI) or PD Dementia (PDD)) (figure 6.3, supplementary table 6.1).[14, 21-28] Five studies (four different cohorts) described a spectral ratio of fast-over-slow EEG power correlating positively with cognition,[12, 15, 17, 18, 29] although in one study the results depended on the cognitive test within the same domain (i.e. either Clock Drawing Test or Block Design Test for visuospatial abilities).[29] Four out of five studies found that a higher dominant frequency correlated positively with cognition.[12, 14, 20, 26] A fifth study reported that five out of seven cognitive tests correlated positively with dominant frequency, while the other two tests showed no correlation.[16] EEG slowing reflected by specific frequency bands, i.e. either increased δ (± 0.5–4 Hz) or θ (4–8 Hz) power, or decreased α (8–13 Hz) or β (13– ±30 Hz) power, showed a trend towards reflecting cognitive dysfunction, although these results were inconsistent. Especially in the β range results were inconclusive, with three studies reporting a positive correlation between a higher absolute and relative β power and a better cognitive function,[14, 16, 26] contrasted by six studies that found no correlation.[12, 20-24]

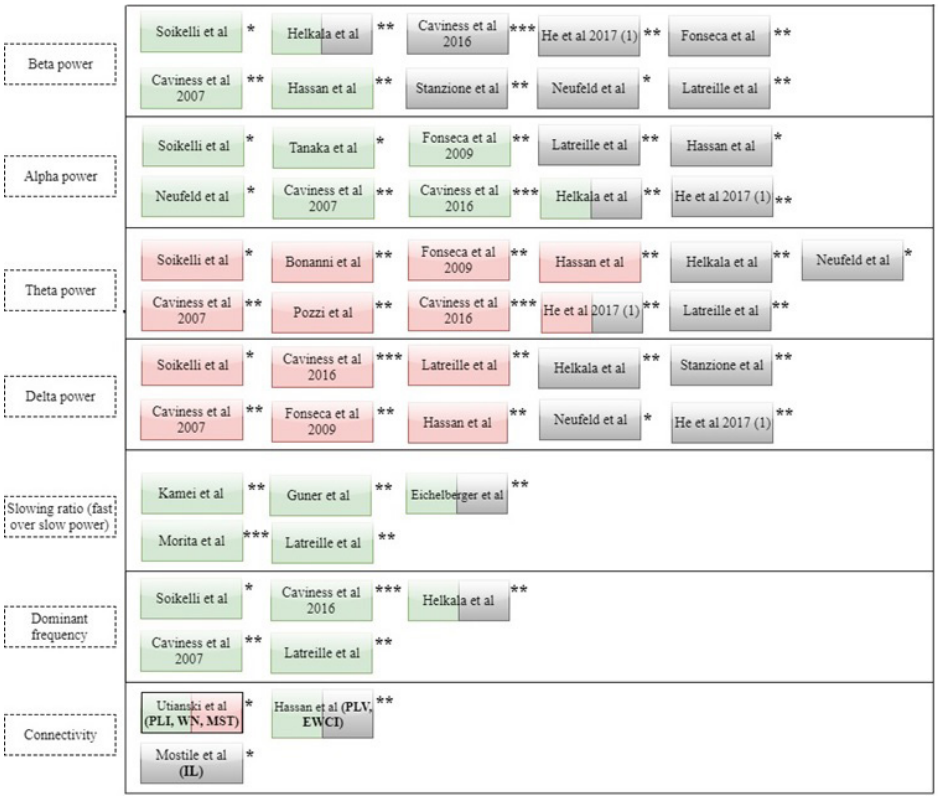


Figure 6.3. Correlation of qEEG measures with cognition
Green indicates that the measure is positively correlated with cognition, red indicates that the measure is negatively correlated with cognition, grey indicates no correlation. Dual-shaded boxes indicate that the sign of the correlation varied per test and/or variable. One asterisk indicates 'medium quality' (JBI); two indicates 'high quality' and three indicates 'very high quality'.
EWCI: Edge-Wise Connectivity Index, IL: Index of Lateralization, MST: Medium Spanning Tree, PLI: Phase Lag Index, PLV: Phase Locking Value, wMNE: weighted Minimum Norm Estimation, WN: Weighted Network

One study (n=88, JBI=6)) compared connectivity and graph theory metrics, i.e. Phase-Lag-Index (PLI), Weighted Network (WN) and Minimum Spanning Trees (MST), with cognitive status (PDD vs. PD-NCOG).[30] Reduced synchronization and network integration, particularly in the α1 band (8–10 Hz), were observed in cognitively impaired patients, although whether the sign of the correlation was positive or negative depended on the type of measure studied. This well-defined cohort was used in four other studies reviewed here.[11, 14, 22, 31] A different large study (n=124, JBI=7) investigated Phase-Locking-Value (PLV) and Edge-Wise Connectivity Index (EWCI).28 Lower α1 and α2 (network) edge-wise connectivity correlated with lower cognitive state, whilst global-level PLV-derived network-metrics were not correlated. EWCI correlated positively with outcomes of cognitive tests. More basic connectivity measures

such as signal asymmetry did not correlate with global cognitive tests.[19]

Longitudinal cognitive assessment

Five studies investigated qEEG measures as predictors of cognitive functioning (figure 6.4, supplementary table 6.2). Four studies investigated the predictive effect of a baseline qEEG measure [12, 31-33] and one study correlated longitudinal changes in EEG rhythms to change in cognition over time.[11]

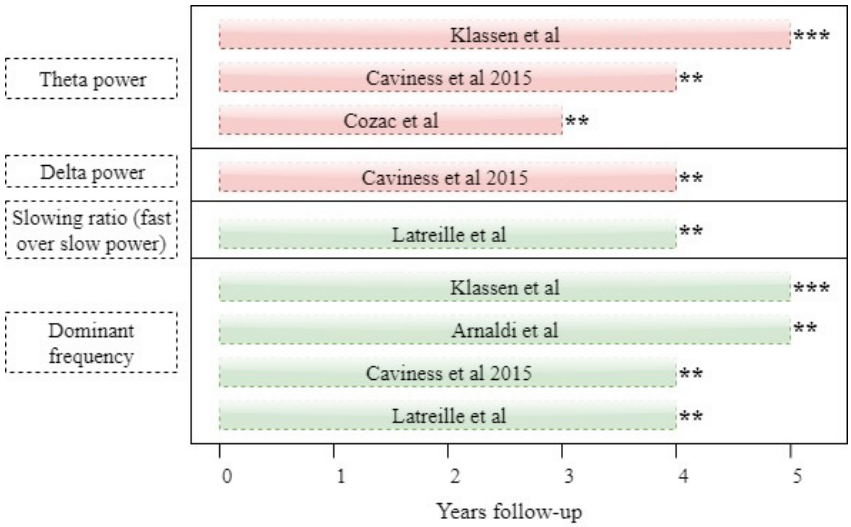


Figure 6.4. Correlation of qEEG measures with cognition in longitudinal follow-up studies
Green indicates that the measure is positively correlated with cognition, red indicates that the measure is negatively correlated with cognitive performance. Grey indicates no correlation. One asterisk indicates 'medium quality' (JBI); two indicates 'high quality' and three indicates 'very high quality'. The length of the bars reflects the length of the follow-up duration. All studies investigated the predictive value of baseline EEG measures, with the exception of Caviness et al which investigated the effect of change in spectral measures over time on longitudinal change in cognitive function.

In three studies, dominant frequency at baseline correlated with cognitive deterioration.[11, 12, 31] Likewise, higher θ power at baseline predicted cognitive deterioration in three studies.[11, 31, 33] A machine-learning algorithm, applying a random forest classifier, identified θ power as the most important classifying feature, although no corresponding model accuracy was reported.[33] A survival analysis showed that dominant frequency was predictive of cognitive worsening with an accuracy of 92% (sensitivity 84%, specificity 80%).[32]

One study examined spectral powers and dominant frequency, but did not report the predictive value of these measures.[10]

Motor function

Thirteen cross-sectional studies investigated a relation between motor function and qEEG (figure 6.5, supplementary table 6.3).Across studies, no consistent pattern of relations emerged between qEEG variables and measures of the motor domain. Four studies found no significant correlations between spectral powers and MDS-UPDRS III subscores or HY stage.[15, 20, 24, 34] Levodopa-induced increases of α and β power correlated with decreased MDS-UPDRS III subscores in one study.[35] Global dominant frequency correlated negatively with the rigidity subscore in one small study (n=12, JBI=6).[8] A ratio of fast-over-slow EEG power correlated negatively to HY stage in two studies using identical participants (mean HY stage 2.7).[18, 36] HY stage further correlated positively with α2 amplitude (n=32, JBI=7),[23] β power (n=52, JBI=8)[37] or θ power (n=135, JBI=7),[21] the latter only at three electrode positions (T5, F4 and O1). β band coherence correlated positively with MDS-UPDRS III scores in one study (n=16, JBI=7),[38] which was not supported by another study including early-onset PD patients (n=52, JBI=8).[37] β bandpower asymmetry correlated positively with HY stage, whilst θ band asymmetry correlated negatively. EEG asymmetry was not correlated to MDS-UPDRS III composite scores (n=34, JBI=6) in any frequency band, although motor asymmetry was not examined.[19]

Responsiveness of qEEG measures to interventions

Five studies investigated responsiveness of qEEG measures to both L-dopa and dopamine agonists (figure 6.6, supplementary table 6.4). Two studies found no effect of long-term oral dopaminergic treatment on spectral measures.[18, 20] In contrast, α and β power increased within 60 minutes of L-dopa administration in one study (n=24, JBI=8),[35] and the L-dopa short-duration response correlated positively with α bandpower asymmetry.[19] L-dopa administration reduced β and γ band coherence, which was increased in PD patients compared to healthy controls in the same study.[38]

Two studies evaluated the responsiveness of qEEG measures to Deep Brain Stimulation (DBS). Switching DBS 'ON' increased dominant frequency amplitude in one study (n=12, JBI=6), although the level of frequency changes depended on the EEG derivation.[8] DBS 'ON' increased frontal and parietal β power in another study (n=15, JBI=8).[48] In both studies, DBS-related artifacts were observed.

Overall, no consistent pattern of responsiveness of qEEG variables was found for oral- or DBS treatment.

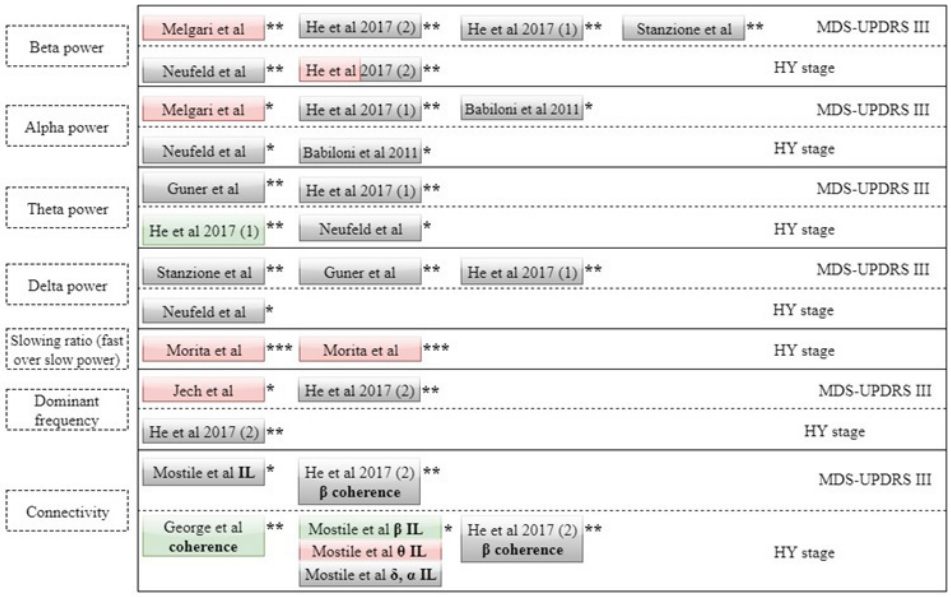


Figure 6.5. Correlation of qEEG measures with motor functioning
Green indicates that the measure is positively correlated with motor impairment, red indicates that the measure is negatively correlated with motor impairment. Gray indicates no correlation. Dual-shaded boxes indicate that the sign of the correlation varied per test and/or variable. One asterisk indicates 'medium quality' (JBI); two indicates 'high quality' and three indicates 'very high quality'.
HY stage: Hoehn and Yahr Stage; IL: Index of Lateralization; MDS-UPDRS III: Movement Disorders Society – Unified Parkinson's Disease Rating Scale III

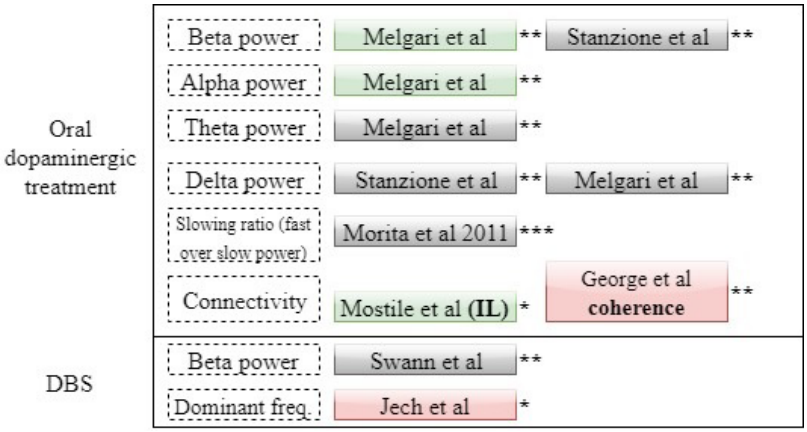


Figure 6.6. Correlation of qEEG measures with treatment
Green indicates that the measure is positively correlated with treatment administration, red indicates that the measure is negatively correlated with treatment. Grey indicates no correlation. One asterisk indicates 'medium quality' (JBI); two indicates 'high quality' and three indicates 'very high quality'. DBS: Deep Brain Stimulation; IL: Index of Lateralization

Other clinical measures

Ten studies investigated a variety of other clinical measures (supplementary table 6.5). Longer disease duration correlated with higher β power in one study (n=15, JBI=6),[9] while in three larger studies of higher quality no significant relation emerged.[18, 21, 37] Depressed PD patients demonstrated lower α1 (7.5–10 Hz) power than non-depressed patients in one study (n=24, JBI=7),[39] whereas the Hamilton Rating Scale for Depression did not correlate with EEG asymmetry in another study (n=34, JBI=6).[19] Higher apathy scores correlated with higher δ power, but not with other spectral measures in one study. Apathy scores correlated negatively with α2 PLI and α2 WN metrics. PLI classified mild vs. low apathy groups (median-split) with an accuracy of 82.5% (sensitivity 70% and specificity 90%).[40] A high-quality (JBI=10) study showed that PD patients with REM sleep behavior disorder (RBD) had a higher (wakefulness) θ power and lower dominant frequency compared to PD patients without RBD.[41] No correlation of coherence with quality of life (as assessed with the QoL-AD) was found in one study (n=32, JBI=6).[42] Olfactory function did not correlate with resting-state qEEG in one study (n=20, JBI=7).[43]

Discussion

The present systematic review included 36 studies examining relations between resting-state qEEG measures and clinical features of PD. The cognitive domain was studied most extensively. Both global and domain-specific cognitive impairments correlated with EEG slowing, i.e. lower α and β power and higher δ and θ power. PD patients with dementia had markedly slower EEGs than patients with a normal cognitive function. QEEG values of MCI patients were ranged between those of PD-NCOG and PDD, likely reflecting the transitional nature of MCI.[14, 22, 23, 31] It should be noticed that these correlations partly depended on the used measurement instrument, as demonstrated by discrepant results obtained when using MoCA or MMSE scores in the same study.[21] It remains unclear which EEG metric best reflects oscillatory slowing and shows the strongest correlation with cognition. Spectral ratios showed consistent significant correlations with cognition across all pertaining studies, whereas other spectral measures, such as the power in individual spectral bands, showed minor inconsistencies between studies. Although relative power reflects a ratio of a certain spectrum band to total bandpower, a spectral ratio such as $(\alpha + \beta) / (\delta + \theta)$ encompasses a larger range of the EEG spectrogram than individual spectral bands and is therefore more informative and may provide a better reflection of EEG slowing. When using individual bandpowers, assessing both absolute- and relative bandpowers seems appropriate, according to the aim of the analysis, to facilitate direct comparison between individuals or to more accurately identify the actual changes that occurred within a specific frequency band.

However, activity above 20 Hz is frequently affected by tonic scalp and neck muscle activity. The individual β and γ band ranges may reflect EMG activity rather than cortical oscillations.[44] Consideration of possible EMG artifacts is therefore required when interpreting spectral power above 20 Hz.[44]

Presence or severity of cognitive impairment correlated with desynchronization in the α bands and reduced network integration,[28, 30] but the sign and strength of the correlation depended strongly on the type of connectivity variable analyzed. Based on the findings of this review, there is still insufficient evidence for the use of measures of connectivity as a biomarker of cognitive function. Careful consideration of the methodology is required when interpreting results on connectivity or network metrics, as exemplified by significant results for edge-wise level network measures (uncorrected for volume conduction) which were not observed on global-level (unweighted) network metrics in the same study.[28]

Ideally, qEEG measures would provide prognostic biomarkers of future clinical deterioration. Five studies reported longitudinal data on cognition and qEEG.[11, 12, 31-33] A slower dominant frequency was shown to be particularly predictive of future cognitive deterioration, both at group level and at an individual level.[11, 12, 31, 32] These findings have also been replicated using MEG.[45] However, although several studies reported 'biomarkers' of cognitive deterioration, only two studies reported biomarkers at an individual level: both θ power [33] and dominant frequency could predict cognitive decline for individual patients.[32] Both measures can be calculated relatively easily in a clinical setting. Whether the utility of dominant frequency and θ power as a biomarker for cognitive decline is similar for every stage of cognitive decline is unknown. We recommend that these variables are interpreted as indicators of potential cognitive decline that warrant further investigation, rather than definitive proof of a transition to a different cognitive state.

Findings on correlations of qEEG and motor dysfunction were inconclusive. Overall, EEG variables did not significantly correlate with the MDS-UPDRS III total score; the only two studies that reported significant correlations had methodological limitations associated with the small sample size [8] or confounding drug-induced spectral changes.[35] Whether spectral differences between ON-medication and OFF-medication state are induced by medication directly or due to improved motor function currently remains unknown. Correlations with HY motor stage were either non-significant, or showed an association between cortical slowing and increased global dysfunction, suggesting that disease progression may have been the underlying cause of both. The correlation of motor function and connectivity depended on the type of connectivity measures, exemplified by a positive correlation with HY stage and β power asymmetry, a negative correlation with θ power asymmetry and a non-

significant correlation with δ and α power asymmetry.[19] Compared to the cognitive domain which involves interactions between large sections of the cortex, motor function is less well reflected by cortical regions other than the motor cortex. Although basal ganglia activity may influence cortical rhythms, resting state qEEG likely has insufficient spatial resolution to pick up focal oscillatory alterations related to motor dysfunction. Task-based registrations, e.g. evaluating μ rhythm, may be more sensitive to reflect motor activity.[46] Techniques with a higher spatial resolution such as MEG or LFPs recording may be more useful, but are less applicable as clinical tools since they are not widely available or invasive.

