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Resting-state EEG alpha/theta ratio related to neuropsychological test performance in Parkinson's Disease

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HIGHLIGHTS

- Parkinson's related performance in the Judgment of Line Orientation Test is influenced by the right occipital α/θ.
- A hemispheric approach of occipital α/θ must be considered for further research.
- The right occipital α/θ is a promising marker for evaluating Parkinson's Disease patients with visuospatial impairment.

ABSTRACT

Objective: To determine possible associations of hemispheric-regional alpha/theta ratio (α/θ) with neuropsychological test performance in Parkinson's Disease (PD) non-demented patients.
Methods: 36 PD were matched to 36 Healthy Controls (HC). The α/θ in eight hemispheric regions was computed from the relative power spectral density of the resting-state quantitative electroencephalogram (qEEG). Correlations between α/θ and performance in several neuropsychological tests were conducted, significant findings were included in a moderation analysis.
Results: The α/θ in all regions was lower in PD than in HC, with larger effect sizes in the posterior regions. Right parietal, and right and left occipital α/θ had significant positive correlations with performance in Judgement of Line Orientation Test (JLOT) in PD. Adjusted moderation analysis indicated that right, but not left, occipital α/θ influenced the JLOT performance related to PD.
Conclusions: Reduction of the occipital α/θ, in particular on the right side, was associated with visuospatial performance impairment in PD.
Significance: Visuospatial impairment in PD, which is highly correlated with the subsequent development of dementia, is reflected in α/θ in the right posterior regions. The right occipital α/θ may represent a useful qEEG marker for evaluating the presence of early signs of cognitive decline in PD and the subsequent risk of dementia.

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1. Introduction

Parkinson's Disease (PD) is defined primarily as a movement disorder pathologically characterized by the loss of nigrostriatal dopaminergic neurons and Lewy bodies in the remaining neurons. In addition to dopamine-related motor symptoms, serotonin, noradrenaline, and acetylcholine may play a key role in the genesis of nonmotor symptoms including cognitive decline. Cognitive decline is among the most common and important nonmotor symptoms in PD, increasing the risk of PD dementia (PDD), although the rate of cognitive decline and time to dementia varies (Armstrong, 2019). Around 36% of PD patients have Mild Cognitive Impairment (MCI) at diagnosis compromising executive function, attention, memory, or visuospatial domains (Aarsland et al., 2017). In PD, early dysexecutive and attentional impairments depend on dopaminergic frontostriatal circuit lesions (Kehagia et al., 2012). Besides, cortical and striatal cholinergic pathways become affected, contributing to frontostriatal dysfunction (Ballinger et al., 2016). Worsening of visual memory, visuospatial abilities, and semantic fluency have been associated with posterior cortical and temporal lobe dysfunction which, to some extent, can improve with cholinergic treatments (Kehagia et al., 2012). Although the cognitive profile in PD is heterogeneous, mild visuospatial impairment represents a higher risk of PDD compared to attentional/executive impairment (Williams-Gray et al., 2007). Synaptic and network dysfunction models have been proposed for explaining different electrophysiological patterns of cognitive decline. For instance, aggregation and accumulation of misfolded proteins cause an imbalance between excitatory and inhibitory neurotransmitter activity (Roberts and Breakspear, 2018). Hence, identifying biomarkers that can reliably measure synaptic and neuronal network disruptions is important for diagnosis and prognosis in neurodegenerative diseases, and may serve as predictors for cognitive decline in PD.

The quantitative electroencephalogram (qEEG) may reflect cholinergic dysfunction (Massa et al., 2020; van der Zande et al., 2018), and some qEEG features seem to be promising biomarkers for PD and other neurodegenerative dementias (Babiloni et al., 2020; Bonanni et al., 2016, 2008; Geraedts et al., 2018). As a case in point, our group has shown that frontal coherence is related to executive function in MCI due to PD (Carmona Arroyave et al., 2019). However, Power Spectral Density (PSD) is one of the most widely used qEEG features, and the progression of cognitive decline in PD patients is associated with increased PSD in delta and theta bands, as well as decreased alpha PSD (Bousleiman et al., 2014; Caviness et al., 2016). Those findings have been interpreted as "slowing-down" in posterior regions (Al-Qazzaz et al., 2014; Schmidt et al., 2013), but synoptic PSD indexes such as the ratio between alpha and theta PSD may enhance the differences between patients and healthy controls (Massa et al., 2020; Schmidt et al., 2013). However, few studies have calculated those indexes in PD, and if so, have computed an average of alpha/theta ratio (α/θ) rather than regional ratios in the right and left hemisphere (Eichelberger et al., 2017; Massa et al., 2020) despite known asymmetries in PSD (Bousleiman et al., 2014). Other works have examined the correlation of qEEG features with global scores of cognition rather than domain-specific neuropsychological impairments (Cozac et al., 2016; Geraedts et al., 2018). With the present study, we aim to determine possible associations of hemispheric-regional α/θ changes with impairment in specific neuropsychological tests in PD patients without dementia. Based on previous preliminary findings, we hypothesize that visuospatial and semantic fluency impairments of PD are associated with a reduction of the α/θ in posterior hemispheric-regions.

2. Methods:

2.1. Participants

We analyzed a non-randomized sample of PD patients from the outpatient service of the Grupo de Neurociencias de Antioquia (Neuroscience group of Antioquia) (Carmona Arroyave et al., 2019). Detailed inclusion criteria were stated in Section 2.2. We excluded participants with parkinsonian syndromes other than PD, other major neurological or psychiatric disorders, and dementia (based on impairment in cognition and function) (Emre et al., 2007), intracranial devices, and current use of other drugs than antiparkinsonian that could alter the qEEG rhythms. PD patients were under stable antiparkinsonian treatment for at least 4 weeks before evaluations and recordings. We included PD patients without MCI (PD-nMCI, n = 22) if Montreal Cognitive Assessment (MoCA) (see below) was 23 or above - according to validation in Colombian population- (Gil et al., 2015), and had no significant cognitive complaints or cognition-related functional decline. Besides, PD patients with MCI (PD-MCI, n = 14), defined following level one task force criteria - Movement Disorders Society (MDS) (Litvan et al., 2012), i.e. subjective cognitive complaints, MoCA < 23, and no significant cognition-related functional decline, were also included. Finally, from an open call for volunteers, we selected 36 participants with normal cognition and no relevant neurologic or psychiatric disorders as Healthy Controls (HC). HC were manually matched to the PD groups based on gender, age, and years of education. The study had the approval of the Ethical Research Committee of the Universidad de Antioquia (Certificate No. 15–10-569). All participants signed informed consent before enrolment in the study. All assessments, including qEEG acquisition, were completed in phase 'On' of levodopa treatment.

