Right on track: Towards improving DBS patient selection and care

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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.

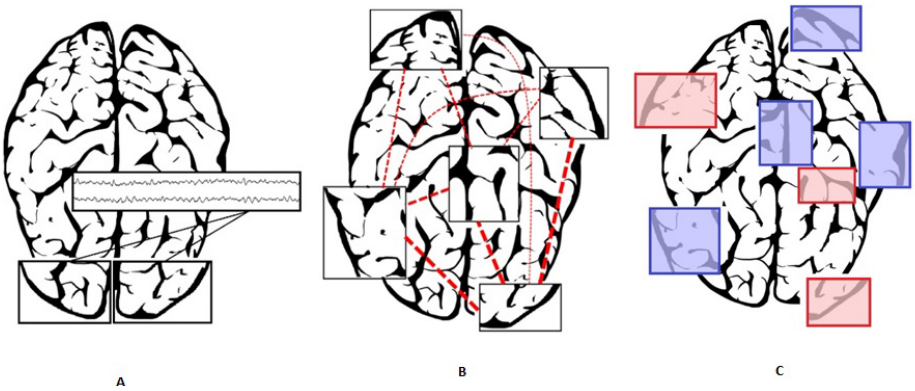

Figure 6.1. Principles of quantitative EEG analyses

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

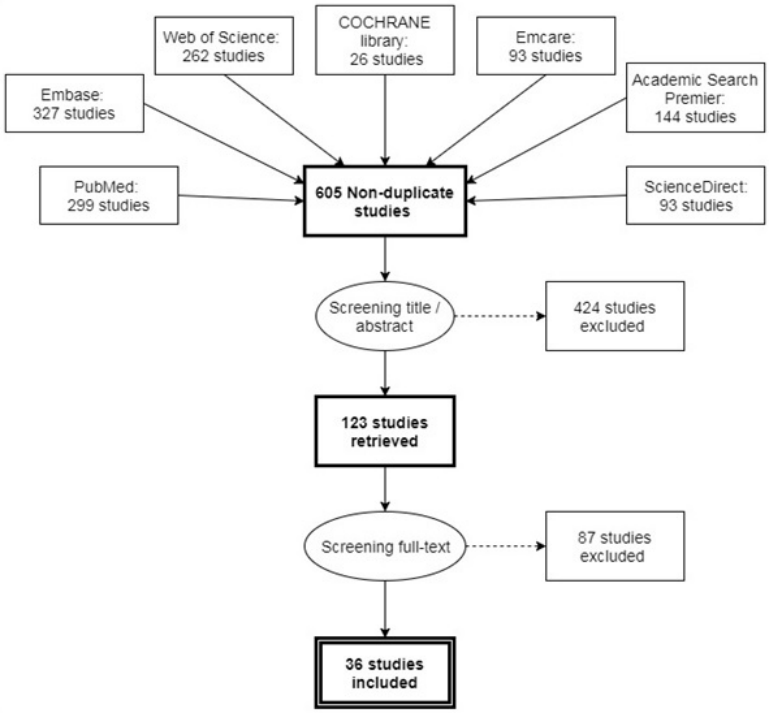

Figure 6.2. PRISMA flow diagram of selected studies.

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]

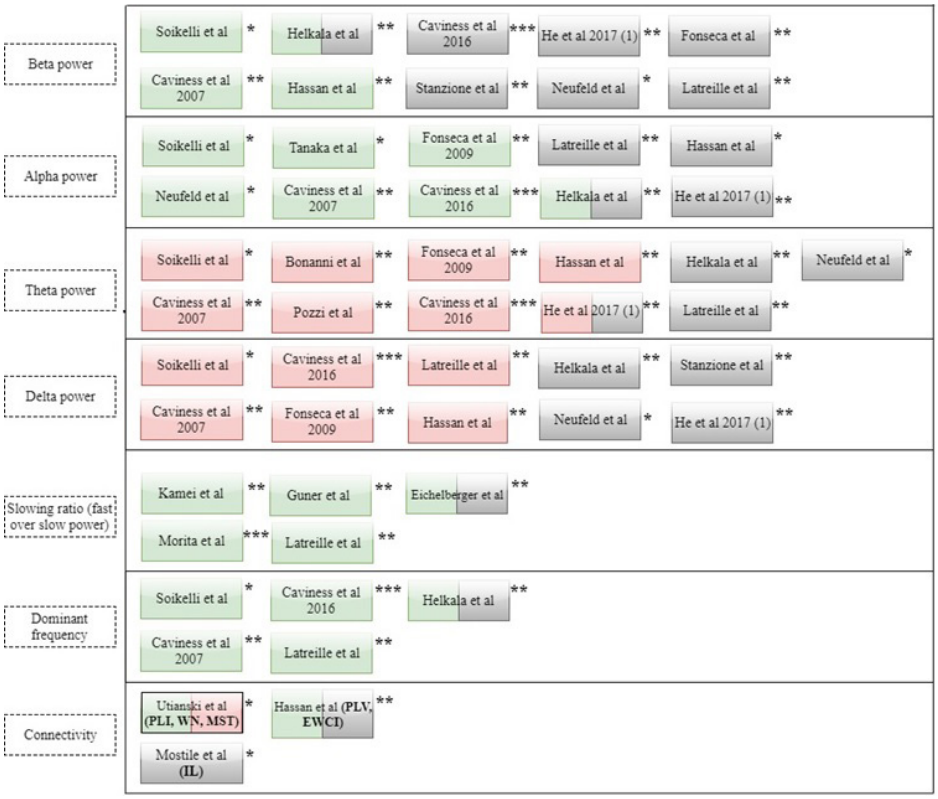

Figure 6.3. Correlation of qEEG measures with cognition
Green indicates that the measure is positively correlated with cognition, red indicates that the measure is negatively correlated with cognition, grey indicates no correlation. Dual-shaded boxes indicate that the sign of the correlation varied per 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]