The effect of treatment on qEEG measures remains equally unclear. Four studies investigated ON-OFF transition, but comparability is limited by differences in design, patient population and qEEG measures. Again, results on connectivity were highly dependent on the type of connectivity measures. This is not surprising, given that the characteristics of connectivity measures are highly variable and may be subject to volume conduction (e.g. synchronization likelihood, PLV, coherence), non-linearity (coherence), and distinction of direct or indirect relations (coherence, PLV, PLI). Phase-based measures, such as PLI, are robust against volume conduction and thereby less sensitive to spurious interactions, and are therefore recommended. Additionally, PLI does not depend on signal-amplitudes although small phase-differences may be missed with increasing noise.[47] Subsequent network metrics that are robust against the effect of network density may be useful, such as MST metrics. Careful consideration of the individual advantages and disadvantages of different connectivity measures is advised.[47]

Both studies on DBS were limited by DBS-related artifacts and require further verification. Especially in these studies, volume conduction may account for the spreading of β power over the frontoparietal EEG electrodes.[48] Moreover, MEG studies showed that DBS induces artifacts within the β band range.[49]

Other clinical characteristics, including disease duration and depression, were studied in a limited number of studies with inconsistent findings. Whereas the correlation between spectral measures and cognitive function emerged as robust, this was not the case for other disease- or clinically-related features.

Limitations of available studies

Several potential confounders across studies may have influenced the results, such as variability in the age range of patients. Since the effect of aging on EEG slowing is well-known, this should be consistently taken into account in the analysis. Various studies did not report whether patients took psychoactive medication, whereas others mentioned that

these drugs were withdrawn 48 hours prior to registration.[21, 37] In two studies, however, the use of psychoactive medication was allowed,[16, 26] which might have influenced the results.[50] As it may not always be safe or ethical to withdraw psychoactive medication, we recommend that studies account for the use of these drugs during their analyses.

Another confounder could be the different definitions of spectral variables used. Three studies on cognition defined dominant frequency as Background Rhythm Frequency (BRF). However, two other studies (investigating the same cohort) defined BRF as the dominant peak in the FFT average at electrodes P3, P4 and Oz by means of visual inspection.[11, 31] Another study defined BRF as the dominant α peak at positions O1 and O2.12 While visual inspection limits reproducibility, the FFT peak may lie outside the α-range in case of severe EEG slowing and may inaccurately reflect the true 'dominant' frequency. Comparability between studies may thus be improved by a uniform definition of 'dominant frequency', e.g. the FFT peak within the range of 4–13 Hz, at similar electrode positions (e.g. O1 and O2 to capture the dominant α peak). Likewise, different cutoff values for frequency bands were used in various studies: 20 studies used classic bandpower definitions (i.e. δ: ± 0.5-4 Hz, θ: 4-8 Hz, α 8-13 Hz, β: 13- ±30 Hz), whilst 14 studies used non-consecutive bandpower definitions (e.g. δ: ± 1.17-3.91 Hz, θ: 4.30-7.81 Hz, α 8.20-12.89 Hz, β: 13.28-30.08 Hz).[17, 18, 36] Two studies did not describe bandpower definitions.[8, 32] Although the differences are small, consecutive bandpower definitions warrants that all spectral information is included, but may lead to overflowing of one frequency band into another.[31] However, using a pre-defined interval may result in loss of potentially interesting data, e.g. when the Fast Fourier Transformation (FFT) peak lies in the out-filtered range. Consecutive bandpower definitions warrant that the crucial FFT peak is analyzed, which is required for correct interpretation of the EEG spectrogram. To this end, we find the use of an average FFT both more practical and accurate with respect to other methods.

MEG-studies demonstrated oversynchronization in early-stage PD patients (relative to controls) which reversed with disease progression, indicating a non-linear correlation of connectivity to clinical symptoms.[51, 52] Although this pattern has not been studied with EEG, these results implicate that the disease stage of the source population needs to be considered when assessing connectivity.[52]

Another issue concerned the definition of the outcomes, for example the classification of PD-MCI. This classification varied over time,[53] which resulted in the Movement Disorders Society delineating diagnostic criteria for PD-MCI in 2012.[54] The variable definitions of MCI used in seven studies may account for discrepancies in results.

Several studies investigated qEEG metrics at electrode-level rather than focal areas of several electrodes.[9, 21, 35, 37, 48] Adjacent electrodes are influenced by common sources or volume conduction and are therefore dependent on the type of reference used. We speculate that the use of global EEG measures may be more informative of widespread cortical involvement (α-synucleiopathy), rather than focal EEG measures.[55] Moreover, the use of single references, such as the central electrode or the mastoid, may be influenced by brain activity and therefore affect the difference in electric potential between electrodes. Whereas spectral analyses are less dependent on the choice of reference, the choice of reference influences both the strength and directionality of functional connectivity.[47] Although the choice of reference may have little clinical consequences, the scientific (pathophysiological) background of these correlations may be limited. Re-referencing towards a source derivation can aid in correctly interpreting localization of findings.[47]

The use of different setups, e.g. polysomnographic registration with two electrodes versus high-density acquisition, may not be directly comparable. The choice of setup depends both on the clinical correlation of interest and on the type of EEG analysis. In case of spectral analyses, we recommend a standard 21-electrode setup to allow sufficient spatial resolution whilst maintaining proper source localization. This setup is also readily utilizable in a clinical setting. For connectivity and network analyses, higher density setups may improve accuracy in identifying brain networks, but careful consideration of source reconstruction is required.[47]

Strengths and limitations of this review

Strengths of our systematic review include the use of the PRISMA guideline, the application of a systematic search strategy and the use of a validated risk of bias assessment tool. When interpreting the findings of this review, it should be considered that differences between studies in (non-standard) methods of EEG acquisition and/or the use of psychoactive medication may have influenced the results. In addition, our review excluded studies with task-based registrations to improve comparability between studies; however, previous literature suggests that centralization and network integration may be task-dependent.[56]

Applicability to clinical practice and knowledge gaps

QEEG is widely available, relatively inexpensive, and easily reproducible. As depression and RBD may manifest early in the course of PD,[2] the few observations supporting associations between qEEG variables and both RBD [41] and depression [19, 39] suggests that oscillatory changes may also be present early in the disease course. Moreover, since RBD may be a risk factor for cognitive impairment in patients with PD,[57] the EEG slowing observed in PD patients with RBD [41] may be an early indicator of cognitive deterioration. The observation that EEG slowing

precedes the development of PDD in the absence of clinically manifest dementia supports the notion that qEEG alterations may have predictive value early in the disease course. One study reported that patients with PDD who received rivastigmine to improve cognitive performance showed increases in α power. However, improvements in cognition were not significantly correlated with qEEG changes.[58] This study did not meet our inclusion criteria and was excluded from this review. Whether the pattern of qEEG slowing related to cognitive impairment is reversible, either with medication or cognitive training, remains unknown.

Spectral analyses may be applied as biomarkers of future (cognitive) deterioration and be utilized to complement current evaluation strategies. Desynchronization patterns reflecting altered connectivity may be more domain-specific but have been sparsely studied. Moreover, interpretation of either desynchronization or oversynchronization may be more difficult than evaluation of spectral changes in widespread clinical practice. There is currently limited evidence for utilizing qEEG to reflect non-cognitive domains or to apply connectivity measures as biomarkers. Moreover, the pattern of correlation is highly dependent on the type of connectivity measure; careful consideration of the nature of the connectivity measure is required for correct interpretation.[47] Future research should focus on studying functional connectivity and network measures to further explore biomarker specificity, and assess the utility scope of advanced EEG analyses. The accuracy of qEEG in reflecting progression of non-cognitive symptoms over time remains unresolved and should be further studied. Solid large prospective studies with sufficient follow-up and longitudinal assessments of other non-cognitive domains, which are currently lacking, should be performed. Big data analysis, i.e. artificial neural networks, machine learning, and deep learning, may further play a role in identifying specific prognostic biomarkers of clinical symptoms. Given the variability in design and analysis in the described studies, standardization in both acquisition and reporting may improve comparison between studies.[59] In order to ensure reliable data analysis, careful selection of epochs free of artifacts or automatic artifact detection is crucial. The use of qEEG as a biomarker in PD likely reflects cortical α-synucleiopathy. Other biomarkers may reflect different aspects of PD pathology, such as cardiac scintigraphy reflecting α-synucleiopathy in the peripheral nervous system. The use of complementary biomarkers may identify different systems-at-risk and may be studied in parallel.

The observed qEEG changes may not be specific for PD patients, although qEEG differentiates between other neurodegenerative diseases such as Alzheimer's Disease and dementia with Lewy Bodies with high accuracy.[60] However, a comparison of qEEG changes between these pathologies was not considered to be a clinical symptom related to PD and therefore beyond the scope of this review.

Conclusion

The correlation between qEEG and cognitive impairment is well established: a lower dominant frequency or increased θ power is correlated with cognition and is predictive of future cognitive deterioration also at the individual level.

At present, there is insufficient evidence to support the use of qEEG metrics to examine other domains or treatment effects in PD patients. Functional connectivity and network analyses may have potential utility as novel specific biomarkers, but further studies are needed to investigate their clinical applicability.

Altogether the results of this review suggest that qEEG provide inexpensive, reliable, and widely available measures that could serve as biomarkers for non-motor disease severity in patients with PD. The availability of objective biomarkers of disease severity and progression in PD could directly contribute to patient management, potentially providing the opportunity of an early diagnosis of non-motor symptoms, a more reliable prognosis, and an objective monitoring of progression, both in the context of clinical practice and clinical trials.

References

1. Barone P, Antonini A, Colosimo C, et al. The PRIAMO study: A multicenter assessment of nonmotor symptoms and their impact on quality of life in Parkinson's disease. Mov Disord 2009;24:1641-1649.
2. Chaudhuri KR, Healy DG, Schapira AH, National Institute for Clinical E. Non-motor symptoms of Parkinson's disease: diagnosis and management. Lancet Neurol 2006;5:235-245.
3. van der Heeden JF, Marinus J, Martinez-Martin P, van Hilten JJ. Importance of nondopaminergic features in evaluating disease severity of Parkinson disease. Neurology 2014;82:412-418.
4. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Clinical pharmacology and therapeutics 2001;69:89-95.
5. Mikolajewska E, Mikolajewski D. Non-invasive EEG-based brain-computer interfaces in patients with disorders of consciousness. Military Medical Research 2014;1:14.
6. Stam CJ. Nonlinear Brain Dynamics. New York: Nova Science, 2006.
7. Stam CJ, Tewarie P, Van Dellen E, van Straaten EC, Hillebrand A, Van Mieghem P. The trees and the forest: Characterization of complex brain networks with minimum spanning trees. Int J Psychophysiol 2014;92:129-138.
8. Jech R, Ruzicka E, Urgosik D, et al. Deep brain stimulation of the subthalamic nucleus affects resting EEG and visual evoked potentials in Parkinson's disease. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology 2006;117:1017-1028.
9. Moisello C, Blanco D, Lin J, et al. Practice changes beta power at rest and its modulation during movement in healthy subjects but not in patients with Parkinson's disease. Brain and behavior 2015;5:e00374.
10. Bonanni L, Thomas A, Tiraboschi P, Perfetti B, Varanese S, Onofrj M. EEG comparisons in early Alzheimer's disease, dementia with Lewy bodies and Parkinson's disease with dementia patients with a 2-year follow-up. Brain : a journal of neurology 2008;131:690-705.
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. Latreille V, Carrier J, Gaudet-Fex B, et al. Electroencephalographic prodromal markers of dementia across conscious states in Parkinson's disease. Brain 2016;139:1189-1199.
13. Critical Appraisal Checklist for Case Series [online]. Available at: http://joannabriggs.org/research/critical-appraisal-tools.html. Accessed 02-01-2018.
14. Caviness JN, Hentz JG, Evidente VG, et al. Both early and late cognitive dysfunction affects the electroencephalogram in Parkinson's disease. Parkinsonism Relat Disord 2007;13:348-354.
15. Guner D, Tiftikcioglu BI, Tuncay N, Zorlu Y. Contribution of Quantitative EEG to the Diagnosis of Early Cognitive Impairment in Patients With Idiopathic Parkinson's Disease. Clinical EEG and neuroscience 2016.
16. Helkala E-L, Laulumaa V, Soikkeli R, Partanen J, Soininen H, Riekkinen PJ. Slow-wave activity in the spectral analysis of the electroencephalogram is associated with cortical dysfunctions in patients with Alzheimer's disease. Behavioral Neuroscience 1991;105:409-415.
17. Kamei S, Morita A, Serizawa K, Mizutani T, Hirayanagi K. Quantitative EEG analysis of executive dysfunction in Parkinson disease. Journal of clinical neurophysiology : official publication of the American

Electroencephalographic Society 2010;27:193-197.

18. Morita A, Kamei S, Mizutani T. Relationship between slowing of the EEG and cognitive impairment in Parkinson disease. J Clin Neurophysiol 2011;28:384-387.
19. Mostile G, Nicoletti A, Dibilio V, et al. Electroencephalographic lateralization, clinical correlates and pharmacological response in untreated Parkinson's disease. Parkinsonism & related disorders 2015;21:948-953.
20. Stanzione P, Marciani MG, Maschio M, et al. Quantitative EEG changes in non-demented Parkinson's disease patients before and during L-dopa therapy. European Journal of Neurology 1996;3:354-362.
21. He X, Zhang Y, Chen J, et al. Changes in theta activities in the left posterior temporal region, left occipital region and right frontal region related to mild cognitive impairment in Parkinson's disease patients. The International journal of neuroscience 2017;127:66-72.
22. Caviness JN, Utianski RL, Hentz JG, et al. Differential spectral quantitative electroencephalography patterns between control and Parkinson's disease cohorts. Eur J Neurol 2016;23:387-392.
23. Fonseca LC, Tedrus GM, Letro GH, Bossoni AS. Dementia, mild cognitive impairment and quantitative EEG in patients with Parkinson's disease. Clin EEG Neurosci 2009;40:168-172.
24. Neufeld MY, Blumen S, Aitkin I, Parmet Y, Korczyn AD. EEG frequency analysis in demented and nondemented parkinsonian patients. Dementia (Basel, Switzerland) 1994;5:23-28.
25. Pozzi D, Petracchi M, Sabe L, Dancygier G, Garcia H, Starkstein S. Quantified electroencephalographic changes in Parkinson's disease with and without dementia. European journal of neurology 1994;1:147-152.
26. Soikkeli R, Partanen J, Soininen H, Paakkonen A, Riekkinen P, Sr. Slowing of EEG in Parkinson's disease. Electroencephalography and clinical neurophysiology 1991;79:159-165.
27. Tanaka H, Koenig T, Pascual-Marqui RD, Hirata K, Kochi K, Lehmann D. Event-related potential and EEG measures in Parkinson's disease without and with dementia. Dementia and geriatric cognitive disorders 2000;11:39-45.
28. Hassan M, Chaton L, Benquet P, et al. Functional connectivity disruptions correlate with cognitive phenotypes in Parkinson's disease. Neuroimage-Clinical 2017;14:591-601.
29. Eichelberger D, Calabrese P, Meyer A, et al. Correlation of Visuospatial Ability and EEG Slowing in Patients with Parkinson's Disease. Parkinsons Dis 2017;2017:3659784.
30. 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.
31. Klassen BT, Hentz JG, Shill HA, et al. Quantitative EEG as a predictive biomarker for Parkinson disease dementia. Neurology 2011;77:118-124.
32. Arnaldi D, De CF, Fama F, et al. Prediction of cognitive worsening in de novo Parkinson's disease: Clinical use of biomarkers. Movement disorders : official journal of the Movement Disorder Society 2017;32:1738-1747.
33. Cozac VV, Chaturvedi M, Hatz F, Meyer A, Fuhr P, Gschwandtner U. Increase of EEG Spectral Theta Power Indicates Higher Risk of the Development of Severe Cognitive Decline in Parkinson's Disease after 3 Years. Frontiers in aging neuroscience 2016;8:284.
34. 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.
35. Melgari JM, Curcio G, Mastrolilli F, et al. Alpha and beta EEG power reflects L-dopa acute administration in

parkinsonian patients. Frontiers in aging neuroscience 2014;6:302.

36. Morita A, Kamei S, Serizawa K, Mizutani T. The relationship between slowing EEGs and the progression of Parkinson's disease. J Clin Neurophysiol 2009;26:426-429.
37. He X, Zhang Y, Chen J, et al. The patterns of EEG changes in early-onset Parkinson's disease patients. The International journal of neuroscience 2017;127:1028-1035.
38. 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.
39. Filipovic SR, Covickovic-Sternic N, Stojanovic-Svetel M, Lecic D, Kostic VS. Depression in Parkinson's disease: an EEG frequency analysis study. Parkinsonism & related disorders 1998;4:171-178.
40. Hatz F, Meyer A, Zimmermann R, Gschwandtner U, Fuhr P. Apathy in Patients with Parkinson's Disease Correlates with Alteration of Left Fronto-Polar Electroencephalographic Connectivity. Frontiers in aging neuroscience 2017;9:262.
41. Gagnon JF, Fantini ML, Bedard MA, et al. Association between waking EEG slowing and REM sleep behavior disorder in PD without dementia. Neurology 2004;62:401-406.
42. Fonseca LC, Tedrus GM, Rezende AL, Giordano HF. Coherence of brain electrical activity: a quality of life indicator in Alzheimer's disease? Arquivos de neuro-psiquiatria 2015;73:396-401.
43. Cozac VV, Auschra B, Chaturvedi M, et al. Among Early Appearing Non-Motor Signs of Parkinson's Disease, Alteration of Olfaction but Not Electroencephalographic Spectrum Correlates with Motor Function. Frontiers in neurology 2017;8:545.
44. Whitham EM, Lewis T, Pope KJ, et al. Thinking activates EMG in scalp electrical recordings. Clin Neurophysiol 2008;119:1166-1175.
45. Olde Dubbelink KT, Hillebrand A, Twisk JW, et al. Predicting dementia in Parkinson disease by combining neurophysiologic and cognitive markers. Neurology 2014;82:263-270.
46. Kumar S, Riddoch MJ, Humphreys G. Mu rhythm desynchronization reveals motoric influences of hand action on object recognition. Front Hum Neurosci 2013;7:66.
47. van Diessen E, Numan T, van Dellen E, et al. Opportunities and methodological challenges in EEG and MEG resting state functional brain network research. Clin Neurophysiol 2015;126:1468-1481.
48. Swann N, Poizner H, Houser M, et al. Deep brain stimulation of the subthalamic nucleus alters the cortical profile of response inhibition in the beta frequency band: a scalp EEG study in Parkinson's disease. The Journal of neuroscience : the official journal of the Society for Neuroscience 2011;31:5721-5729.
49. Cao CY, Zeng K, Li DY, Zhan SK, Li XL, Sun BM. Modulations on cortical oscillations by subthalamic deep brain stimulation in patients with Parkinson disease: A MEG study. Neurosci Lett 2017;636:95-100.
50. Galderisi S, Sannita WG. Pharmaco-EEG: A history of progress and a missed opportunity. Clin EEG Neurosci 2006;37:61-65.
51. Stoffers D, Bosboom JL, Deijen JB, Wolters E, Stam CJ, Berendse HW. Increased cortico-cortical functional connectivity in early-stage Parkinson's disease: an MEG study. Neuroimage 2008;41:212-222.
52. Olde Dubbelink KT, Stoffers D, Deijen JB, et al. Resting-state functional connectivity as a marker of disease

progression in Parkinson's disease: A longitudinal MEG study. NeuroImage Clinical 2013;2:612-619.

53. Petersen RC, Caracciolo B, Brayne C, Gauthier S, Jelic V, Fratiglioni L. Mild cognitive impairment: a concept in evolution. Journal of internal medicine 2014;275:214-228.
54. Litvan I, Goldman JG, Troster AI, et al. Diagnostic criteria for mild cognitive impairment in Parkinson's disease: Movement Disorder Society Task Force guidelines. Mov Disord 2012;27:349-356.
55. Geraedts VJ, Marinus J, Gouw AA, et al. Quantitative EEG reflects Non-Dopaminergic Disease Severity in Parkinson's Disease. Clinical Neurophysiology. https://doi.org/10.1016/j.clinph.2018.04.752
56. Fraga Gonzalez G, Van der Molen MJW, Zaric G, et al. Graph analysis of EEG resting state functional networks in dyslexic readers. Clin Neurophysiol 2016;127:3165-3175.
57. Gagnon JF, Vendette M, Postuma RB, et al. Mild cognitive impairment in rapid eye movement sleep behavior disorder and Parkinson's disease. Ann Neurol 2009;66:39-47.
58. Fogelson N, Kogan E, Korczyn AD, Giladi N, Shabtai H, Neufeld MY. Effects of rivastigmine on the quantitative EEG in demented Parkinsonian patients. Acta neurologica Scandinavica 2003;107:252-255
59. Keil A, Debener S, Gratton G, et al. Committee report: publication guidelines and recommendations for studies using electroencephalography and magnetoencephalography. Psychophysiology 2014;51:1-21.
60. Dauwan M, van der Zande JJ, van Dellen E, et al. Random forest to differentiate dementia with Lewy bodies from Alzheimer's disease. Alzheimer's & dementia(Amsterdam, Netherlands) 2016;4:99-106.