2.2. Clinical and neuropsychological assessment

For determining PD diagnosis, all participants were assessed by a team of two neurologists and one trained physician following the MDS Clinical Diagnostic Criteria for Parkinson's Disease (Postuma et al., 2015). The Hoehn & Yahr scale (Hoehn and Yahr, 1967) and the Unified Parkinson's Disease Rating Scale part III (UPDRS-III) (Goetz, 2003) were used for evaluating the severity of the disease stage and motor symptoms. The two neurologists ruled out alternative diagnoses of parkinsonism and verified pharmacological regimens and the presence of intracranial devices, as per exclusion criteria.

Neuropsychological examinations of PD and HC subjects were performed by a team of four trained psychologists who evaluated MCI and excluded dementia. The cognitive screening was performed using the MoCA test with validated cut-offs for the Colombian population (Gil et al., 2015). The functional level was evaluated through the Barthel Index (Mahoney and Barthel, 1965) and Lawton & Brody scale (Lawton and Brody, 1969). To test executive functions and attention, we administered the Stroop test – Golden version (Stroop) (Golden and Freshwater, 1978), and INECO Frontal Screening battery (IFS) (Torralva et al., 2009) composed of: Luria motor series, conflicting instructions, go-no-go, modified Hayling test, backward months, backward digit span, modified Corsi tapping test and proverb interpretation. Language domain tests included the semantic fluency of animals test (SF) and FAS phonemic fluency test (FAS) (Casals-Coll et al., 2013). Memory was assessed using the delayed free recall of the Memory Capacity Test (MCT-DFR) (Rentz et al., 2010). Visuospatial abilities were evaluated using the Judgment of Line Orientation Test (JLOT) (Benton et al., 1978) and the free-drawn of the clock drawing test

(Clock) (Agrell and Dehlin, 1998). We included the raw scores of each test in the analysis.

3. qEEG recordings and preprocessing

A qEEG was recorded for five minutes in resting-state (i.e. quiet wakefulness with eyes closed) in a Faraday cage. A cap of tin electrodes and 58 scalp leads was placed according to the international 10–10 system with the reference electrode on the right earlobe with subsequent re-reference to average in the preprocessing. Another electrode between Cz and Fz was used as ground. Impedances were kept below 10 kOhm. The sampling frequency was fixed at 1000 Hz. Signals were filtered online with a band-pass (0.05 to 200 Hz) and a notch filter (60 Hz). A semi-automated pipeline was implemented for pre-processing using two MATLAB toolboxes: EEGLAB (Delorme and Makeig, 2004), and a standardized qEEG preprocessing pipeline (PREP) (Bigdely-Shamlo et al., 2015) validated in our group (Suarez-Revelo et al., 2018) with proved test–retest reliability (Suarez-Revelo et al., 2016) (See Supplementary Material for details regarding preprocessing method). For each recording, 50 randomly automatically selected epochs of 2 seconds length and free-of-artifacts, were used to compute relative PSD. We used the multi-taper method available in the MATLAB toolbox Chronux (http://chronux.org) (Mitra and Bokil, 2007) to have less variance, bias, and better frequency resolution on PSD (Babadi and Brown, 2014; Prerau et al., 2017). The magnitude of relative PSD in the selected epochs was averaged for each electrode. Then, relative PSD in each electrode was calculated in four frequency bands: delta (1–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), beta (13–30 Hz), and eight Regions of Interest (ROI), as follows: left frontal (AF3, F1, F3, FC1, FC3), right frontal (AF4, F2, F4, FC2, FC4), left temporal (FC5, C5, CP5, T7, TP7), right temporal (FC6, C6, CP6, T8, TP8), left parietal (CP1, CP3, P1, P3), right parietal (CP2, CP4, P2, P4), left occipital (PO3, PO5, PO7, O1), and right occipital (PO4, PO6, PO8, O2). Finally, we computed the α/θ from the alpha relative PSD/-theta relative PSD and calculated its logarithmic transformation (i.e. natural log) following previously published methods (Massa et al., 2020; Moretti et al., 2004; Schmidt et al., 2013). Delta and frequencies higher than alpha were excluded from the current analysis.

3.1. Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 25. Statistical significance was set at $p < 0.05$. Since α/θ in most of the posterior regions was different when comparing HC and the two PD groups, but not when PD-MCI and PD-nMCI were compared (Supplementary Tables S1–S3), we merged PD-MCI and PD-nMCI in a single PD group to increase our statistical power with greater sample size, and evaluate a wider spectrum of PD. Group comparisons were conducted using independent samples t-test or Mann-Whitney's U for continuous variables, and the Chi-square test for categorical variables. Multiple testing correction of the p-values obtained in the group comparisons of neuropsychological and qEEG data was conducted using the False Discovery Rate (FDR) method, defining a threshold of 0.05. Effect sizes were calculated with Cohen's d. In addition, Receiver Operator Characteristic (ROC) curves for the neuropsychological test and α/θ with the largest effect size were obtained. The cut-off value for the α/θ with the largest effect size was calculated with Youden's J statistic.

To determine any possible confounder effect of dopaminergic treatment over qEEG variables, Pearson correlations between the Levodopa Equivalent Daily Dose (LEDD) and the α/θ in each ROI were conducted. Given no significant results in the latter correlations (Supplementary Table S4), we did not adjust for LEDD the subsequent analyses. Besides, Pearson correlations were used to explore the effect of age on α/θ in HC (Supplementary Table S5), but no significant results were found in most of the posterior regions (i.e. right and left occipital, and right parietal). Therefore, we performed age-unadjusted bivariate correlations to explore the relationship between α/θ in the eight ROI and the scores of the eight neuropsychological tests. However, the results of these exploratory correlations were also confirmed using partial non-parametric correlations controlling for the effect of age (Supplementary Table S6). As JLOT, Clock, and MoCA were non-normally distributed, we performed non-parametric correlations with these variables and Pearson correlations with the remaining. FDR correction was not conducted in these correlations due to the exploratory nature of this step but was made in the subsequent analyses after selecting target ROI and neuropsychological tests.

Finally, to test our hypothesis that PD performance in some neuropsychological tests was influenced by the α/θ, those ROI that were significantly correlated with neuropsychological tests in the exploratory correlations were included independently as a moderator variable through a conditional process analysis (moderation analysis) using the SPSS macro "PROCESS" (Preacher and Hayes, 2004). These moderation analyses were conducted using 10,000 Bootstrap sampling. The p-values of the three resulting moderation models were corrected for multiple testing with the FDR method.