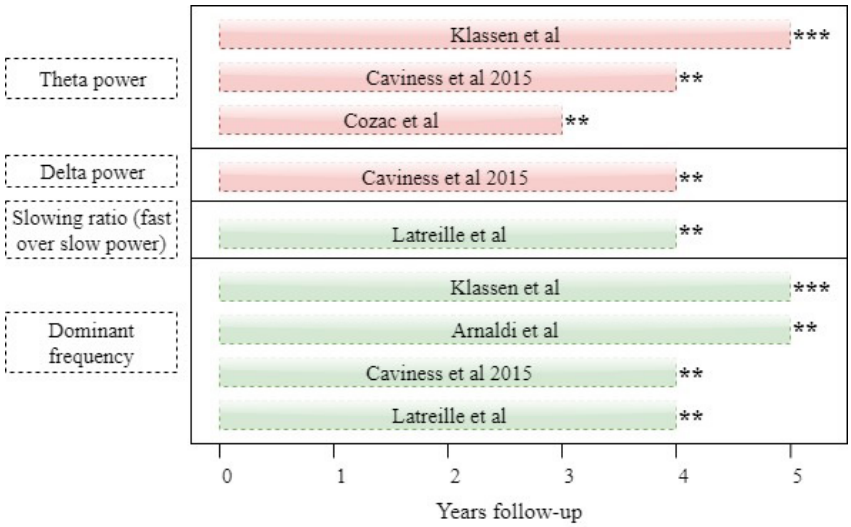

Figure 6.4. Correlation of qEEG measures with cognition in longitudinal follow-up studies
Green indicates that the measure is positively correlated with cognition, red indicates that the measure is negatively correlated with cognitive performance. Grey indicates no correlation. One asterisk indicates '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.

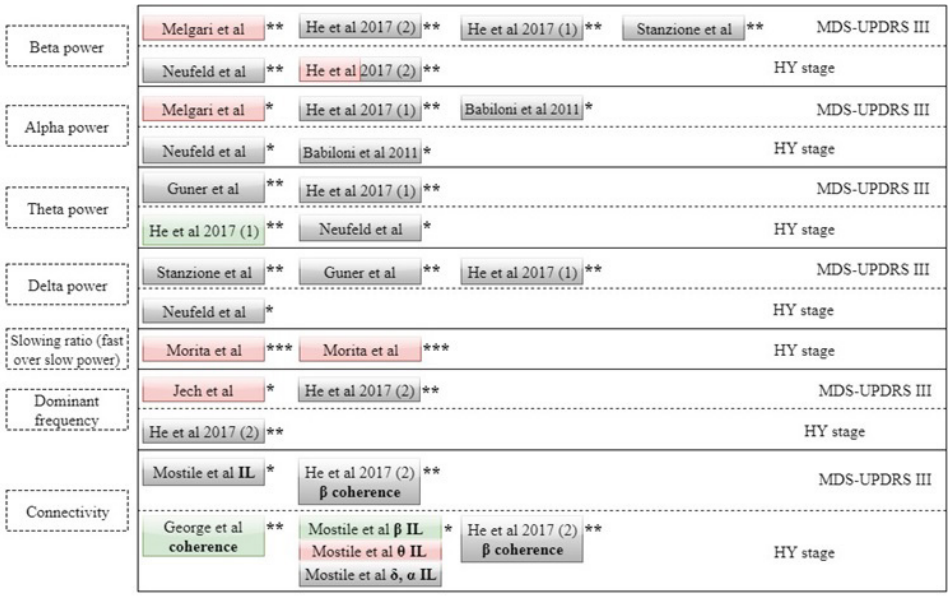

Figure 6.5. Correlation of qEEG measures with motor functioning
Green indicates that the measure is positively correlated with motor impairment, red indicates that the measure is negatively correlated with motor impairment. Gray indicates no correlation. Dual-shaded boxes indicate that the sign of the 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

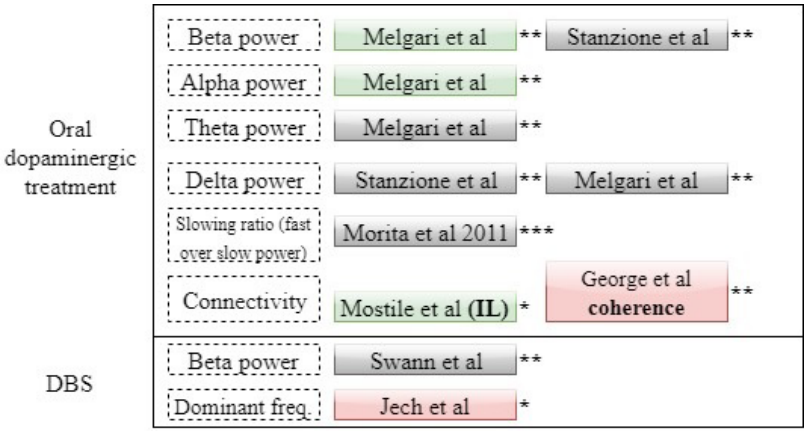

Figure 6.6. Correlation of qEEG measures with treatment
Green indicates that the measure is positively correlated with treatment administration, red indicates that the measure is negatively correlated with treatment. Grey indicates no correlation. One asterisk indicates 'medium quality' (JBI); two indicates '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.

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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.