Supplementary material

6.1 JBI Critical Appraisal Checklist for Case Series

		Yes	No	Unclear	Not Applicable
1.	Were there clear criteria for inclusion in the case series?	☐	☐	☐	☐
2.	Was the condition measured in a standard, reliable	☐	☐	☐	☐
3.	way for all participants included in the case series?				
4.	Were valid methods for identification of the	☐	☐	☐	☐
5.	condition for all participants included in the case series?				
6.	Did the case series have consecutive inclusion of participants?	☐	☐	☐	☐
7.	Did the case series have complete inclusion of participants?	☐	☐	☐	☐
8.	Was there clear reporting of the demographics of the participants in the study?	☐	☐	☐	☐
9.	Was there clear reporting of clinical information of the participants?	☐	☐	☐	☐
10.	Were the outcomes or follow up results of cases clearly reported?	☐	☐	☐	☐
11.	Was there clear reporting of the presenting site(s)/ clinic(s) demographic information?	☐	☐	☐	☐
12.	Was statistical analysis appropriate?	☐	☐	☐	☐
13.	Was there clear reporting of EEG acquisition?	☐	☐	☐	☐

Overall appraisal: Include Exclude Seek further info

Minimum requirements: 1x 'yes' question 1-3, 2x 'yes' question 4-8, 1x 'yes' question 11, at least 6x 'yes' in total.

Supplementary table 6.1 Correlation of qEEG and cognition

Reference	qEEG variable described	Main conclusions
Bonanni et al [10]	Rel. SP, dom. freq., CSA	**Fast** θ: PDD-F>PDD-NF
Caviness et al [14]	Rel. SP, dom. freq.	**Dom. freq.**: PDD<PD-MCI<PD-NCOG. δ: PDD>PD-NCOG, PDD>PD-MCI. θ: PD-MCI>PD-NCOG. α:PDD<PD-NCOG. **β1** and **β2**: PDD<PD-NCOG, PD-MCI<PD-NCOG. + corr.: MMSE with **BRF** and α **power**. Trails B score with **frontal** δ **and** θ **power**. CDT and JLO scores with **parietal** δ **power**. - corr.: MMSE and δ **power**. No correlation: Stroop with **SP**.
Caviness et al [22]	Dom. freq., Rel. SP	**Dom. freq.**: PDD<PD-PD-MCI<PD-NCOG. δ: PD-NCOG<PD-MCI<PDD. θ: PD-MCI>PD-NCOG, α: PD-NCOG>PD-MCI>PD-MCI.
Eichelberger et al [29]	Ratio (α / θ)	Lower **ratio** when incorrectly drawn CDT, lower **par. occ. ratio** with worse ROCF. No corr.: **ratio** with block design test, digit span.
Fonseca et al [23]	Abs. and rel. SP	**Post. rel.** δ: PD-MCI<PDD, PD-NCOG<PDD. **Post. abs.** δ: PD-NCOG<PDD, PD-MCI<PDD. **Post. rel.** θ: PD-NCOG<PD-MCI, PD-NCOG<PDD. **Post. rel.** α: PD-NCOG>PDD.
Guner et al [15]	Ratio α/β over δ/θ power, abs. SP	+ corr.: **ratio** with MMSE. Extensive neuropsychological tests correlated weakly and diffusely with **ratio.**
Hassan et al [28]	Rel. SP, PLV, wMNE, EWCI.	+ corr.: cognitive state and δ**,** θ **power, edge-wise level PLV-derived α1 and α2**. **EWCI** and cognitive score. - corr.: cognitive state and β **power.** No corr.: **α1 and α2 power** and cognitive state. **Global level PLV-derived P_L, C_c, Str, E_G.**
He et al [21]	Rel. SP	**Left post. temp., left occ.,** and **left front.** θ: PD-NCOG<PD-MCI. - corr.: θ **F4** and **T5** with MOCA (particularly visuospatial function and attention). No corr.: **SP** with MMSE.
Helkala et al [16]	Abs. spect. amp., dom. freq..	+ corr: α **amp**. With WAIS VIQ and PIQ, visual and praxic functions and list learning. β **amp.** With WAIS VIQ and PIQ and list learning. **Dom. freq.**. with WAIS VIQ, visual functions, speech understanding, list learning and category fluency.
Kamei et al [17]	Ratio (α + β) / (δ + θ)	+ corr.: **ratio** with BADS
Latreille et al [12]	Abs. SP, ratio (δ +θ) / (α + β), dom. freq.	δ**, ratio**: PD-NCOG<PDD. **Dom. freq.:** PDD<PD-NCOG. No corr.: **qEEG** with extensive neuropsychological tests.
Morita et al [18]	Ratio (α + β) / (δ + θ)	+ corr.: **ratio** with MMSE
Mostile et al [19]	IL	No corr.: **IL** with MMSE or FAB
Neufeld et al [24]	Rel. SP	α: PD-NCOG>PDD.
Pozzi et al [25]	Abs. SP	θ: PD-NCOG<PDD.
Soikkeli et al [26]	Abs. and rel. SP, dom. freq.	**Abs.** and **rel.** δ**, rel.** θ: PD-NCOG<PDD. **Abs.** and **rel.** α and β**, dom. freq.:** PD-NCOG>PDD.
Stanzione et al [20]	Rel. SP, dom. freq..	No corr.: δ and **β1** with WCST.
Tanaka et al [27]	Abs. SP	+ corr.: **total power** and α with intellectual status.

Supplementary table 6.1 continued.

Reference	qEEG variable described	Main conclusions
Utianski et al [30]	Phase-lag-index (PLI), weighted network (WN), minimum spanning tree (MST)	**α1 PLI**: PD-NCOG>PDD, **α1 WN (γ, λ, κ_w)**: PD-NCOG>PDD, **α1 WN (mod.)**: PD-NCOG<PDD, **α2 WN (mod.)**: PD-NCOG<PDD, δ **MST (BC)** PD-NCOG<PDD, **α1 MST (BC, leaf)**: PD-NCOG<PDD; **MST (diam., ecc.)**: PD-NCOG<PDD, **α2 MST (diam.)**: PD-NCOG<PDD. δ and θ **PLI**: PD-NCOG<PD-MCI, **α1 WN (γ, κ_w)**: PD-NCOG>PD-MCI), **α1 MST (leaf)**: PD-NCOG>PD-MCI. + corr.: **α1 PLI, α1 WN (γ, κ_w), α2 WN (κ_w), δ MST (diam., ecc.)** with MMSE. **α1** and **α2 WN (γ),** δ and **α1 WN (κ_w)** and θ and **α1 MST (leaf)** with MOCA. - corr.: θ **WN (γ), α1** and **α2 WN (mod.), δ MST (BC), α2 MST (diam., ecc.)** with MMSE. δ and **α1 WN (mod.)** and θ and **α1 MST (ecc.)** with MOCA.

Supplementary table 6.2 Longitudinal assessments

Reference	qEEG variable described	Main conclusions
Arnaldi et al [32]	Dom. freq.	**Dom. freq.:** 82% acc. In predicting cognitive outcome.
Caviness et al [11]	Change in dom. freq., change in Rel. SP (FU ±4 years)	**δ:** PD-incident dementia > PD-NCOG. + corr.: change in **dom. freq**.with AVLT-LTM, Stroop. - corr.: change in δ with MMSE, AVLT-LTM, Stroop, COWA, Trails B and CDT. Change in θ with Stroop. Change in α with Stroop. Change in β with AVLT-LTM.
Cozac et al [33]	GRMP	- corr.: **GRMP** θ with change-index overall cognition (3 years FU).
Klassen et al [31]	Dom. freq., rel. SP	- corr.: **dom. freq**.with conversion to PDD (5 years FU). + corr.: Θ with conversion to PDD (5 years FU).
Latreille et al [12]	Abs. SP, ratio (δ +θ) / (α + β), BRF	**Temp. ratio and BRF**: predict development PDD (4 years FU).

Supplementary table 6.3 Motor function

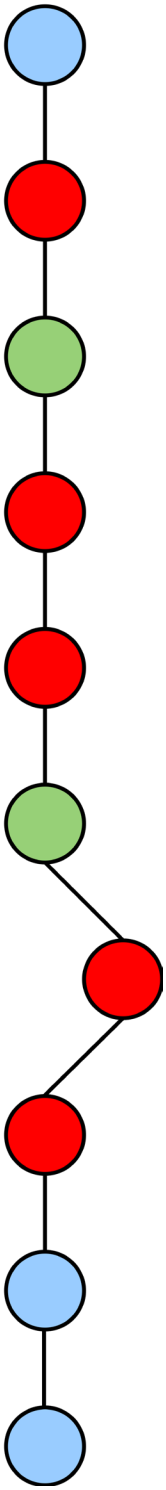
Reference	qEEG variable described	Main conclusions
Babiloni et al [34]	Rel. SP	No corr.: **α1** and MDS-UPDRS III or HY stage.
Fonseca et al [23]	Abs. and rel. SP	+ corr.: **post., frontotemp. and global** **α2** with HY stage.
George et al [38]	SP, coherence	+ corr.: **coherence** and MDS-UPDRS III.
Guner et al [15]	Ratio α/β over δ/θ power, abs. SP	No corr.: δ **and** θ and MDS-UPDRS III.
He et al [21]	Rel. SP	+ corr.: θ **(T5, F4, O1)** with HY stage. No corr.: **SP** and MDS-UPDRS III.
He et al [37]	Dom. freq., rel. SP	- corr.: β **with HY.** no corr.: **rel. SP,** β **coherence, dom. freq**. with HY or MDS-UPDRS III
Jech et al [8]	Dom. freq.	- corr.: **dom. freq.** and MDS-UPDRS III-rigidity.
Melgari et al [35]	Abs. SP	- corr.: post-L-dopa increase in α **(C4)** with rest tremor arms. Post-L-dopa increase in β **(C3, C4, P4)** with rigidity of arms and bradykinesia, β **(P3)** with rigidity of arms.
Morita et al [36]	Ratio (α + β) / (δ + θ)	- corr.: **ratio** with HY stage.
Morita et al [18]	Ratio (α + β) / (δ + θ)	- corr.: **ratio** with HY stage.
Mostile et al [19]	IL	+ corr.: β **IL (F3, F4)** with HY stage. - corr.: θ **IL (F7, F8)** with HY stage. No corr.: **IL** with MDS-UPDRS III
Neufeld et al [24]	Rel. SP	No corr.: **SP** with HY stage.
Stanzione et al [20]	Rel. SP, dom. freq.	No corr.: δ **and** **β1** with MDS-UPDRS III or HY stage

Supplementary table 6.4 Treatment

Reference	qEEG variable described	Main conclusions
George et al [38]	SP, coherence	- corr.: **coherence** with L-dopa.
Jech et al [8]	Dom. freq	- corr.: **power of dom. freq.** with DBS.
Morita et al [18]	Ratio (α + β) / (δ + θ)	No corr.: **ratio** with L-dopa or DA.
Melgari et al [35]	Abs. SP	No corr.: δ **and** θ with L-dopa responsiveness. + corr.: α **(C3, C4, T5, P3, P4, Pz)** with L-dopa, β **power (C4, P3, P4, Pz)** with L-dopa.
Mostile et al [19]	IL	+ corr.: **IL (O1, O2)** with L-dopa SDR.
Stanzione et al [20]	Rel. SP, dom. freq., inter-hemispheric asymm.	No corr.: δ **and dom. freq.** with L-dopa.
Swann et al [48]	Abs. SP	+ corr.: β **(Fz, F1, F2; P5, P7, CP5; P6, P8, CP6)** with DBS-ON.

Supplementary table 6.5 Other

Reference	qEEG variable described	Main conclusions
Cozac et al [43]	Ratio (α / θ)	No corr.: **ratio** with olfactory function.
Filipovic et al [39]	Abs. and rel. SP	**Rel. α1:** depressed<non-depressed.
Fonseca et al [42]	Inter-hemispheric coherences	No corr.: **inter-hemispheric coherences** and QoL.
Gagnon et al [41]	Abs. and rel. SP, dom. freq.	**Abs.** and **rel.** θ **(front., temp., par., occ.), abs.** δ **(front., par., occ.):** PD-RBD>PD-NRBD, **dom. freq.:** PD-RBD<PD-NRBD.
Hatz et al [40]	WN, PLI, rel SP.	+ corr: **Right. Front.** δ. No corr.: **other rel. SP** with AES. - corr.: apathy with **α2 PLI** , **α2 WN** λ, γ, **Kw.** **α2-msPLI** classifies median-split AES with sens. 70%, spec. 90%, AUC 82.5%.
He et al [21]	Rel. SP	No corr.: **SP** with disease duration.
He et al [37]	Dom. freq., rel. SP	+ corr.: **dom. freq**. with disease duration. No corr.: **rel. SP**, β **coherence** with disease duration.
Moisello et al [9]	SP	+ corr.: β with disease duration.
Morita et al [18]	Ratio (α + β) / (δ + θ)	No corr.: **ratio** with disease duration.
Mostile et al [19]	IL	No corr.: **IL** with HPRSD.



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.

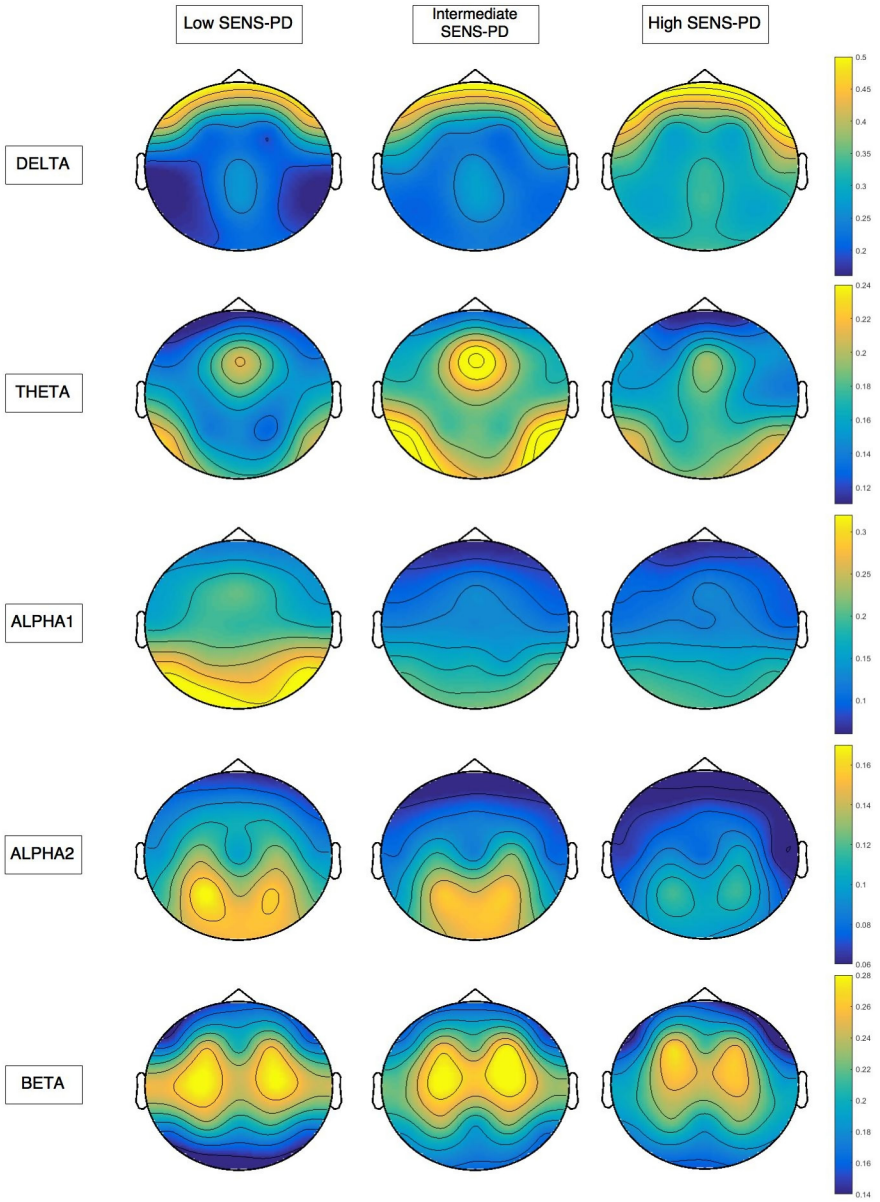


Figure 7.1. Distribution of the mean spectral powers per tertile of disease severity
The high SENS-PD group demonstrated higher power in the slow EEG frequency bands (i.e. δ and θ); the low SENS-PD group demonstrated higher power in the faster EEG frequency bands (i.e. α1, α2 and β), indicating a global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

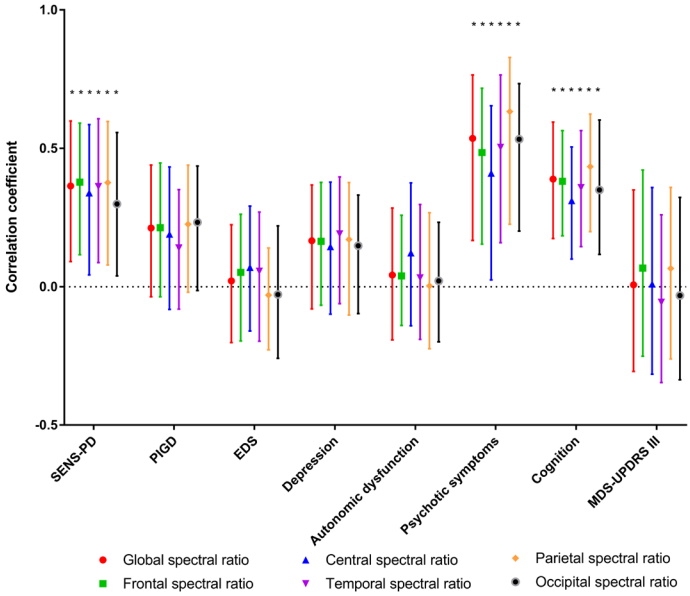


Figure 7.2. Correlation of slow-over-fast spectral ratio and disease severity
Asterisks indicate significant correlations. A spectral ratio of slow-over-fast EEG power correlated significantly with the SENS-PD composite score (i.e. more slow EEG power correlated with increased non-dopaminergic disease 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.

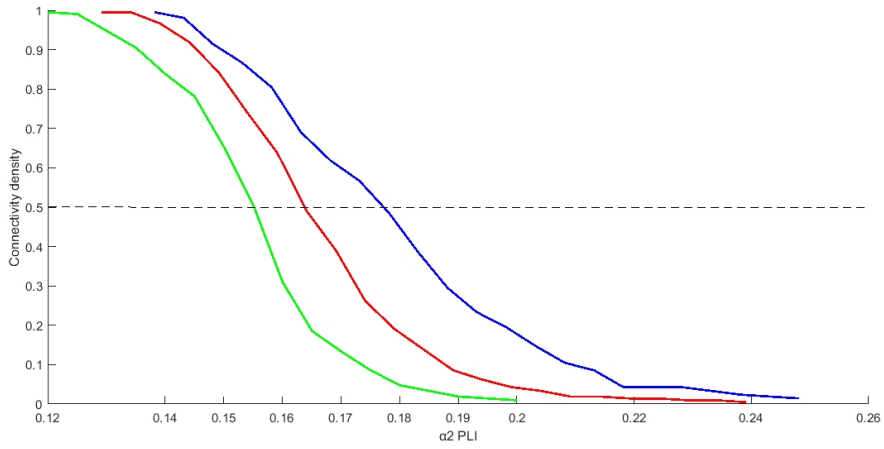


Figure 7.3A. Connectivity density per tertile of non-dopaminergic disease severity (SENS-PD)
Blue: low SENS-PD group, red: intermediate SENS-PD group, green: high SENS-PD group. The high SENS-PD group demonstrated lower α2 PLI density than the low SENS-PD group, indicating a reduction of functional connectivity 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.