4. Results

72 participants were included (HC = 36; PD = 36). Given the matched design of our study, non-significant differences among the groups were found in the demographic characteristics of the sample, Table 1.

The neuropsychological test scores of the PD group were worse in all the neuropsychological tests compared to HC as shown in Fig. 1 and Table 2. In the PD group, the α/θ exhibited statistically significant lower values in all the ROI, Table 2.

When comparing regional α/θ values in PD and HC, large effect sizes were seen, particularly in the occipital regions: right occipital ($t = 4.33$; FDR < 0.001; Cohen's $d = 1.00$), and left occipital ($t = 3.89$; FDR < 0.001; $d = 0.92$). Differences in other ROI also reflected a large effect size in right temporal ($t = 3.82$; FDR < 0.001; $d = 0.90$), left temporal ($t = 3.88$; FDR < 0.001; $d = 0.91$), right parietal ($t = 3.64$; FDR < 0.001; $d = 0.86$), and left frontal ($t = 3.10$; FDR = 0.004; $d = 0.75$). Right frontal ($t = 2.99$; FDR = 0.004; $d = 0.70$) and left parietal ($t = 2.99$; FDR = 0.004; $d = 0.71$) showed moderate effect size. Fig. 2A depicts the mean value of α/θ in each ROI in PD and HC.

The ROC curves for right occipital α/θ and MCT-DFR (the test which exhibit the largest effect size; $t = 6.96$; $p < 0.001$; $d = 1.64$) were presented in Fig. 2B. To separate PD patients from HC, the cut-off value obtained in ROC analysis for α/θ right occipital

Table 1
Demographic and clinical characteristics of the sample.

	HC (n = 36)	PD (n = 36)
Age (years)	63 (6)	63 (8)
Gender (F/M)	12/24	12/24
Education (years)	12(5)	12 (5)
Years from diagnosis	-	5.2 (3.1)
Hoehn & Yahr [a]	-	2 (0)
UPDRS-III score [a]	-	28 (17)

HC: Healthy Controls; PD: Parkinson's Disease; F: Female; M: Male; UPDRS-III: Unified Parkinson's Disease Rating Scale part III.
Values presented in the table are means with Standard Deviation (S.D).
[a] The marked situations show median (interquartile range).

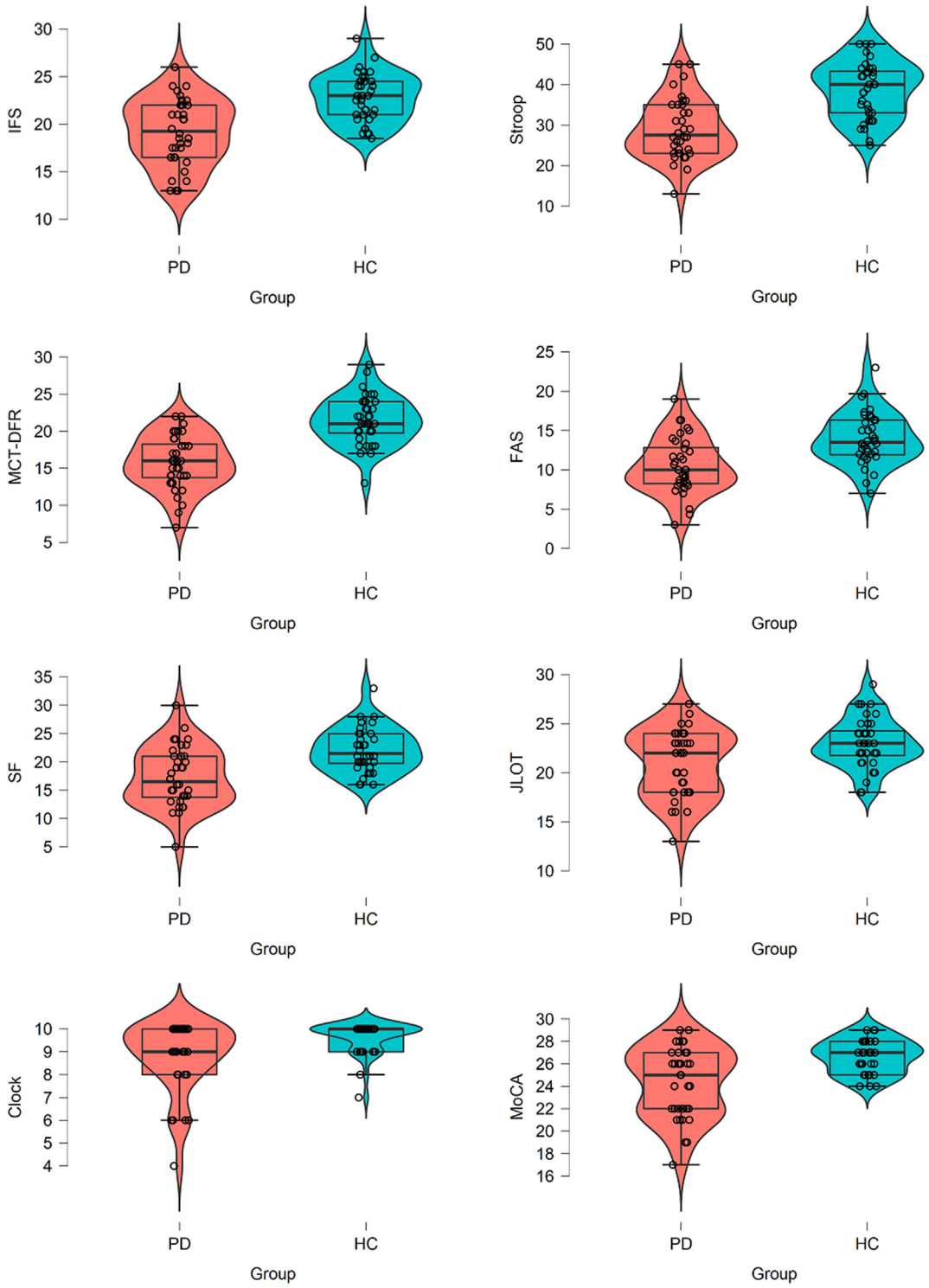

Fig. 1. Performance of PD patients and HC in neuropsychological tests. PD: Parkinson's Disease; HC: Healthy Controls; IFS: INECO Frontal Screening battery; Stroop: Stroop test – Golden version: MCT-DFT: Delayed free recall of the Memory Capacity Test; FAS: FAS phonemic fluency test; SF: Semantic fluency of animals; Clock: Free-drawn of the clock drawing test; JLOT: Judgment of Line Orientation Test; MoCA: Montreal Cognitive Assessment.

was 0.832, providing a sensitivity of 89% (95% CI: 74 – 97%), specificity of 56 % (95% CI: 38 – 72%), positive predictive value of 67% (95% CI: 58 – 75%), negative predictive value of 83% (95% CI: 65–93%), and accuracy of 72% (95% CI: 60–82%).