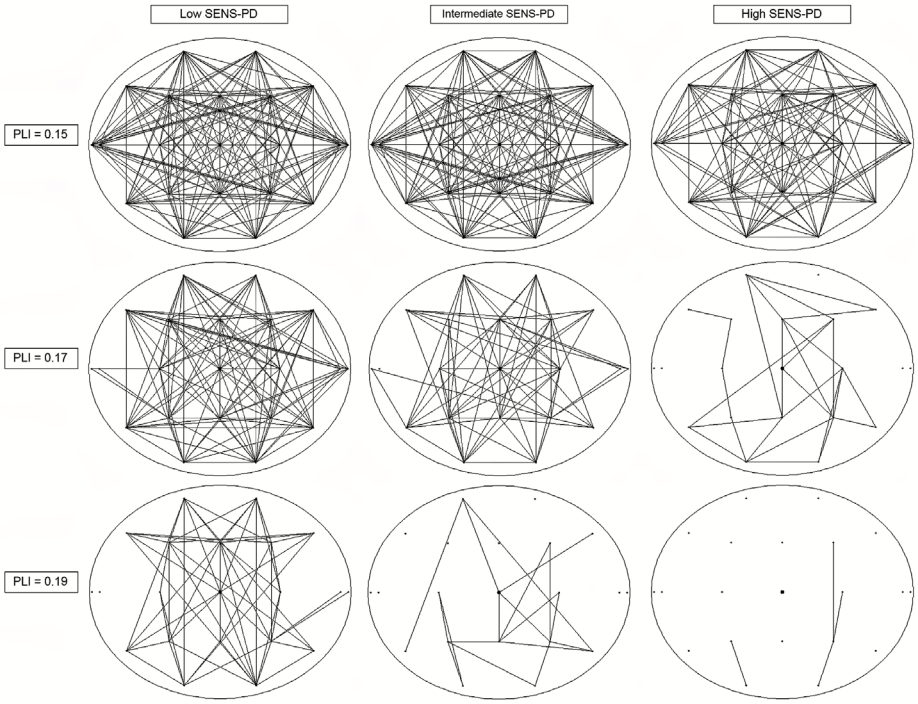


Figure 7.3B. Average network maps of the mean PLI in the α2 band per tertile of disease severity
The α2 PLI network maps are plotted at three thresholds: PLI =0.15, 0.17 and 0.19. A line indicates a level of functional connectivity of at least the threshold-value. With higher SENS-PD scores, the threshold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

Acknowledgements
The authors would like to thank G.E.L. Hendriks, R.H.A.M. Reijntjes, F.I. Kerkhof and the EEG technicians of the LUMC, for their help with the data collection.

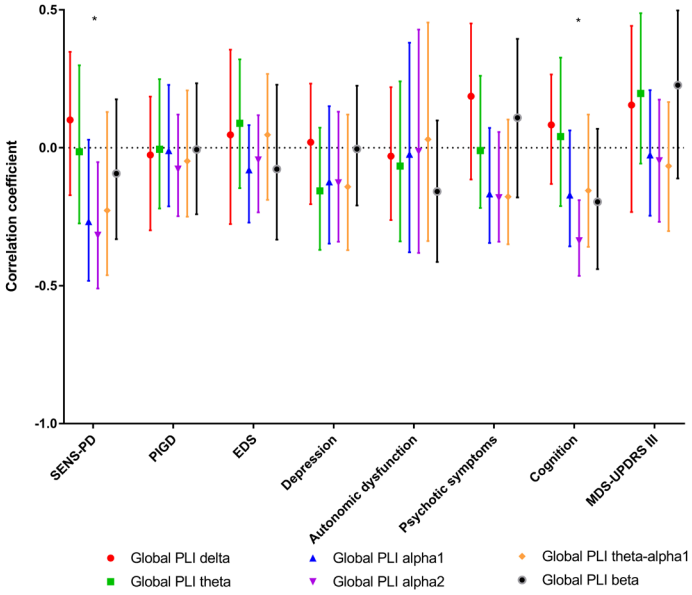
References

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

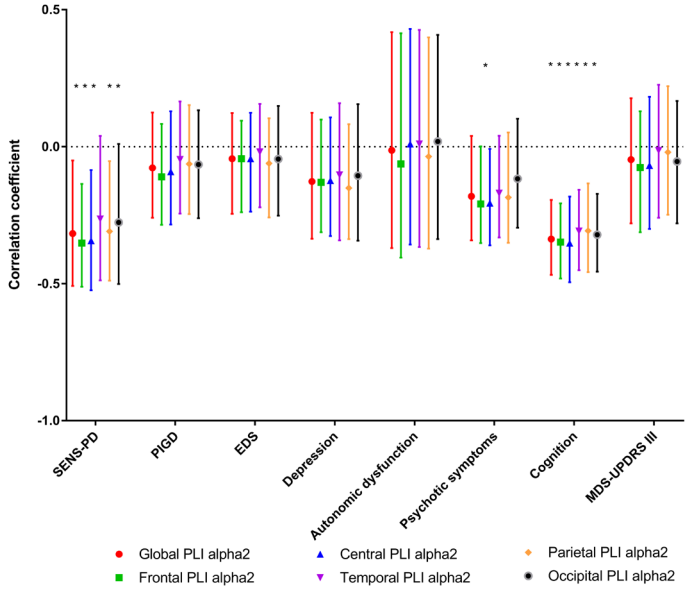
2007;22:41-47.

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

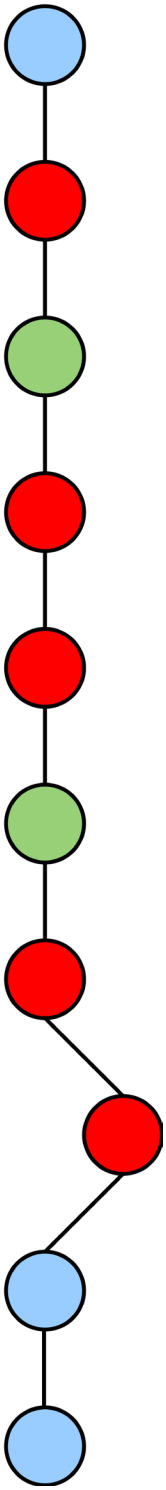
	Overall	Low SENS-PD	Intermediate SENS-PD	High SENS-PD	p[a]	p[b]
Global PLI δ band	0.15 (0.03)	0.15 (0.02)	0.16 (0.03)	0.15 (0.03)	0.104	0.977
Global PLI θ band	0.15 (0.04)	0.16 (0.05)	0.16 (0.04)	0.15 (0.03)	0.301	0.886
Global PLI α1 band	0.22 (0.07)	0.26 (0.09)	0.210 (0.04)	0.21 (0.05)	0.096	0.060
Global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



CHAPTER 8

Machine Learning for automated EEG-based classification of cognition during the DBS screening in Parkinson's Disease patients

Geraedts VJ, Koch M, Contarino MF, Middelkoop HAM, Wang H, van Hilten JJ, Bäck THW, Tannemaat MR

Under review

Abstract

Background

A downside of Deep Brain Stimulation (DBS) for Parkinson's Disease (PD) is that cognitive function may deteriorate postoperatively. Accurate cognitive assessment is crucial in determining DBS eligibility, but interpretability of this assessment is limited due to external influences.

Objective

To explore EEG as complementary biomarker for cognition using a Machine Learning (ML) pipeline to classify DBS candidates.

Methods

A fully automated ML pipeline was applied to 112 PD patients, taking EEG time-series as input and predicted class-labels as output. No arbitrary choices were made during the entire process. The most extreme cognitive performance scores were selected for class differentiation, i.e. best cognitive performance (high-COG, n=20) vs. worst cognitive function (low-COG, n=20). 16674 features were extracted per patient; feature-selection was performed using a Boruta algorithm. A random forest classifier was modelled and 10-fold cross-validation with implemented Bayesian optimization procedure was performed to ensure generalizability. The predicted class-probabilities of the entire cohort were compared to actual cognitive performance.

Results

The final model differentiated both groups with a mean (SD) accuracy of 0.92 (0.02), whereas a model using only occipital peak frequency achieved an accuracy of 0.67 (0.06). The class-probabilities and actual cognitive performance were negatively linearly correlated (β = -0.23 (95%CI (-0.29, -0.18))).

Conclusion

These findings indicate particularly high accuracies when using a compound of automatically extracted EEG biomarkers to classify PD patients according to cognition and is superior to a single spectral EEG feature. Automated EEG assessment may have utility for cognitive profiling of PD patients during the DBS screening.

Introduction

Parkinson's Disease (PD) is the fastest growing neurological disorder worldwide,[1] with both characteristic motor and non-motor symptoms. Patients who develop motor complications may be eligible for These patients may be eligible for Deep Brain Stimulation (DBS), an invasive surgical intervention which is highly effective in relieving motor complications and improves quality of life.[2, 3] Despite good effects on motor functioning and substantial relief of motor complications refractory to oral medication,[3, 4] DBS does not improve cognitive symptoms and some deterioration can be observed in cognitive domains [5, 6] and neuropsychiatric functioning after surgery.[7, 8] The screening process for DBS therefore entails an extensive evaluation of cognitive and neuropsychiatric functioning to rule out severe impairment prior to surgery, in order to determine DBS eligibility.[9, 10] However, accurate evaluations of cognition are limited by factors such as intellectual status,[11] while performance tasks may be subject to misinterpretation due to e.g. motor impairment, fatigue, mood disorder, stress, and personal motivation, which may render results less valid.[12, 13] In addition, neuropsychological screening is time-consuming and stressful for patients. Consequently, there is a need for new biomarkers to complement current neuropsychological assessments of cognition.

A candidate instrument for such complementary assessments is quantitative Electroencephalography (qEEG), which can measure brain activity directly and non-invasively. The utility of qEEG to aid during assessment of cognitive impairment, and even predict cognitive deterioration has been previously established in the general PD population.[14] Particularly spectral features reflecting EEG slowing are related to cognitive deterioration, although recent advances in EEG processing have demonstrated an association of cognitive impairment with connectivity and network dysfunction in cross-sectional studies as well.[15-17] However, these latter metrics have been sparsely studied in comparison to spectral analyses.[14] An extensive evaluation across the numerous possibilities of EEG metrics beyond spectral powers, to determine which metrics have the highest potential for reflecting PD symptoms, is lacking.

A limitation of qEEG analyses is the laborious amount of pre-processing, and particularly, the arbitrary selection of features to include during the final modelling. Traditionally, features from time series are manually selected and computed, which is time-consuming and requires expert knowledge and is therefore difficult to translate to clinical practice. A machine learning (ML) approach may overcome these limitations by providing output, such as a classification of cognitive status, without predefined data-extraction or modelling.[18] Preliminary ML results on determining levels of cognitive severity demonstrated high performance scores, although

limited to predetermined (spectral) features only. These models still require a large degree of pre-processing and manual feature-extraction.[19] Ideally, the ML approach is extended to a fully automated ML pipeline, deemed a 'sequence of data processing components'.[20] Within a ML pipeline, the EEG time series are delivered as input, after which an automated algorithm extracts a large number of features, selects those features which are needed to create a representative EEG profile, and learns and optimizes a ML model, without any intervention in between. Such a pipeline limits the necessity of making arbitrary choices, makes the entire process more efficient, and increases the likelihood of identifying novel biomarkers.

Given the need for complementary objective screening instruments to evaluate cognition during the DBS screening, the aim of our study was to evaluate the utility of a qEEG ML pipeline for determining cognitive status in these patients. To this end, the most 'extreme' DBS candidates were selected to build a supervised learning model, i.e. best vs. worst cognitive scores after a comprehensive neuropsychological test battery. The model could then be applied to evaluate the remaining DBS candidates, during which the association between ML-predictions and the actual levels of cognitive function could be studied.

Methods

Study participants

All consecutive patients who underwent preoperative screenings for DBS at the Leiden University Medical Center (LUMC) between September 2015 and June 2019 were included in the study. All patients fulfilled the criteria for clinically established PD.[21] The study was approved by the local medical ethics committee and all patients gave written informed consent.

EEG acquisition, pre-processing and analysis

EEG acquisition and pre-processing has been described elsewhere.[17] Recordings were made with 21 Ag/AgCl EEG electrodes according to standard 10-20 positions. Patients used their medication according to their individual schedules. Data were re-referenced towards a source derivation approaching the surface Laplacian derivation [22] to amplify spatial resolution.[23] After visual confirmation of artefact-free signals, five consecutive non-overlapping 4096-point epochs were selected for offline analysis in American Standard Code for Information Interchange (ASCII) format. Recordings with less than five epochs were excluded from analyses. Brainwave software was used for computation of clinically used peak frequencies ((BrainWave version 0.9.152.12.26, C.J. Stam; available at http://home.kpn.nl/stam7883/brainwave.html).

Group composition

From the comprehensive neuropsychological evaluations, six neuropsychological domains were identified according to the Diagnostic and Statistical Manual of mental disorders (5th edition, DSM-V).[24] According to DSM-V consensus guidelines, the following cognitive tests were selected for each domain: (1) 'Learning and Memory': Cambridge Cognitive Examination (CAMCOG) memory section,[25] Rey Auditory Verbal Learning Test (RAVLT),[26] and Wechsler Memory Scale (WMS);[27] (2) 'Executive Functioning': CAMCOG abstract reasoning, Digit Cancellation Test (DCT),[28] digit span,[29] Word-colour Stroop Test (Stroop) 3,[30] Trail Making Test (TMT) B;[31] (3) 'Psychomotor speed': Stroop 1 and 2, and TMT A; (4) 'Language': CAMCOG language section and verbal fluency; (5) 'Perceptive-motoric functioning': CAMCOG perception and CAMCOG praxis, and (6) 'Neuropsychiatric status': Becks Depression Inventory (BDI)[32] and Hospital Anxiety and Depression Scale (HADS) A-D.[33] All individual test-scores were standardised (Z-transformed) and averaged per domain for direct comparability. In case of missing data, an average of the remaining test-scores within the pertaining domain was used rather than imputing data, as long as ≥ 2 test-scores remained per domain (except for the domain 'Language' which contains only two tests and for which no data was imputed). A composite Z-score was derived from averaging all domains, if data from ≥ 4 domains were available. Higher Z-scores indicate better cognitive functioning. From the entire dataset, the most extreme patients in terms of cognitive performance were selected: either the highest cognitive composite scores (high-COG, n=20) or the lowest scores (low-COG, n=20). All other patients were classified as 'intermediate cognitive performance (int-COG). Given the nature of the cohort (i.e. DBS candidates who had already underwent a clinical pre-screening),[10] it was deemed unlikely that a sufficient number of patients would fulfil the criteria for either PD Dementia (PDD) or Mild Cognitive Impairment (MCI) and these classes were therefore deemed unsuitable to use for classification purposes.

Secondary outcomes included: motor function (Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part III (range 0-132)),[34] and non-dopaminergic functioning (SEverity of Non-dopaminergic Symptoms in Parkinson's Disease (SENS-PD) scale (range 0-54)),[35] and level II criteria for PD-MCI.[36]

ML Pipeline

A previously reported ML pipeline approach was used for time series classification purposes.[37, 38] Originally developed and applied in the automotive industry to classify time series originating from vehicle-data (i.e. predicting damaged parts after a low-speed crash[37, 38]), the approach was further applied to time series originating from EEGs, particularly to evaluate different ML approaches for classification of PD patients according to their cognitive performance.[39] The resulting ML pipeline consists of four phases: (1) feature-extraction,

(2) feature-selection, (3) training of a classifier, and (4) hyperparameter optimization. All four steps are completely automated, with the EEG time series as input and the class-labels (i.e. high-COG or low-COG) as output. The library 'Time Series FeatuRe Extraction on basis of Scalable Hypothesis tests' (tsfresh) was used to extract features from the time series,[40, 41] resulting in 16674 features per EEG (794 comprehensive features for each of the 21 time series).[42] Feature selection was performed using the Boruta algorithm, by testing the variable importance (VIMP) of each feature against that of 'shadow features', which are created by random shuffling of the real features. The VIMP of shadow and real features are obtained from a random forest model trained thereon. A real feature would be selected if its VIMP frequently dominates the maximal VIMP of shadow features, in multiple independent trials.[42] After feature-selection, this feature set is used to train a Random Forest Classifier (RFC). A RFC is an ensemble of decision trees; the resulting decision is the majority vote from all decision trees.[43] The hyperparameters of the RFC, such as the number of decision trees and their individual tree depths, are optimized with a variant of Bayesian Optimization technique called Mixed Integer Parallel Efficient Global Optimization (MIP-EGO)[44, 45] for mixed-integer categorical search spaces.[46] To ensure generalizability of the RFC, a cross-validation procedure was adopted: the data is randomly split into 10 folds, after which training was performed on 9 folds and tested on the remaining fold. This process was repeated until each fold has served as test set; the average of all test scores of the computations represents the final score. A secondary assessment of interval validity was based on a combination of cross-validation and split-sample validation: cross-validated model-training based on 50% of the data and validated on the remaining sample. This approach was repeated for 60-90% of the data used for model-building with the remaining sample used for internal validation purposes, although it should be noted that cross-validation is superior to split-sample validation to assess internal validity especially for small sample sizes.[47] A detailed description of the applied ML Pipeline is published elsewhere.[39] Since all four steps are fully automated, no arbitrary choices on feature-extraction or feature-selection were made during the model-building-process.

Application of the pipeline to EEG data

Both occipital and global peak frequencies, routinely used for clinical purposes, were used as standard-features. All five epochs were averaged per patient, in order to obtain more robust time series and to limit intra-individual variability.[39] The features from each individual computation-run were selected and combined. The resulting model with the combined features was evaluated for model performance. A comparison was drawn between a model using only the occipital peak frequency as a single classifying feature and the ML Pipeline using a combination of the routinely-used peak frequency and the automatically extracted features from the EEG time series.

The final selected model with the best-classifying performance was then applied to the unclassified patients (i.e. those with 'intermediate' cognitive performance scores) and the predicted probabilities of being classified as low-COG were calculated for all patients. A linear regression model was fitted with these predicted probabilities as an outcome, and the composite global cognitive score subdivided into three splines in accordance with the original cognitive classification as independent variables.

Statistical analysis

Demographic, clinical, and neuropsychological variables, as well as electrophysiological spectral features, were compared between the high-COG and low-COG groups using Student T-tests if normally distributed, and Mann-Whitney U tests if not-normally distributed in case of continuous variables, and Pearson's χ^2 Tests in case of categorical data. The ML Pipeline, as well as a model using only occipital peak frequency as classifying feature, was evaluated using accuracy, sensitivity, and specificity metrics.

Missing values, other than cognitive performance scores, were imputed using multiple imputation with five iterations in case of ≤15% missing data.
All analyses were performed using IBM Statistical Package for the Social Sciences (SPSS) 25 Software (SPSS inc., Chicago, Illinois, USA).

Data availability

Anonymized data may be shared upon request.

Results

Patient characteristics

A total of 112 patients were included. Patients classified as high-COG were younger, and with a younger age-at-onset than low-COG patients. Non-dopaminergic disease severity, as well as motor functioning during 'ON' was better in high-COG patients, whereas motor functioning during 'OFF' did not differ (see table 8.1). Composite cognitive Z scores were inherently different between the high-COG and low-COG groups with approximately 1.5 standard deviations (SD) difference (mean (SD) 0.78 (0.57) vs. -0.78 (0.54), respectively). High-COG patients had similarly better scores for the domains 'Learning and Memory', 'Perceptive-motoric functioning', 'Executive functioning', and 'Language'. Strikingly, scores for the domains 'Neuropsychiatric functioning' and 'Psychomotoric speed' were lower for the high-COG patients than for the low-COG patients.

Table 8.1. Demographic and clinical characteristics

	High-COG	Low-COG	P *	Int-COG
N	20	20		72
Age [a]	59.5 (54.6 – 66.4)	67.8 (60.1 – 72.1)	0.004	63.5 (57.7 – 68.0)
Age at onset [b]	48.2 (9.3)	55.4 (9.6)	0.023	51.1 (10.7)
% Female (n) [c]	45 (9)	10 (2)	0.031	37.5 (27)
MDS-UPDRS III 'ON' [a]	18.5 (11 – 22.5)	23 (19 – 36)	0.012	20.5 (13.3 – 30)
MDS-UPDRS III 'OFF' [a]	46.5 (39.3 – 55.5)	48.5 (41 – 57)	0.718	44 (36 – 55)
SENS-PD [b]	9.2 (4.0)	15.3 (4.8)	<0.001	12.4 (4.8)
Z Psychomotoric speed [a]	-0.71 (-0.97 - -0.38)	0.55 (-0.27 - 1.30)	<0.001	-0.23 (-0.60 – 0.18)
Z Language [a]	0.88 (0.50 - 1.24)	-0.93 (-2.11 - - 0.45)	<0.001	0.04 (-0.35 – 0.53)
Z Neuropsychiatric functioning [a]	-0.40 (-0.78 – 0.28)	0.16 (-0.39 – 0.41)	0.108	-0.12 (-0.42 – 0.37)
Z Executive functioning [a]	0.59 (0.28 – 0.74)	-0.71 (-1.64 - -0.35)	<0.001	0.08 (-0.23 – 0.40)
Z Perceptive-motoric functioning [a]	0.40 (0.40 – 0.76)	-1.35 (-1.61 - -0.63)	<0.001	0.40 (-0.06 – 0.76)
Z Learning and Memory [a]	0.92 (0.34 – 1.07)	-0.79 (-1.83 - -0.32)	<0.001	0.06 (-0.28 – 0.50)
Z Global Cognition [b]	0.78 (0.57)	-0.78 (0.54)	<0.001	0.09 (0.22)
% PD-MCI (≥2 domains ≤ -1.5 SD) (n)	0	30 (6)		0
% PD-MCI ((≥2 domains (-1, -1.5) SD (n)	0	15 (3)		3 (2)

* High-COG (20 patients with highest cognitive scores) vs. Low-COG (20 patients with lowest cognitive scores)
Int-COG = all patients with intermediate cognitive scores
[a] Mann Whitney U tests (median (interquartile range)); [b] Student T tests (mean (standard deviation)); [c] Pearson $\chi 2$ tests
MDS-UPDRS III: Movement Disorders Society – Unified Parkinson's Disease Rating Scale III; SENS-PD: SEverity of Non-dopaminergic Symptoms in Parkinson's Disease

High-COG patients had spectrally faster EEGs than low-COG patients, demonstrated by particularly higher occipital peak frequencies (mean (SD) 9.0 (0.9) vs. 7.8 (1.4) Hz) and lower ratios of slow-over-fast relative powers $((\delta + \theta) / (\alpha 1 + \alpha 2 + \beta))$ (median (interquartile range) 0.69 (0.49 – 0.86) vs. 1.21 (0.57 – 2.20) (table 8.2 and figure 8.1).

Table 8.2 EEG spectral characteristics

	High-COG	Low-COG	P *	Int-COG
Occipital peak frequency [a]	9.0 (0.9)	7.8 (1.4)	0.003	8.4 (1.4)
Total peak frequency [a]	8.8 (0.8)	7.9 (1.4)	0.013	8.2 (1.1)
Relative δ power [b]	0.21 (0.18 – 0.27)	0.24 (0.17 – 0.39)	0.369	0.26 (0.20 – 0.35)
Relative θ power [b]	0.15 (0.11 – 0.20)	0.20 (0.13 – 0.31)	0.068	0.17 (0.12 – 0.26)
Relative α1 power b	0.23 (0.16 – 0.30)	0.16 (0.07 – 0.22)	0.024	0.14 (0.09 – 0.21)
Relative α2 power [b]	0.11 (0.09 – 0.17)	0.07 (0.06 – 0.11)	0.008	0.09 (0.06 – 0.13)
Relative β power [b]	0.19 (0.16 – 0.25)	0.16 (0.12 – 0.23)	0.327	0.19 (0.15 – 0.25)
Slowing ratio $((\delta + \theta) / (\alpha 1 + \alpha 2 + \beta))$ b	0.69 (0.49 – 0.86)	1.21 (0.57 – 2.20)	0.026	1.07 (0.59 – 1.43)

* High-COG vs. Low-COG
[a] Student T-test (mean (standard deviation)); [b] Mann Whitney U test (median (interquartile range))

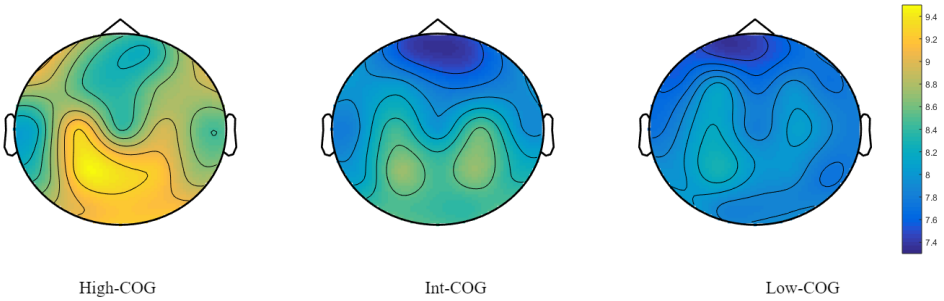


Figure 8.1 Spectral plots (peak-frequency) per cognitive class
Peak frequencies were calculated in Hz. Patients with high cognitive performance scores (high-COG) have spectrally faster EEGs than patients with lower cognitive performance scores (low-COG).

Patients classified as int-COG had clinical, cognitive, and spectral scores situated between low-COG and high-COG scores, respectively.

ML Pipeline performance

The accuracy (mean (SD)) of the average of all individual runs of the pipeline was 0.81 (0.01). After a secondary series of cross-validation runs incorporating all features from the individual runs, the extended model performance increased to 0.92 (0.02). Using only the occipital peak frequency as a classifying feature, the accuracy was lower: 0.67 (0.06) (see table 8.3). The list of features (n=13) selected by the ML pipeline included the clinically used 'occipital peak frequency'. All features were in a VIMP range of 4-15% (see supplementary table 8.1). A combination of cross-validation and split-sample validation demonstrated good internal validity for all splits (see supplementary figure 8.1).

Table 8.3 Machine learning model performances

	Occipital peak frequency only	Mean of all individual cross-validation runs	All features from all cross-validation runs
Accuracy	0.67 (0.06)	0.81 (0.01)	0.92 (0.02)
Sensitivity	0.74 (0.09)	0.82 (0.04)	0.90 (0.04)
Specificity	0.59 (0.04)	0.83 (0.07)	0.94 (0.02)

Data expressed as mean (standard deviation)

Calibration

A scatterplot demonstrating the correlation between actual cognitive functioning and the predicted probability of being classified as low-COG is shown in figure 8.2, demonstrating a negative trend (i.e. a lower probability of being classified as low-COG correlates to better

cognition: β = -0.23 (95%CI -0.29 - -0.18)). Both the high-COG and the low-COG groups contributed to this negative trend (spline-high-COG: β = -0.289 (95% CI -0.37 - -0.20), spline-low-COG: β = -0.26 (95%CI -0.34 - -0.17)), but the int-COG patients, who were not used during model-training, did not (spline-int-COG: β = 0.12 (95%CI -0.05 – 0.30).

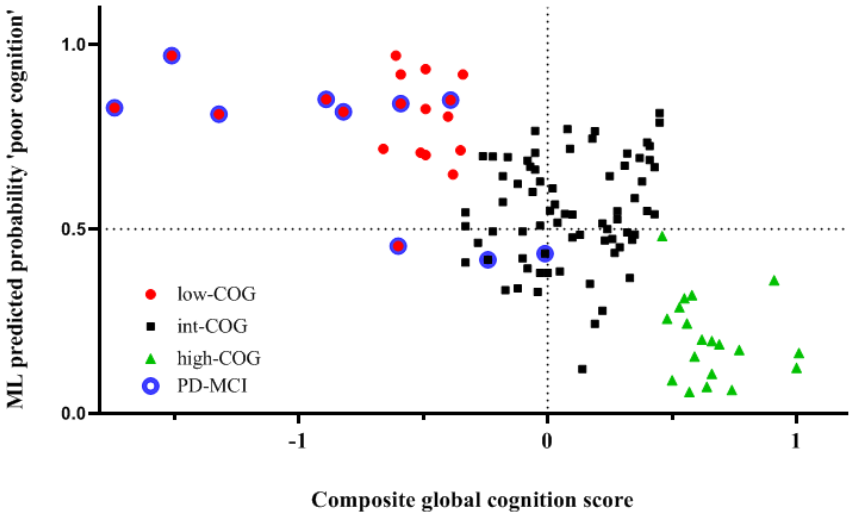


Figure 8.2 Predicted probability of being classified 'low-COG' vs. actual cognitive performance

Discussion

In this study, we show that DBS candidates with PD with either clinically determined 'good' or 'poor' cognition may be classified according to their cognitive function based on a fully automated EEG-assessment.

Contrary to previous studies which highlight singular, or few features to distinguish patients with different levels of cognitive impairment,[15-17, 19, 48] we showed that a compound of multiple EEG-biomarkers provides the highest accuracy in classifying patients.
Our final model performs slightly better than previously reported ML algorithms, which report accuracies between 74% [16] and 88%.[19] Betrouni and colleagues differentiated five groups of PD patients, with different levels of cognitive impairment using support vector machines (accuracy=84%) and k-nearest neighbour models (88%).[19] Although different electrode-densities were used, analyses were limited to spectral features in an effort to prevent

overfitting. As the dataset was subdivided into five different categories based on cognitive clusters, the two groups with worst cognitive function were smallest, containing respectively five and nine patients. In contrast, the results described above demonstrate the advantage of automated feature-extraction and simultaneous analysis to both increase the accuracy and limit the need for laborious pre-processing. Pragmatically, the use of spectral features to reflect EEG slowing is currently still easier to translate to routine clinical practice than applying a ML pipeline to new EEG data, although less accurate. Another study added connectivity metrics, i.e. Phase-Lag-Index (PLI) to spectral features resulting in 396 features (66 spectral- and 330 PLI features).[16] Although the reported accuracies were lower, PLI features discriminated better between PD patients with or without MCI (spectral features: Area-under-the-curve (AUC) = 0.64; PLI features: AUC = 0.74). Our model does not include between-channel connectivity metrics but rather focuses on synchronization patterns within one individual time series. Our accuracy may yet be further increased by including connectivity- or network features. However, the amount of computation runtime increases exponentially when automated models are expanded in such way.[16] Given that the number of features reflecting between-channel connectivity extends several folds beyond the feature-selection delineated here, the computation runtime may become too protracted for practical purposes.[49]

Although the ML pipeline treats all patients within one subgroup equally, despite within-group differences in cognitive functioning, the association between the predicted class-probability and actual cognitive performance follows a linear correlation. This trend is predominantly fuelled by the patients on which the model was trained, i.e. high-COG and low-COG patients. Patients classified as int-COG were poorly predicted and no linear trend could be discerned for this subgroup. The final model including all features from the separate cross-validation was inherently not based on 'unseen data' and therefore runs the risk of overfitting, despite several safeguards such as multiple cross-validation runs and Bayesian hyperparameter optimization. This was unavoidable given the small sample size, and the accuracies from the final model are therefore best interpreted as the best approximated maximum, with accuracies from the averaged cross-validation runs as minimum. The risk of overfitting may also partly explain why the model-performance in the int-COG group was ineffective. Other explanations include the limited variability in the int-COG group (by definition, all patients had cognitive scores within 1.5 SD) and variation in cognitive performance within this limited range is likely to occur regardless of the degree of cortical PD pathology and reflect normal variation also found in the otherwise 'normal' population. Furthermore patients with an 'intermediate' cognition were never included during the initial-model building and therefore constitute a separate class which is unrecognized by the model.

In contrast to previous studies that explored a wide range of cognitive functioning in PD patients, our results focus on PD patients undergoing the screening procedure for DBS. DBS candidates often have a relatively longer disease duration to allow for several treatment options before considering DBS surgery and often have more severe PD symptoms than newly-diagnosed PD patients. Furthermore, severe cognitive impairment is a contraindication for DBS [9, 10] and patients with obvious cognitive deficits will not be referred for screening, indicating that the range of cognitive function is likely much smaller in the DBS population than in the global PD population, emphasizing the sensitivity of this ML pipeline.

As with all supervised learning models, the crucial determinant of the models' validity is the correct labelling (either high-COG or low-COG, or another arbitrarily defined label). In this study, an extensive neuropsychological test battery was used to determine cognitive functioning of six consensus-based domains,[24] and a derived composite score reflecting global cognition. However, cognitive (dys)function is not a purely binary classification: performance is rated in a spectrum of possible scores and a derived binary classification may be subject to discussion. In this study, classes of cognitive functioning were determined in a data-driven fashion by taking the twenty best- and worst performing patients from the entire cohort. This was an a priori defined classification, as it was deemed unlikely that there would be sufficient DBS candidates with either MCI or PDD. However, it should be noted that both a classification based on the neuropsychological test battery, and cognitive-screening-tests reported previously,[39] yielded similar model performances suggesting high accuracy regardless of the exact tests used for cognitive profiling.

Our results therefore indicate the utility of using qEEG as complementary biomarker to assess cognitive function, but do not provide an answer towards the pathophysiological mechanism underlying cognitive deficits. We speculate that higher-density source-space setups may provide a better indication of such an underlying mechanism, possibly using Magnetoencephalography (MEG) to better reflect subcortical structures.[18] However, such an approach would have lower practical utility as it would be more difficult to implement high-density EEG or MEG in routine clinical practice. Nevertheless, this study demonstrates the cortical spatial expansion of the mechanism underlying cognitive impairment.

The ultimate ground truth in terms of clinical impact would be a classification based on long-term postoperative cognitive functioning. This data is however not available, whereas patients with poor preoperative functioning, as identified by the neuropsychological test battery, may be rejected for DBS surgery after screening and thus not contribute to follow-up data.

Strengths of our study include the automated ML pipeline which circumvents making arbitrary choices on pre-processing and feature selection, the large number of extracted features, and extensive cognitive profiling on which the initial classification was based. The use of cross-validation warrants the internal validity of our model. To our knowledge, ours is the only cohort of consecutively included DBS candidates with PD with EEG data available in the literature. Given the uniqueness of our cohort, no external validity can therefore be assessed. Despite multiple cross-validation runs, the algorithm was trained on only 20 vs. 20 patients. This constitutes a small sample size to base definitive conclusions on and requires validation in a larger cohort. Nevertheless, our results clearly demonstrate the utility of qEEG during the DBS screening for automated cognitive profiling and the superiority of a compound of EEG features over a single spectral feature.

The classification was based on the most extreme patients with composite scores of six Z-transformed domains. The domains 'Neuropsychiatric functioning' and 'Psychomotoric speed' were paradoxically worse in patients classified as high-COG than low-COG. Also, high-COG patients were younger and had less severe motor- and non-dopaminergic symptoms. However, these factors do not constitute a contra-indication for surgery.

Future studies may confirm the external validity of our model within the population of DBS candidates and evaluate the use of such a ML pipeline on other neurodegenerative diseases with cognitive impairment such as Alzheimer's Disease of Dementia with Lewy Bodies.[50] In such a way, it could be determined whether biomarkers differentiating cognitive subtypes are disease-specific (i.e. different biomarkers for different diseases), or whether there is a neurophysiological compound underlying cognitive impairment across neurodegenerative diseases. Furthermore, the ultimate goal of the ML pipeline would be to determine its utility as a predictor of cognitive deterioration rather than cross-sectional classification of cognitive functioning.

Strikingly, the model proposed here was originally developed for the automotive industry and applied here to a vastly different research field. This suggests that the origin of the time series, i.e. whether a signal originates from an EEG or from a vehicle, is not important during analyses. We speculate that multidisciplinary approaches such as these may advance healthcare-research and valorise these higher-order analysis-techniques through applications in fundamentally different fields.

We emphasize that currently, the EEG analyses described here are not intended to replace the neuropsychological assessments during the DBS screening and should be seen as complementary. However, these results provide strong evidence of the utility of qEEG as a

biomarker for cognitive performance during the DBS screening and may have potential both in clinical practice and for future clinical trials studying disease modifying therapy.

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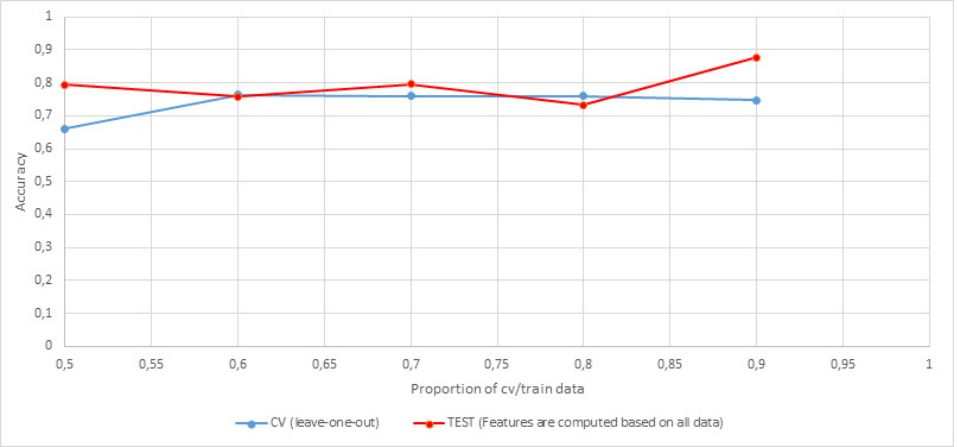
References

1. Collaborators GBDPsD. Global, regional, and national burden of Parkinson's disease, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol 2018;17:939-953.
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. Okun MS, Gallo BV, Mandybur G, et al. Subthalamic deep brain stimulation with a constant-current device in Parkinson's disease: an open-label randomised controlled trial. Lancet Neurol 2012;11:140-149.
5. 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.
6. 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.
7. Smeding HM, Speelman JD, Huizenga HM, Schuurman PR, Schmand B. Predictors of cognitive and psychosocial outcome after STN DBS in Parkinson's Disease. J Neurol Neurosurg Psychiatry 2011;82:754-760.
8. Drapier D, Drapier S, Sauleau P, et al. Does subthalamic nucleus stimulation induce apathy in Parkinson's disease? J Neurol 2006;253:1083-1091.
9. Lang AE, Houeto JL, Krack P, et al. Deep brain stimulation: preoperative issues. Mov Disord 2006;21 Suppl 14:S171-196.
10. Geraedts VJ, Kuijf ML, van Hilten JJ, Marinus J, Oosterloo M, Contarino MF. Selecting candidates for Deep Brain Stimulation in Parkinson's disease: the role of patients' expectations. Parkinsonism Relat Disord 2019.
11. 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.
12. Duckworth AL, Quinn PD, Lynam DR, Loeber R, Stouthamer-Loeber M. Role of test motivation in intelligence testing. Proceedings of the National Academy of Sciences of the United States of America 2011;108:7716-7720.
13. Duckworth AL, Yeager DS. Measurement Matters: Assessing Personal Qualities Other Than Cognitive Ability for Educational Purposes. Educ Res 2015;44:237-251.
14. Geraedts VJ, Boon LI, Marinus J, et al. Clinical correlates of quantitative EEG in Parkinson disease: A systematic review. Neurology 2018;91:871-883.
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. Chaturvedi M, Bogaarts JG, Kozak Cozac VV, et al. Phase lag index and spectral power as QEEG features for identification of patients with mild cognitive impairment in Parkinson's disease. Clin Neurophysiol 2019;130:1937-1944.
17. Geraedts VJ, Marinus J, Gouw AA, et al. Quantitative EEG reflects non-dopaminergic disease severity in Parkinson's disease. Clin Neurophysiol 2018;129:1748-1755.