We then conducted exploratory correlations between hemispheric-regional α/θ and neuropsychological test scores in the PD group. Significant positive correlations between performance in JLOT and α/θ were found in right parietal (rho = 0.362; p = 0.030), right occipital (rho = 0.407; p = 0.014), and left occipital regions (rho = 0.382; p = 0.022), see Fig. 3. We did not find any other significant correlations in these exploratory analyses, see Table 3. We confirmed these results controlling for the effect of age and obtained significant findings in the same ROI (Supplementary Table S6). All these p-values were not corrected given the exploratory nature of these correlations.

Table 2
Neuropsychological and qEEG characteristics of the sample.

	HC (n = 36)	PD (n = 36)	FDR
Neuropsychological Characteristics			
Executive/attention			
IFS [b]	22.8 (2.5)	19.2 (3.5)	**<0.001**
Stroop [b]	38.7 (6.9)	29 (7.4)	**<0.001**
Memory			
MCT – DFR [b]	21.4 (3.3)	15.8 (3.6)	**<0.001**
Language			
FAS [b]	14 (3.3)	10.5 (3.6)	**<0.001**
SF [b]	22.1 (3.9)	17.4 (5.3)	**<0.001**
Visuospatial abilities			
Clock [a,c]	10 (1)	9 (2)	**0.005**
JLOT [a,c]	23 (4)	22 (6)	**0.023**
Global cognition			
MoCA [a,c]	27 (3)	25 (5)	**0.002**
qEEG – α/θ			
α/θ right frontal [b]	0.40 (0.49)	0.05 (0.51)	**0.004**
α/θ left frontal [b]	0.41 (0.51)	0.03 (0.51)	**0.004**
α/θ right temporal [b]	0.54 (0.38)	0.15 (0.48)	**<0.001**
α/θ left temporal [b]	0.57 (0.37)	0.18 (0.48)	**<0.001**
α/θ right parietal [b]	0.69 (0.47)	0.26 (0.53)	**<0.001**
α/θ left parietal [b]	0.63 (0.50)	0.27 (0.52)	**0.004**
α/θ right occipital [b]	0.81 (0.58)	0.22 (0.60)	**<0.001**
α/θ left occipital [b]	0.74 (0.56)	0.20 (0.61)	**<0.001**

HC: Healthy Controls; PD: Parkinson's Disease; FDR: False discovery ratio; IFS: INECO Frontal Screening battery; Stroop: Stroop test – Golden version: MCT-DFT: Delayed free recall of the Memory Capacity Test; FAS: FAS phonemic fluency test; SF: Semantic fluency of animals; Clock: Free-drawn of the clock drawing test; JLOT: Judgment of Line Orientation Test; MoCA: Montreal Cognitive Assessment; qEEG: Quantitative electroencephalogram.
p-values were FDR corrected. FDR values < 0.05 are printed in bold.
Values presented in the table are means with Standard Deviation (S.D).
[a] The marked situations shown median (interquartile range).
[b] Independent samples t-test [c] Mann-Whitney U test.

Further, we tested the moderation effect of each region significantly correlated with the JLOT performance of PD patients using three independent moderation analyses (i.e. one moderation model per each ROI). Among the three moderation models, we only found significant effects after the FDR correction in the model that included the α/θ in the right occipital region as a moderator of the JLOT performance related to PD diagnosis ($p < 0.005$; FDR = 0.014).

Fig. 4 shows the moderation model including the α/θ in the right occipital region. Three different pathways in this model were examined: a direct pathway from the group (HC vs. PD) to JLOT performance (X to Y) (b = -3.3; p = 0.002); a direct pathway from α/θ in right occipital in both groups (W) to JLOT performance (Y) (b = 0.32; p = 0.594); the conditional effect of α/θ in right occipital (W) on the relation between PD diagnosis (X) and JLOT performance (Y) (b = -2,6; p = 0.034). Therefore, the α/θ in the right occipital region influenced significantly the effect of PD diagnosis in JLOT performance.

Conversely, no significant moderation effects were found in the two remaining models that included the right parietal (p = 0.115) and the left occipital (p = 0.066) ROI as moderators (Figure S3 - Supplementary Material). Finally, we explored the conditional effect of different values of the α/θ – right occipital on the relationship between PD diagnosis and JLOT performance. Natural Log transformed α/θ - right occipital values below 0.633 significantly modulate the JLOT performance related to PD (Supplementary Figures S1 and S2). Thus, low α/θ (i.e. slowing-down) in the right occipital region, influenced the JLOT impairment related to PD diagnosis.

5. Discussion

In this study, we investigated the associations between hemispheric-regional α/θ (i.e. slowing-down of the qEEG) and neuropsychological performance in non-demented PD patients. We observed, in most of the posterior regions, significant correlations between α/θ and performance in JLOT, which tested visuospatial abilities. The lower the α/θ in right and left occipital, and right parietal regions, the worse the performance in the JLOT test. However, after examining how posterior α/θ influences the JLOT performance related to PD diagnosis, only the slowing-down in the right occipital region showed significant effects. The latter suggests a hemispheric asymmetric effect that has to be considered in further research since hemispheric asymmetry in theta, alpha, and beta PSD have been reported previously in PD (Bousleiman et al., 2014; Yuvaraj et al., 2014).

PSD has been one of the most widely explored qEEG features (Al-Qazzaz et al., 2014; Geraedts et al., 2018; van der Zande et al., 2018), and also is an easily obtainable marker that can reflect cholinergic pathways damage (Moretti et al., 2004). Both dopaminergic and cholinergic dysfunctions explain the cognitive symptoms in PD as indicated in a dual syndrome hypothesis: Early dysexecutive syndrome and attentional impairments have been related to frontostriatal dopaminergic dysfunction secondary to caudate denervation (Kehagia et al., 2012). On the other hand, deficits in visual memory, visuospatial abilities, and semantic fluency that improve with cholinergic treatments have been associated with posterior cortical and temporal lobe dysfunction (Kehagia et al., 2012). Additionally, cholinergic impairment appears to be greater in PD than in Alzheimer's Disease, seems to trigger the global cognitive decline and progression to dementia, and precedes further basal forebrain cell loss (Ballinger et al., 2016; Bohnen et al., 2015). Apart from functional mechanisms, structural changes such as reduced cortical thickness in the right hemisphere (including right occipital) have been identified in PD patients with formed hallucinations and low performance in JLOT, supporting the link between visuospatial impairment, complex visual hallucinations, and progression to PDD (Ffytche et al., 2017).