18. Bonanni L. The democratic aspect of machine learning: Limitations and opportunities for Parkinson's disease. Mov Disord 2019;34:164-166.
19. Betrouni N, Delval A, Chaton L, et al. Electroencephalography-based machine learning for cognitive profiling in Parkinson's disease: Preliminary results. Mov Disord 2019;34:210-217.
20. Geron A. Hands-on Machine Learning with Scikit-Learn & TensorFlow : Concepts, Tools, and Techniques to build Intelligent Systems2017.
21. Postuma RB, Berg D, Stern M, et al. MDS clinical diagnostic criteria for Parkinson's disease. Mov Disord 2015;30:1591-1601.
22. Hjorth B. Source derivation simplifies topographical EEG interpretation. American Journal of EEG Technology 1980;20:121-132.
23. 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.
24. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (5th ed. ed.). Arlington: VA: American Psychiatric Publishing, 2013.
25. Huppert FA, Brayne C, Gill C, Paykel ES, Beardsall L. CAMCOG--a concise neuropsychological test to assist dementia diagnosis: socio-demographic determinants in an elderly population sample. The British journal of clinical psychology 1995;34 (Pt 4):529-541.
26. Vakil E, Blachstein H. Rey Auditory-Verbal Learning Test: structure analysis. Journal of clinical psychology 1993;49:883-890.
27. Wechsler D. Wechsler memory scale. San Antonio, TX, US: Psychological Corporation, 1945.
28. Dekker R, Mulder JL, Dekker PH. De ontwikkeling van vijf nieuwe Nederlandstalige tests. Leiden: PITS, 2007.
29. Richardson JT. Measures of short-term memory: a historical review. Cortex; a journal devoted to the study of the nervous system and behavior 2007;43:635-650.
30. Scarpina F, Tagini S. The Stroop Color and Word Test. Front Psychol 2017;8:557-557.
31. Tombaugh TN. Trail Making Test A and B: Normative data stratified by age and education. Archives of Clinical Neuropsychology 2004;19:203-214.
32. Beck AT, Steer RA, Ball R, Ranieri W. Comparison of Beck Depression Inventories -IA and -II in psychiatric outpatients. Journal of personality assessment 1996;67:588-597.
33. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta psychiatrica Scandinavica 1983;67:361-370.
34. Goetz CG, Tilley BC, Shaftman SR, et al. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. Mov Disord 2008;23:2129-2170.
35. 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.
36. Litvan I, Goldman JG, Troster AI, et al. Diagnostic criteria for mild cognitive impairment in Parkinson's disease: Movement Disorder Society Task Force guidelines. Mov Disord 2012;27:349-356.
37. Koch M, Bäck T. Machine Learning for Predicting the Impact Point of a Low Speed Vehicle Crash. 2018 17th IEEE International Conference on Machine Learning and Applications (ICMLA); 2018 17-20 Dec. 2018: 1432-1437.

38. Koch M, Wang H, Bäck T. Machine Learning for Predicting the Damaged Parts of a Low Speed Vehicle Crash. 13th International Conference on Digital Information Management 2018: 179-184.
39. Koch M, Geraedts V, Wang H, Tannemaat MR, Bäck T. Automated Machine Learning for EEG-Based Classification of Parkinson's Disease Patients. 2019 IEEE International Conference on Big Data. Los Angeles2019: 4845-4852.
40. Christ M, Kempa-Liehr AW, Feindt M. Distributed and parallel time series feature extraction for industrial big data applications. arXiv e-prints [serial online] 2016. Available at: https://ui.adsabs.harvard.edu/abs/2016arXiv1610077717C. Accessed October 01, 2016.
41. Christ M, Braun N, Neuffer J, Kempa-Liehr AW. Time Series FeatuRe Extraction on basis of Scalable Hypothesis tests (tsfresh – A Python package). Neurocomputing 2018;307:72-77.
42. Kursa MB, Rudnicki WR. Feature Selection with the Boruta Package. 2010 2010;36:13 %J Journal of Statistical Software.
43. Hastie T, Tibshirani R, Friedman J. The Elements of Statistical Learning: Data Mining, Inference, and Prediction, Second Edition: Springer New York, 2009.
44. Wang H, Emmerich M, Bäck T. Cooling Strategies for the Moment-Generating Function in Bayesian Global Optimization. 2018 IEEE Congress on Evolutionary Computation (CEC); 2018 8-13 July 2018: 1-8.
45. Wang H, Stein Bv, Emmerich M, Back T. A new acquisition function for Bayesian optimization based on the moment-generating function. 2017 IEEE International Conference on Systems, Man, and Cybernetics (SMC); 2017 5-8 Oct. 2017: 507-512.
46. Yang K, Blom Kvd, Bäck T, Emmerich M. Towards single- and multiobjective Bayesian global optimization for mixed integer problems. 2019;2070:020044.
47. Steyerberg EW. Validation in prediction research: the waste by data splitting. Journal of clinical epidemiology 2018;103:131-133.
48. Klassen BT, Hentz JG, Shill HA, et al. Quantitative EEG as a predictive biomarker for Parkinson disease dementia. Neurology 2011;77:118-124.
49. García-Martín E, Rodrigues CF, Riley G, Grahn H. Estimation of energy consumption in machine learning. Journal of Parallel and Distributed Computing 2019;134:75-88.
50. Dauwan M, van der Zande JJ, van Dellen E, et al. Random forest to differentiate dementia with Lewy bodies from Alzheimer's disease. Alzheimers Dement (Amst) 2016;4:99-106.

Supplementary material



Supplementary Figure 8.1 Split-sample vs cross-validation

Supplementary Table 8.1 Model features

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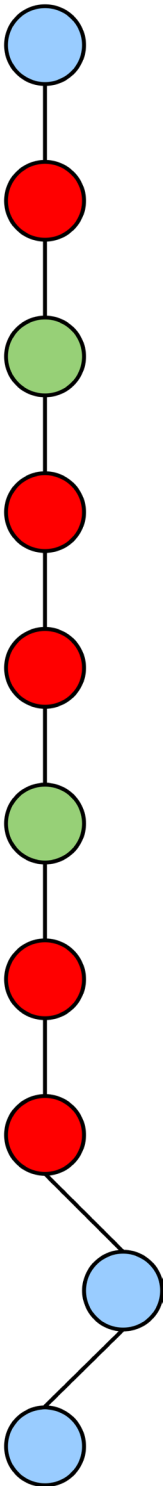
'Pz-Cz__fft_coefficient__coeff_68__attr_"imag"'

All featured were derived from the library 'Time Series FeatuRe Extraction on basis of Scalable Hypothesis tests' (tsfresh) Christ M, Braun N, Neuffer J, Kempa-Liehr AW. Time Series FeatuRe Extraction on basis of Scalable Hypothesis tests (tsfresh – A Python package). Neurocomputing 2018;307:72-77.



CHAPTER 9

Summary

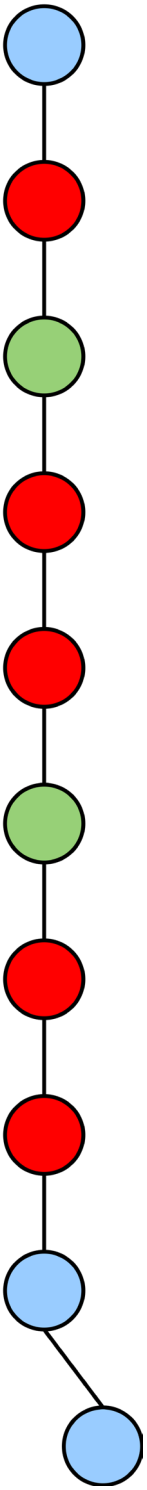
Deep Brain Stimulation (DBS) is an effective treatment to ameliorate motor complications in Parkinson's Disease (PD) patients and improve Quality of Life (QoL). Careful screening for DBS eligibility is crucial to select optimal candidates for surgery. To further optimize the screening process of PD patient eligibility there are still some unmet needs. First, there is a need of information on rejection policies after referral for DBS. Second, there is a need for information on factors that influence patients' postoperative satisfaction and QoL. Finally, there is a need for novel biomarkers to complement the current DBS screening battery. This thesis addresses these aspects and identifies directions for future research.

In **Chapter 2**, the reasons for rejection after an out-patient based pre-screening visit after referral for DBS were assessed by performing a chart review of 289 patients referred to the Leiden University Medical Center (LUMC) or the Maastricht University Medical Center (MUMC). The most frequent reason for rejection was suboptimal oral treatment or satisfying control of symptoms with oral treatment, which constituted 50% of the rejections. Twenty-three percent of referred patients had unrealistic expectations of DBS surgery, i.e. a desire to have relief of a symptom that is typically DBS-unresponsive. Moreover, the chart review showed that in 38% of rejections, unrealistic expectations contributed to the reason to reject (2nd most encountered reason to reject), although only in 4% constituted 'unrealistic expectations' the only reason to reject for DBS surgery. Impaired balance or medication-resistant freezing contributed in 36% of rejected patients to the reason to reject, whereas cognitive impairment was considered a reason to reject in 30% of rejections. These results suggest that the yield of appropriate referrals to DBS centers can be improved by educating referring neurologists on the contraindications for DBS surgery. Further, needless referrals can be avoided by determining whether patients have persistent unrealistic expectations of DBS surgery. In **Chapter 3**, studies on preoperative factors influencing postoperative QoL were systematically reviewed. From the 18 included studies, it was derived that only high baseline levodopa-responsiveness of motor symptoms appears to contribute to higher postoperative QoL (although not confirmed by all studies), whereas the majority of studied factors did not appear to influence QoL on group-level. Strikingly, various relative contra-indications for DBS surgery such as cognitive impairment and psychiatric dysfunction appear to be unrelated to postoperative QoL. However, it should be noted that these factors were only present to a limited degree (i.e. no severe cognitive impairment or severe psychiatric dysfunction was present in the studied cohorts) and results cannot be simply extrapolated to more severe symptom loads. These results suggest that QoL after DBS might be highly individually determined and results depend heavily on study design, used scale, and cultural background. In **Chapter 4**, a comparison between intraoperative test stimulation and postoperative stimulation settings was drawn in 119 PD patients after DBS of the Subthalamic Nucleus (STN). In the majority of cases, the postoperatively selected contact corresponded with the

intraoperatively defined 'best depth', or was immediately dorsal to it. More importantly, higher stimulation intensities were required postoperatively than intraoperatively to relieve rigidity or to induce capsular side-effects. We speculate that these findings stem from differences in current directionality (i.e. current vector), differences in current propagation due to increased encapsulation of the electrode used for chronic stimulation, and differences in sizes of the 'volume of tissue activated'. These results may ultimately be used to increase the efficiency of identification of the postoperative stimulation settings. In **Chapter 5**, we aimed to study whether postoperative ON-OFF testing (i.e. a stimulator-challenge-test (SCT)) alters patients' perceived impression of DBS effects and improves satisfaction after surgery in 54 patients. Both patient-reported satisfaction of surgery and impression of change due to DBS increased after SCT. The severity of motor impairment, as well as responsiveness of motor symptoms due to DBS, were not associated with subjective outcomes. A higher level of non-dopaminergic disease severity, relatively unchanged after DBS, influenced both satisfaction and impression of change. SCT may accurately quantify postsurgical motor improvement and appears indicated in case of suboptimal satisfaction following DBS STN.

In the second part of this thesis, biomarkers derived from Electroencephalography (EEG) were evaluated for usage during the DBS screening. In **Chapter 6**, studies on the correlation between quantitative EEG (qEEG) measures and clinical symptoms were reviewed. From the 36 included studies it can be concluded that metrics reflecting EEG slowing (derived from spectral analyses) correlate with cognitive impairment and may predict future cognitive deterioration. qEEG biomarkers appear particularly suited to reflect cognitive (dys)function, but there is little evidence to support their use in reflecting motor function or other clinical domains in PD. Metrics reflecting connectivity or network synchronization were scarcely evaluated and never applied in a longitudinal design. In **Chapter 7**, a correlation between qEEG metrics and non-dopaminergic severity was demonstrated in 63 PD candidates for DBS. Both global EEG slowing and reduced functional connectivity in the $\alpha 2$ band (i.e. a lower Phase-Lag-Index (PLI)) were associated with higher non-dopaminergic disease severity. These correlations appear driven by the non-dopaminergic subdomains 'cognition' and 'psychotic symptoms', whereas there was no association of qEEG metrics with motor functioning. It appears that cortical biomarkers (i.e. qEEG metrics) correlate best to 'cortically-mediated' symptoms, such as cognition or psychiatric functioning. These results suggests that qEEG may have complementary value during the DBS screening process in determining neuropsychological functioning, apart from formal assessment of cognition or psychiatric functioning. In **Chapter 8,** an automated Machine Learning pipeline for classification of cognitive function in DBS candidates is evaluated. An EEG-based evaluation of the raw time series, without arbitrary choice of feature-selection, provides an accuracy of 92% in differentiating between PD patients with either clinically-determined 'good cognitive

function' or 'poor cognitive function' based on the cognitive 'extremes' in the entire cohort. The calibration of predicted class probability versus cognitive performance scores demonstrated a good correlation of the underlying model to actual functioning. Patients that had 'intermediate' cognitive performance scores did not classify as either previously defined class and had indeterminate predicted class probabilities. Although external validation was not possible due to the uniqueness of the studied cohort, the Machine Learning algorithm demonstrated good internal validity and provides a proof-of-concept for automated classification of cognitive profiles based on EEG-data of DBS candidates.



CHAPTER 10

General discussion

Status of DBS care and considerations for improvement

The timeliness of referral for DBS is likely to become a greater issue in the nearby future. Referring neurologists may anticipate on increasingly long waiting lists and also refer patients at an earlier stage as a likely consequence of the results of the EARLYSTIM trial.[1] Better understanding of DBS referral practices could potentially improve DBS care from a referral-perspective.

Our findings show that 26% of the DBS referrals are rejected on the basis of factors that can be established prior to the referral, suggesting there is room for improvement of the referral process which in turn may reduce waiting lists of outpatient DBS centers and disappointment following rejection. Many of the current screening tools advocate a high sensitivity and low specificity to ensure that patients are not withheld a 'potentially better therapy' than oral therapy in the form of DBS.[2] However given the potential risks of DBS surgery, one should keep in mind the 'first do no harm' principle and the decision on eligibility should be made on an individual basis regardless of disappointment following justifiable rejection. There is no easy way to develop a dichotomous classification algorithm (i.e. rejected vs. accepted patients) that could aid clinicians with appropriate referrals. In fact, such a classification algorithm was attempted by our group (data not shown), but was discarded as the obtained accuracies turned out to be particularly low. The reported areas-under-the-curve are therefore best interpreted as a demonstration of the additional benefit of adding patients' expectations to a screening model, rather than absolute accuracies. A major limitation lies in the dispersity of the 'rejected class', which can be crudely subdivided into two classes: (1) patients rejected due to 'too advanced' disease fulfilling one or more exclusion criteria, or (2) patients referred 'too early' and with room for adjustment of medical (oral) therapy, i.e. not fulfilling the inclusion criteria for DBS surgery. The first subgroup ('too advanced') may have several contraindications for surgery, such as cognitive impairment, balance impairment, or medication-resistant freezing.

In contrast, the second subgroup ('too early') appears to consist of patients with a relatively good cognition and balance, but is characterized by the absence of (debilitating) motor complications whilst under optimal oral therapy (patients had thus either mild or no motor complications or suboptimal oral therapy). The patients who are ultimately accepted for DBS are in the spectrum between those more extreme subgroups which opposes a binary classification algorithm. An unfortunate but occasionally-encountered scenario during data collection was when patients were initially referred 'too early' for DBS, and ultimately ended up re-appearing for DBS screening when the disease had progressed beyond eligibility.

Not all contraindications are considered by clinicians to be equally important in all patients, as exemplified by 'unrealistic expectations' contributing to the reason to reject in 38% of rejected patients. It may be argued that 'unrealistic expectations' may be modifiable and therefore not a strict contraindication for surgery per se, whereas for example severe cognitive impairment would constitute a clear and definitive contraindication for surgery. Moreover, contraindications for surgery often clustered within patients, as exemplified by 'unrealistic expectations' being associated with the presence of other exclusion criteria. Both clinicians and patients should weigh the risks per domain (i.e. cognition, balance, etc.) and determine whether the benefits generated by DBS outweigh the individual risks.

An equally striking but different issue is that there is a 23% chance that a referred patient has unrealistic expectations of surgery. Several mechanisms may underlie this observation: (1) the patient was not or inadequately educated by the referring neurologist, (2) the patient was adequately educated by the referring neurologist but the patient retained unrealistic expectations nonetheless. Improving patient education on the potential benefits of DBS through the national Parkinson patient association may reduce this problem, whereas clinical meetings to keep referring neurologists up-to-date with the most recent developments on DBS effects would circumvent the first mechanism. Concerning preoperative expectations of DBS, two crucial questions remain: (1) to what degree should expectations be leading (or even be an exclusion criterion per se)?, and (2) what is the effect of preoperative expectations on postoperative outcomes? It is up to the physicians' discretion to answer the first question on an individual basis, although a shared-decision-making approach seems particularly appropriate with regard to elective brain surgery. Our dataset included an insufficient number of patients who had unrealistic expectations prior to surgery and nevertheless received DBS surgery to study the effect of unrealistic expectations on postoperative outcomes.

Chapter 3 attempts to answer which preoperative factors influence postoperative subjective outcomes in the form of QoL. Apparently, QoL after STN DBS is particularly heterogeneous and individually influenced, as well as dependent on both used scale and follow-up duration. Although the provided overview summarizes all available studies, a quantitative synthesis was not provided due to differences in outcome measures, study design, follow-up and likely heterogeneity between studies.[3] Moreover, several aspects influencing QoL outcomes were not addressed in any study, such as the high level of individual variation,[4] cultural influences,[5] social adjustments, and interpretability of the different metrics. The choice to classify studies based on statistical significance is clearly subject to debate,[6] however we stand by our conclusions as the reported effect sizes for all factors considered 'non-significant' were relatively small and unlikely to yield a meaningful clinical contribution after pooling of the studies and increasing the sample size.[7] Interestingly, several contra-indications for surgery

such as impaired cognition or psychiatric dysfunction have limited effects on postoperative QoL, albeit within the limits of current clinical practice. No inferences on a wider spectrum of symptoms than that is currently studied can be made. Although selection criteria for DBS eligibility are based on likelihood of 'success' such as motor improvement or absence of cognitive decline, DBS effects on QoL should be considered on an individual basis as well.

Chapter 4 has provided some suggestions for improving the efficiency of finding the optimal chronic DBS settings by demonstrating that the search space for the optimal contact point may be reduced, and by demonstrating that postoperatively higher stimulus intensity is required to induce any clinical effect (either therapeutic- or side-effect) with respect to intraoperative testing. Whether this translates into actual improvements in terms of increased clinical efficiency needs to be validated and the magnitude of effect in terms of time-gain is yet unknown. Nevertheless, optimization of DBS settings will likely become increasingly time-intensive given developments in DBS setting-modalities such as increasing number of contacts per DBS lead or directional steering (i.e. more test-options available). Faster optimization would in theory mean less visits to the hospital, shorter visits to the neurologists, fewer costs, shortened 'adjustment phase' to alterations in everyday life, potentially higher patient satisfaction and improved QoL. The proposed mechanisms behind the observed differences between intraoperative test stimulation and postoperative stimulation settings need to be studied in further detail, e.g. by validating our findings in different targets such as pallidal or thalamic DBS.

Chapter 5 indicates a clear area to improve postsurgical DBS care, by partly answering the question which factors influence postoperative satisfaction. STN DBS exerts its primary effect on motor function, and generally has no effect on symptoms unresponsive to dopaminergic treatment. Apparently, motor performance scores were not associated with postoperative satisfaction whereas non-dopaminergic dysfunction correlated to lower valuations of surgery. 'That what does not improve' therefore appears to have a bigger impact than 'that that does improve' in terms of satisfaction, although the relief of motor complications, i.e. severity of dyskinesias or 'OFF' time, was not examined in detail as all patients had similar postoperative profiles of mild or negligible motor complications. As patients' satisfaction is one of the ultimate goals of any intervention, insight into factors influencing post-intervention satisfaction is of paramount importance. Since we demonstrated that the severity of non-dopaminergic symptoms was relatively unchanged after DBS, it may be that patients retained the unrealistic expectations described in chapter 2, of wanting relief from those symptoms despite patient-education prior to surgery (although preoperative expectations were not incorporated in this study). Another hypothesis is that due to the relief of motor complications, these are no longer the most prominently debilitating symptoms

and other symptoms take on a more prominent role in patients' lives resulting in more severe valuations on patient-reported outcomes. Careful monitoring and (multidisciplinary) treatment of non-dopaminergic symptoms may be a potential target for studies targeting improving clinical care.

Patients' insight into DBS effects and subsequent improved appreciation of this intervention can be mediated by a SCT, particularly in suboptimally satisfied patients. Patients with maximum scores in terms of satisfaction do not necessarily have to be subjected to a SCT to enhance subjective valuations further, as indicated by some patients who report a decline in postoperative satisfaction following SCT (as patients with maximal scores can only retain their scores or decline on the Likert scales). However, there are other reasons to perform SCT apart from improving postoperative satisfaction, such as accurate assessment of DBS motor benefit and comparing results to the preoperative Levodopa Challenge Test to identify whether DBS settings have to be adjusted accordingly for maximal benefit. It is questionable whether the observed improvements in postoperative satisfaction are sustained over time, or whether repeated SCTs would lead to sustained patients' perception and postoperative satisfaction. These considerations should be determined on an individual basis by both treating physicians and patients. Nevertheless, we recommend to incorporate SCTs into routine postoperative care after DBS especially in case of suboptimal satisfaction.

Future perspectives with regard to DBS care

Part A of this thesis proposes means to improve DBS referral practices prior to surgery, increase the optimization of DBS settings during the early postoperative phase, and increase patients' postoperative satisfaction one year after surgery.

Future studies should identify whether more extensive education of the pros and cons of DBS surgery would lead to an improvement of referral practice and fewer unrealistic expectations of DBS, as well as investigate the cause of these unrealistic expectations in the first place. Several potential factors which are insufficiently studied with regard to predicting QoL after DBS, such as social functioning or genetic factors, need to studied in greater detail. The proposed mechanism to increase the efficiency of finding the optimal DBS settings needs to be evaluated in terms of the magnitude of actual time-gain. Furthermore, an extrapolation of the findings from chapter 4 towards different targets needs to be performed to determine the generalizability of our findings. Lastly, it needs to be studied whether increases in postoperative satisfaction after SCT are sustained over time and whether repeated SCTs may be useful if increases in satisfaction are not sustained.

The utility of quantitative EEG during the DBS screening

An overview of EEG features that correlated to PD symptoms is provided in chapter 6. Similar to chapter 3, a quantitative synthesis is not provided. Ideally, a biomarker should not have to depend on a pooling of results to show clinical utility. Spectral EEG markers have been abundantly studied, likely due both to an easier computation as well as more straightforward interpretability. The choice of spectral metric does not appear to matter much, since spectral measures are highly interrelated after all. However, there are legion opportunities to define 'connectivity' [8] and only a small subset of those has been studied in relation to PD symptoms. A comparison between multiple types of connectivity metrics may provide greater insight into the pathophysiological mechanism behind the correlation between qEEG metrics and PD symptoms. Moreover, connectivity metrics have not been properly compared amongst one another and it is currently unknown which is the 'best metric' in terms of discriminating power for any PD symptom. Even beyond single connectivity metrics, combining several metrics into coherent networks to define an EEG-profile may determine the neurophysiological signature of a patient with e.g. PD-MCI or PDD.[9]

Most studies focus on the correlation of qEEG with cognition: no longitudinal studies focussed on another domain than cognition. Spectral analyses show promise in predicting progression of cognitive (dys)function. There is limited evidence for biomarkers transcending spectral analyses to predict progression in any domain. It needs to be elucidated whether the mechanism of cognitive decline after STN DBS is similar to the cognitive deterioration in the general PD population which is not attributable to an intervention. Second, although spectral analyses have the best chance of finding their way to clinical practice given the relative ease of computation and interpretation, new and potentially more complex biomarkers should be evaluated against the current 'gold standard' of spectral analyses in order to identify whether discriminating accuracy in term of cognitive function can be further improved.

The utility of qEEG as a biomarker of cortically mediated symptoms was further demonstrated in chapter 7, which shows a correlation of qEEG with the cortical symptoms cognition and psychotic symptoms, but not with autonomic function, balance impairment of motor symptoms. It may be hypothesized that both correlations are mediated through a common mechanism, i.e. disturbances within an α-network. This would explain the correlation with α-connectivity, whereas the correlation with relative α -power would resonate throughout the other relative spectral powers as long as the correlation with α-power is sufficiently strong. Whereas the concept of an α-network in relation to cortically mediated PD symptoms is interesting, a drawback of the studied phase-based connectivity measures is that it only demonstrates a temporal relationship and provides no insight into causation. Metrics

focussing on directed entropy could possibly localize the (causal) 'driver' behind cortical dysfunction if combined with source localization rather than studying effects in sensor space. The concept of several distinct subnetworks corresponding to the distinct PD symptoms may fuel multimodal neurophysiological analyses, with differences in terms of spectral density and penetration (i.e. MEG vs. EEG), as well as differences in recording conditions depending on the symptom of interest. The use of resting-state EEG is the standard technique for studying cognition, but may be less applicable for studying motor networks for which perturbation tests may be more applicable.[10, 11] Perturbation tests for cognition are less feasible due to learning-effects and consequential attention-wandering.

Apart from the contribution to knowledge on the pathophysiological mechanism of PD symptoms, chapter 7 provides some evidence for the feasibility of using qEEG during the screening for DBS as a complementary biomarker. Earlier studies have shown that a composite score of non-dopaminergic symptoms, may provide a more complete and accurate evaluation of disease severity and progression in PD.[12, 13] Given the correlation of the qEEG measures global slowing and global desynchronization with a composite score of non-dopaminergic symptoms, these EEG markers likely reflect cortical involvement of α-synucleinopathy. Consequently, qEEG measures hold potential to contribute to the process of determining a patient's candidacy for DBS surgery. A diffuse slower and desynchronized EEG may be a warning sign for clinicians deciding on DBS eligibility and may tip the scales towards a negative recommendation for DBS surgery, whereas a fast and synchronous EEG may support a recommendation for DBS. The predictive properties of EEG slowing were demonstrated in chapter 6, and in combination with the positive results from chapter 7, would support the suggestion to use qEEG as a predictive biomarker of future cognitive decline after STN DBS. Notably, the role of qEEG in terms of prediction of future deterioration after STN DBS has not been studied yet and requires further research.

Both the concept of identification of novel biomarkers, as well as the concept of a cognitive subnetwork or a cognitive EEG-profile, was studied further in chapter 8. Whereas conventional analyses study EEG either in signal-space or in source-space, a machine learning algorithm has the potential to study the EEG in feature-space given the massive feature extraction provided by the application of an EEG feature-library. The feature library used here (*tsfresh*) does not consider inter-channel connectivity and could be extended several folds further. However, the studied algorithms nicely demonstrate the additional value of applying a feature-space beyond spectral analyses, as the accuracy of a coherent EEG profile clearly transcends that of the occipital peak frequency as a representative and easy-to-use spectral metric. A compound of numerous EEG markers may approach a cognitive subnetwork, even though the spectrum of cognitive (dys)function is relatively limited in DBS patients.

Although the use of such an extensive algorithm has the potential to identify new biomarkers and provides new insight into the pathophysiological mechanism, the goal of this study was to provide a proof-of-concept of prediction rather than to study causal mechanisms. Statements on such mechanisms should be avoided given the limitations of this study, such as the relatively small sample size, the absence of consensus-based diagnostic criteria for class labels, and the lack of external validation. All these limitations are unfortunate but were unavoidable. Regardless, we demonstrate good internal validation and consistency of our results, both in terms of diagnostic accuracy and in terms of calibration (i.e. predicted probabilities of cognitive class vs. actual cognitive function). To our knowledge, there are no other cohorts of consecutively included DBS patients that have been evaluated by means of qEEG, rendering external validation impossible.

The nature of the DBS cohort also limits the utility of diagnostic criteria for class labels, as severe cognitive dysfunction is a contraindication for both DBS surgery and referral and these patients would be rejected for the DBS screening as explained in chapter 2. The use of the 'cognitive extremes' in our cohort based on standardization of cognitive domains based on DSM-V criteria [14] was considered to be a straightforward and easily reproducible approach. The neuropsychological evaluation is currently the only gold standard to label cognition, despite its sensitivity to external influences. Using these 'cognitive extremes' limits bias to the largest extent and maximizes the distance between the two classes despite the relatively homogeneous global cognitive profile as compared to the entire possible spectrum of cognitive (dys)function in PD.

Again, the machine learning approach does not provide any indication of future cognitive deterioration and needs to be studied in a longitudinal setting to determine its clinical utility, as well as undergo external validation and assessment of clinical impact.[15, 16]

An interesting aspect of the machine learning algorithm is that it was never developed with EEG in mind. Originally, it was developed for utility in the automotive industry to study the effects of low-impact crashes on vehicles, in order to determine whether a check-engine-light has to start blinking. Its utility on EEG data resembles this check-engine-light, as a warning sign considering DBS eligibility. The data-structure of both vehicle-data and EEG data is relatively similar, which allows for similar analysis-algorithms being applied to data of different origins. The algorithm merely recognizes a signal originating from a time series and disregards the origin. Upon examining oscillations within a time series, the clinical neurophysiologist will instantly recognize a time series originating from an EEG or EMG signal, whereas the automotive engineer will not likely recognize a time series as an EEG but will sooner consider a different origin. Interpretations are influenced by prior knowledge

and area-of-expertise, which is once more highlighted by the cover of this thesis. Clinical researchers are prone to recognize the cover image as a brain with the coloured circles representing possible EEG electrode locations, or sources of brain activity (figure 10.1). Upon removing the background behind the coloured circles, an acyclic graph may be recognized by researchers proficient in graph theory research , or clinical epidemiologist interested in directed acyclic graphs to model causal relationships and confounding (figure 10.2).[17] The actual image however was based on the subway-network of the inner city of Munich (figure 10.3), something a conductor operating these metros would sooner have recognized than an EEG-system. The machine learning algorithm applied in chapter 8 was not constrained by previous knowledge other than class label and did not focus on any particular feature.

Chapter 8 also highlights the valorisation of such a multi-disciplinary approach, as clinicians are generally insufficiently proficient with the complex mathematical computations required for advanced machine learning analyses. Clinical research may highly profit from collaborating with other research fields and examining joint approaches for research aims for advanced analyses and novel modelling strategies.

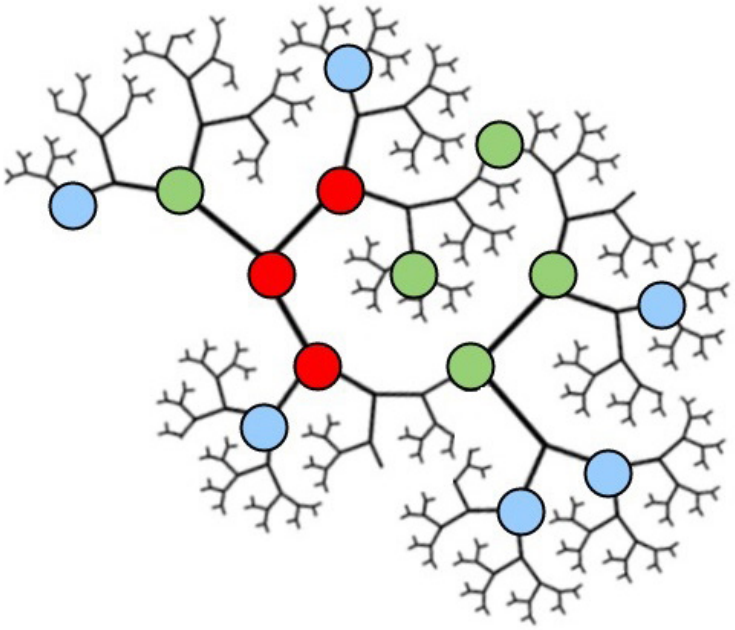


Figure 10.1 Cover image: brain with EEG electrode positions.
Red: hubs with high degree; green: nodes with lower degree; blue: leaf-nodes

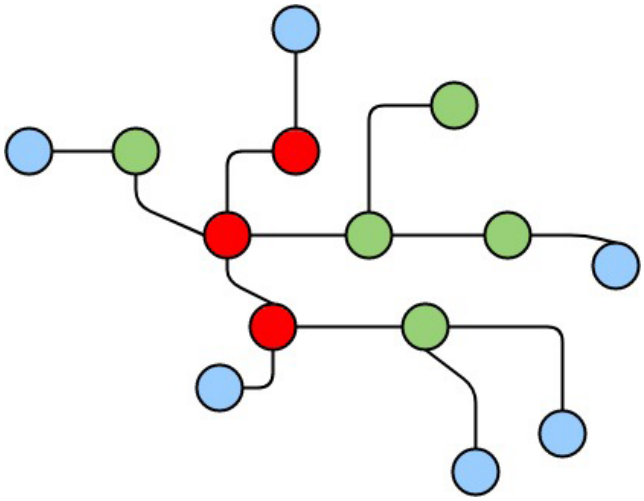


Figure 10.2 Cover image: acyclic graph

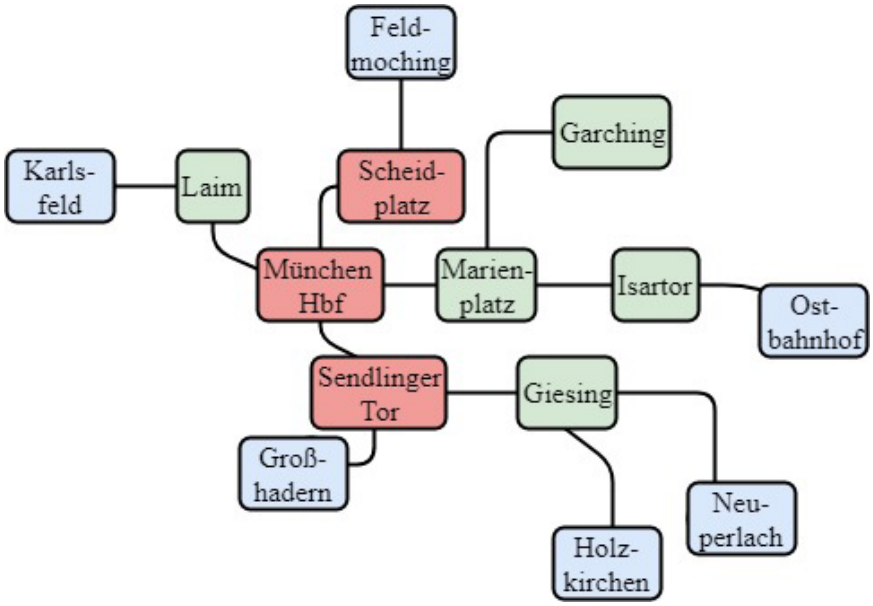


Figure 10.3 Cover image: subway-network Munich

Future perspectives with regard to using EEG during the DBS screening

Part B of this thesis demonstrates the feasibility and utility of applying qEEG during the DBS screening, particularly as a biomarker of current cognitive performance. Although some speculations on pathophysiological mechanisms can be made on the basis of chapters 6-8, the application of qEEG currently lies clearly within the domain of prediction as opposed to causality. Given the promising results, the utility of qEEG as a predictor of future deterioration after DBS needs to be determined in future studies, as well as determining the clinical impact of incorporating qEEG during the DBS screening.[15, 16] Moreover, it has to be determined which method has the greatest practical utility. Spectral biomarkers which have the most evidence-based utility based on previous literature, are easier to compute, interpret, and implement. In contrast, a compound-approach as shown in chapter 8 is more difficult to compute and implement, but appears to have a greater discriminating potential and therefore would result in greater accuracy. For the short-term future, spectral analyses may have a more immediate impact on DBS care whereas machine learning approaches need to undergo several verification and validation steps before implementation in routine clinical practices can be definitively recommended.

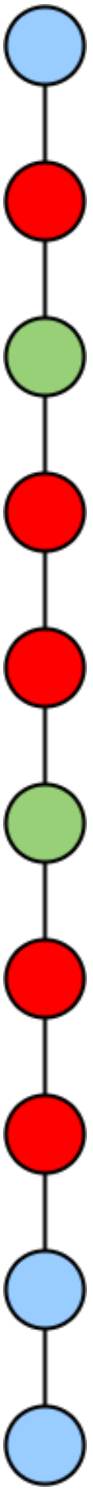
Concluding remarks

In conclusion, this thesis answers and raises an almost equal number of questions. Many issues may play a role in DBS screening and care. The findings presented in this thesis provide some new directions for future studies aiming to improve the screening and care of DBS patients.

An important final note to consider is a quote from Alan Alda (famous actor and science journalist) on his PD diagnosis: "it hasn't stopped my life at all". To improve patients' welfare after the PD diagnosis is the ultimate goal, and the research detailed in this thesis is only a first step along the track towards improving the screening and care of DBS patients.

References

1. Schuepbach WM, Rau J, Knudsen K, et al. Neurostimulation for Parkinson's disease with early motor complications. N Engl J Med 2013;368:610-622.
2. Coleman RR, Kotagal V, Patil PG, Chou KL. Validity and Efficacy of Screening Algorithms for Assessing Deep Brain Stimulation Candidacy in Parkinson Disease. Mov Disord Clin Pract 2014;1:342-347.
3. Ioannidis JPA, Patsopoulos NA, Rothstein HR. Reasons or excuses for avoiding meta-analysis in forest plots. BMJ (Clinical research ed) 2008;336:1413-1415.
4. Donaldson GW, Moinpour CM. Individual differences in quality-of-life treatment response. Medical care 2002;40:Iii39-53.
5. Molzahn AE, Kalfoss M, Schick Makaroff K, Skevington SM. Comparing the importance of different aspects of quality of life to older adults across diverse cultures. Age and Ageing 2010;40:192-199.
6. Altman DG, Bland JM. Statistics notes: Absence of evidence is not evidence of absence. BMJ 1995;311:485.
7. Thiese MS, Ronna B, Ott U. P value interpretations and considerations. J Thorac Dis 2016;8:E928-E931.
8. van Diessen E, Numan T, van Dellen E, et al. Opportunities and methodological challenges in EEG and MEG resting state functional brain network research. Clin Neurophysiol 2015;126:1468-1481.
9. Geraedts VJ, van Hilten JJ, Contarino MF, Tannemaat MR. Unravelling the Parkinson's disease network: Taking the connectome beyond the brain. Clin Neurophysiol 2019;130:2017-2018.
10. Yang Y, Guliyev B, Schouten AC. Dynamic Causal Modeling of the Cortical Responses to Wrist Perturbations. Front Neurosci 2017;11:518-518.
11. Friston KJ. Functional and effective connectivity: a review. Brain connectivity 2011;1:13-36.
12. van der Heeden JF, Marinus J, Martinez-Martin P, van Hilten JJ. Importance of nondopaminergic features in evaluating disease severity of Parkinson disease. Neurology 2014;82:412-418.
13. 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.
14. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (5th ed. ed.). Arlington: VA: American Psychiatric Publishing, 2013.
15. Steyerberg EW, Vergouwe Y. Towards better clinical prediction models: seven steps for development and an ABCD for validation. Eur Heart J 2014;35:1925-1931.
16. Steyerberg EW, Moons KGM, van der Windt DA, et al. Prognosis Research Strategy (PROGRESS) 3: prognostic model research. PLoS Med 2013;10:e1001381-e1001381.
17. Ferguson KD, McCann M, Katikireddi SV, et al. Evidence synthesis for constructing directed acyclic graphs (ESC-DAGs): a novel and systematic method for building directed acyclic graphs. International journal of epidemiology 2019.