In line with those findings, both PSD and frequency features may also exhibit impairments in non-dopaminergic ascending systems (Massa et al., 2020), but the alpha frequency is relatively independent of cholinergic dysfunction (Moretti et al., 2004). Cholinergic deficits lead to cortico-cortical and cortico-thalamo-cortical dysfunction resulting in slowing-down of the qEEG rhythms (Franciotti et al., 2020). This slowing-down can be observed with increasing PSD in low-frequency bands (i.e. delta and theta) while reducing in high-frequencies (i.e. alpha and beta) (Eichelberger et al., 2017; Geraedts et al., 2018). In consequence, the full integrity of cholinergic systems, and cortico-cortical dynamics are reflected by alpha PSD (Moretti et al., 2004). Besides, global deafferentation due to pathophysiological processes (i.e. functional or anatomic injuries on cholinergic systems) and non-specific thalamic systems may be involved in the augment of delta and theta PSD (Llinás et al., 1999; Schmidt et al., 2013). Therefore, combining alpha and theta PSD in a synoptic index of the alpha-to-theta transition frequency may be useful for indicating the cholinergic dysfunction, and enhancing the differences between HC and patients with neurodegenerative diseases such as Alzheimer's Disease (Moretti et al., 2004; Schmidt et al., 2013), dementia with Lewy bodies (Bonanni et al., 2016, 2008) and PD (Massa et al., 2020). Nevertheless, further research is needed to determine the patterns of α/θ related to MCI, but a recent publication has shown similar α/θ in PD-MCI and PD-nMCI in concordance with our results (Massa et al., 2020).

To evaluate the resting-state qEEG correlates of cognitive decline in PD, we suggest to use specific neuropsychological tests for cognitive domains, rather than screening tests for global cognition due to the heterogeneity of cognitive symptoms in PD (Kehagia et al., 2012; Williams-Gray et al., 2007). In our study, an α/θ association with MoCA was not observed. Similarly, PSD and

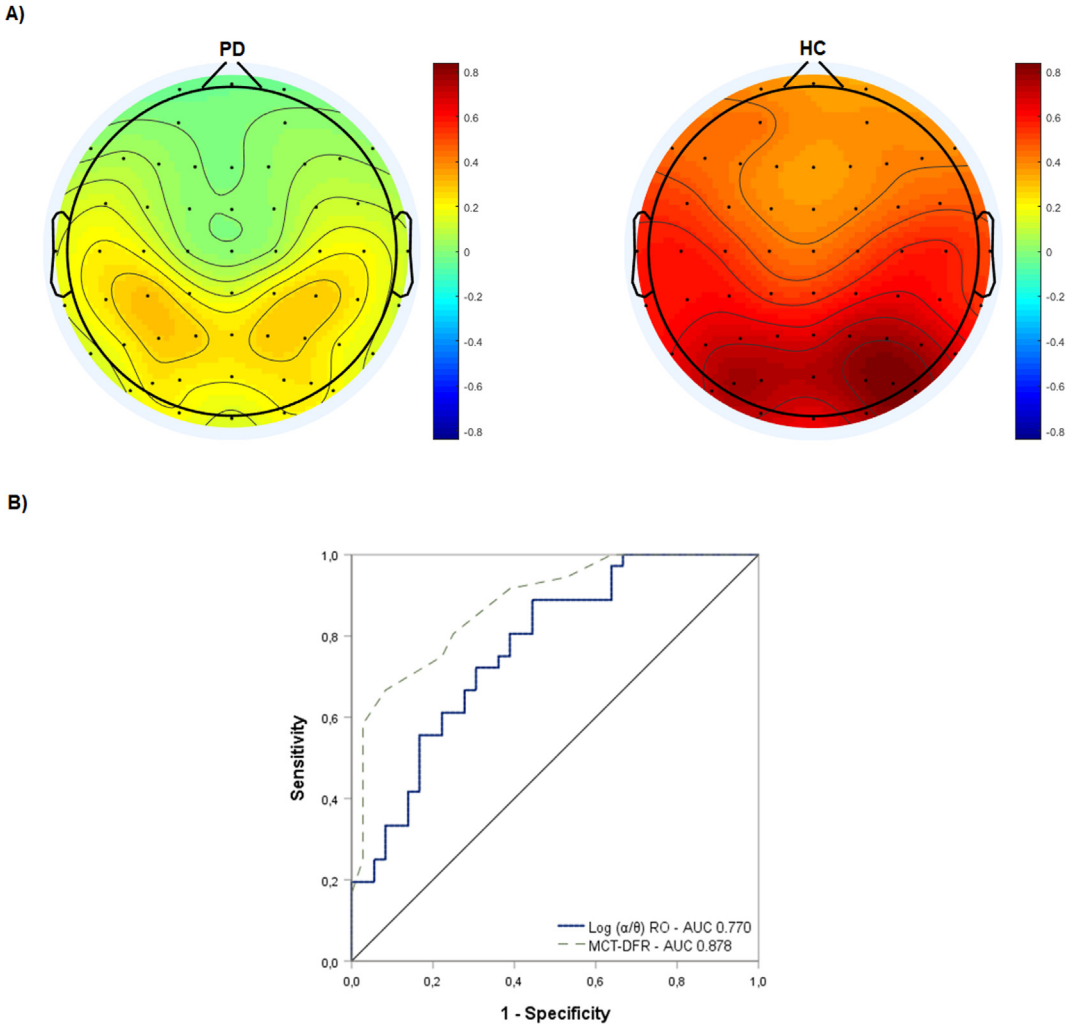

Fig. 2. Log (α/θ) values and its accuracy to separate PD patients from HC. A. Topographic plot of the Log (α/θ) in the PD and HC groups. The color bars indicate the mean values of the Log (α/θ) in each group, a high value indicates less slowing down of the qEEG rhythms. B. ROC curves for the right occipital α/θ and MCT-DFR. The blue line represents the ROC curve for the right occipital α/θ, the green dotted (dashed) line represents the ROC curve for the MCT-DFR. R: Right; L: Left; CI: Confidence Interval; RO: Right occipital; AUC: Area Under Curve. For interpretation of the colors in this figure, the reader is referred to the web version of this article.

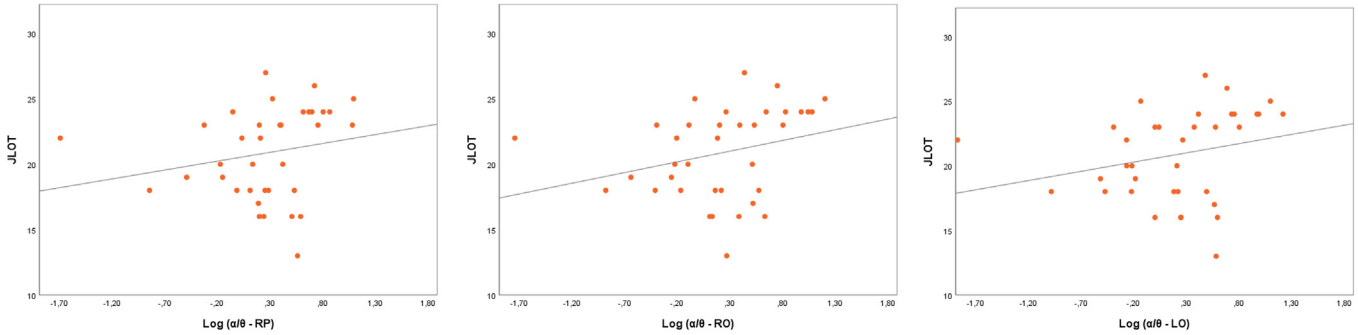

Fig. 3. Correlation plots between JLOT performance and the Log (α/θ) in the right parietal, and the right and left occipital regions in the PD group. RP: right parietal; RO: right occipital; LO: left occipital; JLOT: Judgement of Line Orientation Test.

tests of global-cognition (e.g. Mini-Mental State Examination) have not always shown significant correlations, but specific neuropsychological tests have exhibited consistent results (van der Hiele et al., 2007). One previous work has associated visuospatial impairments with occipital and parietal α/θ in non-demented PD patients (Eichelberger et al., 2017), yet PD-MCI patients were not included and those results cannot be extrapolated to PD-MCI. In our study, a reduced right occipital α/θ ratio was associated with an impairment in visuospatial functions measured by JLOT, but not with performance on the clock drawing test. The clock drawing test presented a ceiling effect (i.e. scores of 10 ± 1 in HC, and 9 ± 2 in PD), thus, bivariate correlations could be affected by the minimal variation in this variable. Another possible explanation for the different associations is that the JLOT test is considered a "pure"

Table 3
Exploratory correlations between α/θ and neuropsychological performance in PD patients.

Log (α/θ)	IFS [a]	Stroop [a]	MCT-DFR [a]	FAS [a]	SF [a]	Clock [b]	JLOT [b]	MoCA [b]
R. Frontal	−0.182	0.093	−0.072	−0.202	0.032	−0.064	0.315	−0.174
L. Frontal	−0.135	0.135	−0.070	−0.194	0.047	−0.092	0.321	−0.177
R. Temporal	−0.122	0.027	0.052	−0.118	0.034	−0.014	0.254	−0.044
L. Temporal	−0.163	0.011	−0.061	−0.111	0.059	−0.044	0.324	−0.163
R. Parietal	−0.200	0.024	−0.098	−0.162	0.044	−0.133	**0.362**	−0.205
L. Parietal	−0.120	0.067	0.022	−0.151	0.079	−0.079	0.237	−0.165
R. Occipital	−0.077	0.128	0.026	−0.194	0.112	−0.092	**0.407**	−0.081
L. Occipital	−0.066	0.101	0.036	−0.191	0.072	−0.057	**0.382**	−0.086

IFS: INECO Frontal Screening battery; Stroop: Stroop test – Golden version: MCT-DFT: Delayed free recall of the Memory Capacity Test; FAS: FAS phonemic fluency test; SF: Semantic fluency of animals; Clock: Free-drawn of the clock drawing test; JLOT: Judgment of Line Orientation Test; MoCA: Montreal Cognitive Assessment; R: Right; L: Left. Coefficients with unadjusted $p < 0.05$ are printed in bold.
[a] Pearson correlation.
[b] Spearman correlation.

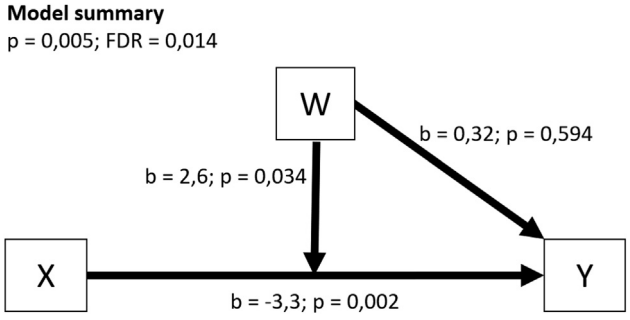

Fig. 4. Moderation effect of the α/θ - right occipital on JLOT performance related to PD. JLOT was used as the dependent variable (Y) while group (HC vs. PD) was the independent variable (X). The effect of α/θ - right occipital independently of PD diagnosis (W) over JLOT performance was examined. The moderation effect of W (α/θ - right occipital) on the PD-related JLOT performance (X to Y) was also considered. PD: Parkinson's Disease; HC: Healthy Control; JLOT: Judgement of Line Orientation Test; FDR: False Discovery Ratio.

visual-perceptual task, without major involvement of the motor component, whereas the clock drawing test assesses both visuospatial, visuoconstructive, and executive functions (Watson et al., 2013). Thus, in line with our findings, injuries in the right lateral superior occipital gyri and other areas of the visual dorsal stream such as the supramarginal gyri have been proposed as the neuropathological substrate related to decreased performance in the JLOT. Therefore, JLOT seems to represent a good clinical test for the right occipitoparietal functioning (Tranel et al., 2009), whereas the clock drawing test depends more on the right parietal and left inferior frontoparietal opercular lesions and it is not a very specific test for the right posterior functioning in chronic injuries (Tranel et al., 2008). Further research is necessary to elucidate the role of Lewy pathology in neurophysiological and neuropsychological impairment of different Lewy body diseases.

With all the above, our findings seem to support that slowing-down in the right occipital region is related to visuospatial performance patterns in non-demented PD patients. We suggest that the right occipital α/θ may be a promising marker of dementia risk in PD since patients with mild visuospatial impairment had more rapid progression PDD (Kehagia et al., 2012; Williams-Gray et al., 2007).

6. Limitations

There are some limitations to this study. The cross-sectional design and non-randomized sample may affect the statistical power and the external validity of our results in other populations. Also, the lack of follow-up did not make us able to determine the progression to PD-MCI or PDD in PD subjects. In addition, the effect of dopamine agonists on cortical excitability (i.e. widespread variations in delta and alpha sources) (Babiloni et al., 2019) has to be considered. However, little effect of dopaminergic treatments has been related to PSD changes (George et al., 2013) as reported in our results (Table S6 – Supplementary Material), also it is unlikely that medication effects would only apply to specific brain regions (i.e. left but not right occipital). Also, the lack of correction for multiple testing in some of our analyses should be considered when interpreting our results. This important limitation of our exploratory study encourages future investigations to replicate our results and provide external validation to our findings.