APPENDICES

Abbreviations
Nederlandse samenvatting
Dankwoord
Curriculum vitae
Publications

Abbreviations

AD	Alzheimer's disease
ADL	Activities of daily living
AUC	Area under the curve
BDI	Becks depression inventory
DBS	Deep brain stimulation
DLB	Dementia with Lewy bodies
EDS	Excessive daytime sleepiness
EEG	Electroencephalography
EMG	Electromyography
FFT	Fast Fourier transform
GIC	Global impression of change
GSS	Global satisfaction with surgery
GPi	Globus pallidum interna
High-COG	Best cognitive performance (group)
HY	Hoehn and Yahr (stage)
IC	Internal capsule
Int-COG	Intermediate cognitive performance (group)
JBI	Joanna Briggs institute – risk of bias assessment score
L-dopa	Levodopa
LFP	Local field potentials
Low-COG	Worst cognitive performance (group)
MCI	Mild cognitive impairment
MDRS	Mattis dementia rating scale
MDS-UPDRS	Movement disorders society – unified PD rating scale
MEG	Magnetoencephalography
MER	Microelectrode recording
ML	Machine learning
MMSE	Mini-mental state examination
MST	Minimum spanning tree
NCOG	Cognitively normal
PD	Parkinson's disease
PDD	Parkinson's disease dementia
PDQ39	Parkinson's disease questionnaire 39
PIGD	Postural instability and gait difficulty
PLI	Phase-lag-index
PRISMA	Preferred reporting items for systematic reviews and meta-

	analyses
RBD	REM sleep behaviour disorder
RFC	Random forest classifier
SCT	Stimulation challenge test
SENS-PD	Severity of predominantly nondopaminergic symptoms in PD
SF36	Short form 36
STN	Subthalamic nucleus
Tsfresh	Time series Feature extraction on basis of scalable hypothesis tests
VIM	Ventral intermediate nucleus of the thalamus
VIMP	Variable importance
VTA	Volume of tissue activated
qEEG	Quantitative electroencephalography
QoL	Quality of life
ZI	Zona incerta

Nederlandse samenvatting

Diepe Hersen Stimulatie (*Deep Brain Stimulation – DBS)* is een effectieve behandeling om motorcomplicaties te verlichten in patiënten met de Ziekte van Parkinson (ZvP) en hun kwaliteit van leven te verbeteren. Een nauwkeurige screening ten aanzien van DBS-geschiktheid is cruciaal om optimale kandidaten voor DBS te selecteren. Echter, dit screeningsproces kan verder worden geoptimaliseerd door enkele openstaande vragen te beantwoorden. Allereerst is er behoefte aan informatie betreffende het beleid rondom afwijzing voor de operatie na verwijzing voor de DBS screening. Ten tweede is er behoefte aan informatie over factoren die invloed uitoefenen op postoperatieve tevredenheid en kwaliteit van leven. Tot slot is er behoefte aan nieuwe biomarkers om de DBS screening in het kader van ZvP aan te vullen. Dit proefschrift adresseert deze aspecten en biedt aanknopingspunten voor vervolgonderzoek.

In **hoofdstuk 2** worden de redenen voor afwijzing na een poliklinische pre-screening voor DBS beschreven, gebaseerd op een statusonderzoek van 289 Parkinsonpatiënten verwezen naar het Leids Universitair Medisch Centrum (LUMC) of het Maastricht Universitair Medisch Centrum (MUMC). De meest frequent gerapporteerde reden voor afwijzing was suboptimale behandeling met orale medicatie of voldoende symptomatische controle met de huidige behandeling (50% van alle afwijzingen). Tevens hadden 23% van de verwezen patiënten onrealistische verwachtingen ten aanzien van DBS, d.w.z. een behoefte om een symptoom te verhelpen dat doorgaans niet reageert op DBS. Uit het statusonderzoek bleek verder dat deze onrealistische verwachtingen in 38% van de afwijzingen bijdroegen aan de beslissing om de patiënt af te wijzen voor DBS (2e meest gerapporteerde reden voor afwijzing), hoewel deze reden in slechts 4% van alle afwijzingen de enige reden was. Balansstoornissen of medicatie-gerelateerde *freezing* droeg in 36% van alle afwijzingen bij aan de beslissing tot afwijzing, terwijl cognitieve achteruitgang in 30% van alle afwijzingen hieraan bijdroeg. Deze resultaten lijken er op te wijzen dat de verwijzingen voor DBS tot meer geschikte kandidaten zou leiden door nascholing van verwijzende neurologen op het gebied van de contra-indicaties voor DBS. Verder kunnen mogelijk onnodige verwijzingen worden voorkomen door voorafgaande aan de verwijzing te achterhalen of patiënten persisterende onrealistische verwachtingen hebbenen van DBS. In **hoofdstuk 3** werden wetenschappelijke studies besproken over preoperatieve factoren die invloed hebben op postoperatieve kwaliteit van leven, d.m.v. een systematische review. Uit de 18 geïncludeerde studies kon worden opgemaakt dat alleen hoge levodopa-responsiviteit van motore symptomen, voorafgaande aan de operatie, bijdroeg aan postoperatieve kwaliteit van leven (hoewel niet bevestigd door alle studies). De meerderheid van de bestudeerde factoren leken geen effect te hebben op kwaliteit van leven op groepsniveau. Opvallend genoeg hadden diverse factoren die gelden als (relatieve) contra-

indicaties voor DBS geen effect op postoperatieve kwaliteit van leven, zoals verminderd cognitief functioneren of psychiatrische klachten. Hierbij moet wel de kanttekening worden geplaatst dat deze factoren slechts in geringe mate aanwezig waren (d.w.z. geen ernstige cognitieve of psychiatrische klachten gerapporteerd in de bestuurde patiëntengroepen); de resultaten kunnen daarom ook niet eenvoudig worden geëxtrapoleerd naar patiënten met ernstiger klachten. Onze resultaten wijzen er op dat kwaliteit van leven sterk individueel bepaald is en dat de resultaten erg afhankelijk zijn van studie-opzet, gebruikte schaal om kwaliteit van leven te bepalen en culturele achtergrond. In **hoofdstuk 4** werd een vergelijking getrokken tussen intra-operatieve test-stimulatie en postoperatieve stimulatie-instellingen bij 199 patiënten met ZvP na DBS van de Nucleus Subthalamicus (STN). In de meerderheid van de patiënten kwam het postoperatief geselecteerde contactpunt overeen met de intra-operatief geïdentificeerde 'beste diepte', of lag direct dorsaal hieraan. Een nog belangrijker resultaat was dat de stimulus-intensiteit die leidt tot een effect, ofwel verlichting van rigiditeit of het opwekken van capsulaire bijwerkingen, hoger lag in de postoperatieve situatie dan intra-operatief. We speculeren dat verschillende oorzaken deze bevinding kunnen verklaren, namelijk verschillen in roomrichting (stroomvector), de stroomverdeling ten gevolge van toegenomen inkapseling van de elektrode gebruikt voor de chronische stimulatie en de grootte van het bereikte weefsel. Deze resultaten kunnen bijdragen aan de verbetering van de efficiëntie van de postoperatieve instelfase door snellere identificatie van de optimale instellingen. In **hoofdstuk 5** werd onderzocht of een postoperatieve ON-OFF test (*stimulator challenge test – SCT)* een effect had op de waarneming van patiënten van het effect van DBS, evenals of er een effect van een SCT was op postoperatieve tevredenheid, in 54 patiënten. Zowel patiënt-gerapporteerde tevredenheid na DBS als de subjectieve beleving van verandering na DBS verbeterden na SCT. De ernst van motore symptomen, evenals de responsiviteit van deze klachten op DBS, hadden geen invloed op deze subjectieve uitkomsten. Een hogere ernst van non-dopaminerge klachten, relatief onveranderd na DBS, had een negatieve invloed op zowel tevredenheid als gevoel van verandering. Een SCT kan de postoperatieve motore verbetering nauwkeurig kwantificeren en lijkt geïndiceerd indien er sprake is van suboptimale tevredenheid na DBS STN.

In het tweede deel van dit proefschrift werden biomarkers vanuit elektroencephalographie (EEG) geëvalueerd voor toepassing tijdens de DBS screening. In **hoofdstuk 6** werden wetenschappelijke studies over de correlatie tussen kwantitatieve EEG (*quantitative EEG – qEEG)* en klinische symptomen van ZvP systematisch besproken. Uit de 36 geïncludeerde studies kon worden opgemaakt dat maten die EEG vertraging weergeven (uit spectrale analyses) correleren met verminder cognitief functioneren en tevens toekomstige cognitieve achteruitgang kunnen voorspellen. qEEG biomarkers lijken met name geschikt om cognitief (dis)functioneren weer te geven, maar er is slechts beperkt bewijs dat toepassing

binnen andere domeinen ondersteunt. Maten die connectiviteit of netwerk synchronisatie weergeven zijn nauwelijks bestudeerd en nooit onderzocht in een longitudinale studie-opzet. In **hoofdstuk 7** werd een correlatie tussen qEEG maten en non-dopaminerge ziekte-ernst gedemonstreerd in 64 patiënten met ZvP, allen kandidaat voor DBS. Zowel globale EEG vertraging en verminderde functionele connectiviteit in de α2 band (d.w.z. een lagere *Phase-Lag-Index (PLI)*) waren geassocieerd met een hogere non-dopaminerge ziekte-ernst. Deze correlaties lijken met name gedreven door de non-dopaminerge sub-domeinen 'cognitie' en 'psychotische symptomen', terwijl er geen associatie was tussen qEEG maten en motorisch functioneren. Het lijkt erop dat corticale biomarkers (qEEG maten) het beste correleren met 'corticaal gemedieerde' symptomen zoals cognitie en psychiatrisch functioneren. Deze resultaten suggereren dat qEEG toegevoegde waarde heeft tijdens het DBS screeningsproces om het neuropsychologisch functioneren te weergeven, los van een formele beoordeling van cognitie of psychiatrisch functioneren. In **hoofdstuk 8** werd een geautomatiseerde *Machine Learning* pijplijn voor classificatie van cognitief functioneren in DBS kandidaten besproken. Een op EEG gebaseerde evaluatie van de ruwe tijdseries, zonder arbitraire keuzes t.a.v. EEG-kenmerken geselecteerd voor analyse, leverde een accuratesse van 92% voor de differentiatie tussen patiënten met ZvP met ofwel een klinisch bepaalde 'goede cognitie' of 'matige cognitie', gebaseerd op de 'cognitieve extremen' uit het totale cohort. De kalibratie van de voorspelde 'klasse-waarschijnlijkheid' en daadwerkelijk functioneren toonde een goede correlatie. Hoewel externe validatie niet mogelijk was vanwege het unieke karakter van het bestuurde cohort toonde dit *Machine Learning* algoritme een goede interne validiteit. Tevens kan dit worden gezien als een *proof-of-concept* dat het goed mogelijk is om een dergelijk algoritme toe te passen op DBS kandidaten om hun cognitieve profiel te classificeren op basis van hun EEG-data.

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Curriculum Vitae

Victor J. Geraedts (September 16th, 1991) was born in Zoetermeer, the Netherlands. In 2009, he completed his pre-university education and started his study Biomedical Sciences at Leiden University. In 2012, he started his study Medicine at Leiden University concomitantly. For his Bachelor thesis, he started working on the *Profiling Parkinson's Disease* (PROPARK) study under supervision of prof. dr. J.J. van Hilten, and was later awarded the prof. E.L. Noach research prize for his thesis. In 2012, he started the Master Biomedical Sciences 'Health', and in 2013 the Master Medicine, both at Leiden University. In 2014, he performed his first Master thesis at the Max-Planck-Institute of Psychiatry in Munich, Germany under supervision of prof. dr. G.K. Stalla and dr. C.S. Sievers, on the subject of Quality of Life in pituitary adenomas. After finalizing this thesis, he was given a contract to continue his research, with a particular focus on Acromegaly. His second Master thesis was at the Leiden University Medical Centre under supervision of prof. dr. J.J. van Hilten and dr. M.R. Tannemaat, on the subject of quantitative EEG in Parkinson's Disease patients. In 2017, he graduated both the Master Biomedical Sciences and the Master Medicine.

After graduation, he started his PhD project at the department of Neurology under supervision of prof. dr. J.J. van Hilten, dr. M.F. Contarino, and dr. M.R. Tannemaat, on the *Optimizing Patient Selection for Deep Brain Stimulation of the Subthalamic Nucleus in Parkinson's Disease* (OPTIMIST) study. In 2019, he concomitantly started his training to become a registered Epidemiologist at the department of Clinical Epidemiology. During his PhD, he focussed on studying potential improvements of Deep Brain Stimulation (DBS) care and translate research findings directly to clinical practice in movement disorders, as well as studying the practical utility of quantitative EEG during the screening for DBS. Part of this thesis (Chapter 7) was awarded the Storm van Leeuwen – Magnus Prize in 2018. Victor currently works as a researcher on several projects related to prediction modelling of DBS effects in both patients and caregivers, and automated assessment of Clinical Neurophysiology metrics.

Victor is an enthusiastic marathon-runner and currently lives in Zoetermeer with his wife Katrien.

Publications

- Kefalas M, Koch M, **Geraedts VJ**, Wang H, Bäck THW, Tannemaat MR. Automated Machine Learning for the classification of normal and abnormal Electromyography data. *Under review.*

- Yin Z & **Geraedts VJ** & Wang Z, Contarino MF, Dibeklioglu H, van Gemert J. Assessment of Parkinson's Disease severity from videos using deep architectures. *Under review.*

- **VJ Geraedts**, van Ham RAP, van Hilten JJ, Mosch A, Hoffmann CFE, van der Gaag NA, Contarino MF. Difference in thresholds for side effects between intraoperative test stimulation and postoperative stimulation after pallidal and thalamic Deep Brain Stimulation. *Under review.*

- Van Hienen MM, Contarino MF, Middelkoop HAM, van Hilten JJ, **Geraedts VJ**. Effect of deep brain stimulation on caregivers of patients with Parkinson's Disease: a systematic review. *Under review.*

- **Geraedts VJ**, Koch M, Contarino MF, Middelkoop HAM, Wang H, van Hilten JJ, Bäck THW, Tannemaat MR. Machine learning for automated EEG-based biomarkers of cognitive impairment in Deep Brain Stimulation candidates with Parkinson's Disease. *Under review.*

- Van 't Westende C, Peeters-Scholte CMPCD, Jansen L, Van Egmond-van Dam JC, Tannemaat MR, Wiggers-de Bruine ST, Van den Berg-Huysmans AA, **Geraedts VJ**, Gouw AA, Steggerda SJ, Stam CJ, Van de Pol LA. The Degree of Prematurity Affects Functional Brain Activity in Preterm Born Children at School-Age: an EEG study. Early Hum Dev 2020.

- **Geraedts VJ**, Feleus S, Marinus J, van Hilten JJ, Contarino MF. What predicts Quality of Life after STN DBS in Parkinson Disease? A systematic review. Eur J Neurol 2019.

- Van Prooije TH & **Geraedts VJ**, de Bie RMA, van Hilten JJ & Post B. Farmacologische behandeling bij de Ziekte van Parkinson: op zoek naar de balans. Tijdschrift voor de Neurologie en Neurochirurgie 2019.

- Koch M, **Geraedts VJ**, Wang H, Tannemaat MR, Bäck THW. Automated Machine Learning for EEG-Based Classification of Parkinson's Disease Patients. IEEE International Conference on Big Data 2019.

- Khodakarami H, Ricciardi L, Contarino MF, Pahwa R, Lyons KE, **Geraedts VJ**, Morgante F, Leake A, Paviour D, De Angelis A, Horne M. Prediction of the levodopa challenge test in Parkinson's Disease using data from a wrist-worn sensor. Sensors 2019.

- **Geraedts VJ**, van Hilten JJ, Contarino MF, Tannemaat MR. Unravelling the Parkinson's Disease network: Taking the connectome beyond the brain. Clin Neurophysiol 2019.

- **Geraedts VJ**, van Hilten JJ, Marinus J, Mosch A, Naarding KJ, Hoffmann CFE, van der Gaag NA, Contarino MF. Stimulation challenge test after STN DBS improves postoperative satisfaction in Parkinson's Disease patients. Parkinsonism Relat Disord 2019.

- **Geraedts VJ**, Kuijf M, Marinus J, van Hilten JJ, Oosterloo M, Contarino MF. Selecting candidates for Deep Brain Stimulation in Parkinson's Disease: the role of patients' expectations. Parkinsonism Relat Disord 2019.

- **Geraedts VJ**, van Ham RAP, Marinus J, van Hilten JJ, Hoffmann CFE, van der Gaag NA, Contarino MF. Intraoperative test stimulation of the subthalamic nucleus reduces the search space for chronic stimulation settings in Parkinson's disease. Parkinsonism Relat Disord. 2019 May.

- Boon LI, **Geraedts VJ**, Hillebrand A, Tannemaat MR, Contarino MF, Stam CJ, Berendse HW. A systematic review of MEG-based studies in Parkinson's disease: The motor system and beyond. Hum Brain Mapp 2019.

- **Geraedts VJ**, Boon LI, Marinus J, Gouw AA, van Hilten JJ, Stam CJ, Tannemaat MR, Contarino MF. Clinical correlates of quantitative EEG in Parkinson's disease: a systematic review. Neurology 2018.

- Dekker L & **Geraedts VJ**, Hund H, Cannegieter SC, Nogueira R, Goyal M, van den Wijngaard IR. Importance of reperfusion status after intra-arterial thrombectomy for prediction of outcome in anterior circulation large vessel stroke. Interv Neurol Apr 2018.

- **Geraedts VJ**, Marinus J, Gouw AA, Mosch A, Stam CJ, van Hilten JJ, Contarino MF, Tannemaat MR. Quantitative EEG reflects Non-Dopaminergic Disease Severity in Parkinson's Disease. Clin Neurophysiol. 2018.

- **Geraedts VJ**, Andela CD, Sievers C, Stalla GK, van Furth WR, Pereira AM, Biermasz NR. Predictors of quality of life in acromegaly: no consensus on biochemical parameters.

Front Endocrinol (Lausanne) 2017.

- Van der Heeden JF, Marinus J, Martinez-Martin P, Rodriguez-Blazquez C, **Geraedts VJ**, Van Hilten JJ. Postural instability and gait are associated with severity and prognosis of Parkinson Disease. Neurology 2016.

- Dimopoulou C, **Geraedts V**, Stalla GK, Sievers C. Neuropsychiatric and cardiometabolic comorbidities in patients with previously diagnosed Cushing's disease: a longitudinal observational study. BMJ Open 2015.

- **Geraedts VJ**, Dimopoulou C, Auer M, Schopohl J, Stalla GK, Sievers C. Health Outcomes in Acromegaly: Depression and Anxiety are Promising Targets for Improving Reduced Quality of Life. Front Endocrinol (Lausanne) 2014.