Moreover, our work has several strengths. Even if there are more sophisticated features on qEEG than relative PSD (Al-Qazzaz et al., 2014), highly refined techniques may apart us from the usefulness in a clinical setting (van der Hiele et al., 2007). Thus, we aimed to improve PSD extraction with our proposed signal processing methods. Therefore, we implemented a standardized, validated, and reliable method for qEEG preprocessing (Bigdely-Shamlo et al., 2015; Suarez-Revelo et al., 2018; 2016). PREP pipeline is a semi-automatic algorithm that enhances a more uniform statistical behavior of qEEG data, even between different paradigms, headsets, or collections of data (Bigdely-Shamlo et al., 2015). Also, we used a highly accurate method for obtaining PSD features based on multi-tapers. The multi-taper method has been widely recommended due to its better tradeoff among variance, bias, frequency resolution for PSD, and for assessing attenuation estimations when compared with the single-tapers and Welch method (Babadi and Brown, 2014; Prerau et al., 2017). Besides, assessing our participants with an extensive neuropsychological battery allowed us to evaluate neuropsychological patterns in several cognitive domains which are highly heterogeneous in PD patients (Aarsland et al., 2017; Kehagia et al., 2012; Williams-Gray et al., 2007), and most of the statistical methods we used to test our hypothesis has been also implemented previously, supporting our analysis (van der Hiele et al., 2007).

7. Conclusion

Slowing-down in the right occipital α/θ seems to be associated with, and influences, the visuospatial performance impairments related to PD diagnosis. Single averaged measures of occipital α/θ must be avoided due to possible hemispheric asymmetry, but further research is needed to confirm this hypothesis. The right occipital α/θ may represent a promising qEEG feature for evaluating PD patients with mild visuospatial impairments, who have a higher risk of progression to PDD (Kehagia et al., 2012; Williams-Gray et al., 2007).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2021.01.001.

References

Aarsland D, Creese B, Politis M, Chaudhuri KR, Ffytche DH, Weintraub D, et al. Cognitive decline in Parkinson disease. Nat Rev Neurol 2017;13:217–31. https://doi.org/10.1038/nrneurol.2017.27.

Agrell B, Dehlin O. The clock-drawing test. Age Ageing 1998;27:399–403.

Al-Qazzaz NK, Ali SHBM, Ahmad SA, Chellappan K, Islam MS, Escudero J. Role of EEG as Biomarker in the Early Detection and Classification of Dementia. Sci World J 2014. https://doi.org/10.1155/2014/906038.

Armstrong MJ. Lewy Body Dementias. Contin Lifelong Learn Neurol 2019;25:128–46. https://doi.org/10.1212/CON.0000000000000685.

Babadi B, Brown EN. A review of multitaper spectral analysis. IEEE Trans Biomed Eng 2014;61:1555–64. https://doi.org/10.1109/TBME.2014.2311996.

Babiloni C, Blinowska K, Bonanni L, Cichocki A, De Haan W, Del Percio C, et al. What electrophysiology tells us about Alzheimer's disease: a window into the synchronization and connectivity of brain neurons. Neurobiol Aging 2020;85:58–73. https://doi.org/10.1016/j.neurobiolaging.2019.09.008.

Babiloni C, Del Percio C, Lizio R, Noce G, Lopez S, Soricelli A, et al. Levodopa may affect cortical excitability in Parkinson's disease patients with cognitive deficits as revealed by reduced activity of cortical sources of resting state electroencephalographic rhythms. Neurobiol Aging 2019;73:9–20. https://doi.org/10.1016/j.neurobiolaging.2018.08.010.

Ballinger EC, Ananth M, Talmage DA, Role LW. Basal Forebrain Cholinergic Circuits and Signaling in Cognition and Cognitive Decline. Neuron 2016;91:1199–218. https://doi.org/10.1016/j.neuron.2016.09.006.

Benton AL, Varney NR, Hamsher K Des. Visuospatial Judgment: A Clinical Test. Arch Neurol 1978;35:364–7. https://doi.org/10.1001/archneur.1978.00500300038006.

Bigdely-Shamlo N, Mullen T, Kothe C, Su K-M, Robbins KA. The PREP pipeline: standardized preprocessing for large-scale EEG analysis. Front Neuroinform 2015;9. https://doi.org/10.3389/fninf.2015.00016.

Bohnen NI, Albin RL, Müller MLTM, Petrou M, Kotagal V, Koeppe RA, et al. Frequency of cholinergic and caudate nucleus dopaminergic deficits across the predemented cognitive spectrum of parkinson disease and evidence of interaction effects. JAMA Neurol 2015;72:194–200. https://doi.org/10.1001/jamaneurol.2014.2757.

Bonanni L, Franciotti R, Nobili F, Kramberger MG, Taylor J-P, Garcia-Ptacek S, et al. EEG Markers of Dementia with Lewy Bodies: A Multicenter Cohort Study. J Alzheimer's Dis 2016;54:1649–57. https://doi.org/10.3233/JAD-160435.

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 2008;131:690–705. https://doi.org/10.1093/brain/awm322.

Bousleiman H, Zimmermann R, Ahmed S, Hardmeier M, Hatz F, Schindler C, et al. Power spectra for screening parkinsonian patients for mild cognitive impairment. Ann Clin Transl Neurol 2014;1:884–90. https://doi.org/10.1002/acn3.129.

Carmona Arroyave JA, Tobón Quintero CA, Suárez Revelo JJ, Ochoa Gómez JF, García YB, Gómez LM, et al. Resting functional connectivity and mild cognitive impairment in Parkinson's disease. An electroencephalogram study. Future Neurol 2019;14. https://doi.org/10.2217/fnl-2018-0048. FNL18.

Casals-Coll M, Sánchez-Benavides G, Quintana M, Manero RM, Rognoni T, Calvo L, et al. Spanish normative studies in young adults (NEURONORMA young adults project): Norms for verbal fluency tests. Neurología 2013;28:33–40. https://doi.org/10.1016/j.nrleng.2012.02.003.

Caviness JN, Utianski RL, Hentz JG, Beach TG, Dugger BN, Shill HA, et al. Differential spectral quantitative electroencephalography patterns between control and Parkinson's disease cohorts. Eur J Neurol 2016;23:387–92. https://doi.org/10.1111/ene.12878.

Cozac VV, Gschwandtner U, Hatz F, Hardmeier M, Rüegg S, Fuhr P. Quantitative EEG and cognitive decline in Parkinson's disease. Parkinsons Dis 2016. https://doi.org/10.1155/2016/9060649.

Delorme A, Makeig S. EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. J Neurosci Meth 2004;134:9–21.

Eichelberger D, Calabrese P, Meyer A, Chaturvedi M, Hatz F, Fuhr P, et al. Correlation of Visuospatial Ability and EEG Slowing in Patients with Parkinson's Disease. Parkinsons Dis 2017;2017:3659784. https://doi.org/10.1155/2017/3659784.

Emre M, Aarsland D, Brown R, Burn DJ, Duyckaerts C, Mizuno Y, et al. Clinical diagnostic criteria for dementia associated with Parkinson's disease. Mov Disord 2007;22:1689–707. https://doi.org/10.1002/mds.21507.

Ffytche DH, Pereira JB, Ballard C, Chaudhuri KR, Weintraub D, Aarsland D. Risk factors for early psychosis in PD: Insights from the Parkinson's Progression markers initiative. J Neurol Neurosurg Psychiatry 2017;88:325–31. https://doi.org/10.1136/jnnp-2016-314832.

Franciotti R, Pilotto A, Moretti DV, Falasca NW, Arnaldi D, Taylor J-P, et al. Anterior EEG slowing in dementia with Lewy bodies: a multicenter European cohort study. Neurobiol Aging 2020;93:55–60. https://doi.org/10.1016/j.neurobiolaging.2020.04.023.

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 Clin 2013;3:261–70. https://doi.org/10.1016/j.nicl.2013.07.013.

Geraedts VJ, Boon LI, Marinus J, Gouw AA, van Hilten JJ, Stam CJ, et al. Clinical correlates of quantitative EEG in Parkinson disease. Neurology 2018;91:871–83. https://doi.org/10.1212/WNL.0000000000006473.

Gil L, Ruiz De Sánchez C, Gil F, Romero SJ, Pretelt Burgos F. Validation of the Montreal Cognitive Assessment (MoCA) in Spanish as a screening tool for mild cognitive impairment and mild dementia in patients over 65 years old in Bogotá, Colombia. Int J Geriatr Psychiatry 2015;30:655–62. https://doi.org/10.1002/gps.4199.

Goetz CC. The Unified Parkinson's Disease Rating Scale (UPDRS): Status and recommendations. Mov Disord 2003;18:738–50. https://doi.org/10.1002/mds.10473.

Golden C, Freshwater S. Stroop Color and Word Test: A Manual for Clinical and Experimental Use. Chicago, IL: Stoelting Co; 1978.

van der Hiele K, Vein AA, Reijntjes RHAM, Westendorp RGJ, Bollen ELEM, van Buchem MA, et al. EEG correlates in the spectrum of cognitive decline. Clin Neurophysiol 2007;118:1931–9. https://doi.org/10.1016/j.clinph.2007.05.070.

Hoehn MM, Yahr MD. Parkinsonism: Onset, progression, and mortality. Neurology 1967;17:427–42. https://doi.org/10.1212/wnl.17.5.427.

Kehagia AA, Barker RA, Robbins TW. Cognitive impairment in Parkinson's disease: The dual syndrome hypothesis. Neurodegener Dis 2012;11:79–92. https://doi.org/10.1159/000341998.

Lawton MP, Brody EM. Assessment of Older People: Self-Maintaining and Instrumental Activities of Daily Living1. Gerontologist 1969;9:179–86. https://doi.org/10.1093/geront/9.3_Part_1.179.

Litvan I, Goldman JG, Tröster AI, Schmand BA, Weintraub D, Petersen RC, et al. Diagnostic criteria for mild cognitive impairment in Parkinson's disease: Movement Disorder Society Task Force guidelines. Mov Disord 2012;27:349–56. https://doi.org/10.1002/mds.24893.

Llinás RR, Ribary U, Jeanmonod D, Kronberg E, Mitra PP. Thalamocortical dysrhythmia: A neurological and neuropsychiatric syndrome characterized by magnetoencephalography. Proc Natl Acad Sci U S A 1999;96:15222–7. https://doi.org/10.1073/pnas.96.26.15222.

Mahoney FI, Barthel DW. Functional Evaluation: The Barthel Index. Md State Med J 1965;14:61–5.

Massa F, Meli R, Grazzini M, Famà F, De Carli F, Filippi L, et al. Utility of quantitative EEG in early Lewy body disease. Park Relat Disord 2020;75:70–5. https://doi.org/10.1016/j.parkreldis.2020.05.007.

Mitra PP, Bokil H. Observed Brain Dynamics. New York: Oxford University Press; 2007. https://doi.org/10.1093/acprof:oso/9780195178081.003.0012.

Moretti DV, Babiloni C, Binetti G, Cassetta E, Dal Forno G, Ferreric F, et al. Individual analysis of EEG frequency and band power in mild Alzheimer's disease. Clin Neurophysiol 2004;115:299–308.

Postuma RB, Berg D, Stern M, Poewe W, Olanow CW, Oertel W, et al. MDS clinical diagnostic criteria for Parkinson's disease. Mov Disord 2015;30:1591–601. https://doi.org/10.1002/mds.26424.

Preacher KJ, Hayes AF. SPSS and SAS procedures for estimating indirect effects in simple mediation models. Behav Res Meth Instruments Comput 2004;36:717–31. https://doi.org/10.3758/BF03206553.

Prerau MJ, Brown RE, Bianchi MT, Ellenbogen JM, Purdon PL. Sleep neurophysiological dynamics through the lens of multitaper spectral analysis. Physiology 2017;32:60–92. https://doi.org/10.1152/physiol.00062.2015.

Rentz DM, Locascio JJ, Becker JA, Moran EK, Eng E, Buckner RL, et al. Cognition, reserve, and amyloid deposition in normal aging. Ann Neurol 2010;67:353–64. https://doi.org/10.1002/ana.21904.

Roberts JA, Breakspear M. Synaptic assays: using biophysical models to infer neuronal dysfunction from non-invasive EEG. Brain 2018;141:1583. https://doi.org/10.1093/brain/awy136.

Schmidt MT, Kanda PAM, Basile LFH, da Silva Lopes HF, Baratho R, Demario JLC, et al. Index of alpha/theta ratio of the electroencephalogram: a new marker for Alzheimer's disease. Front Aging Neurosci 2013;5:60. https://doi.org/10.3389/fnagi.2013.00060.

Suarez-Revelo J, Ochoa-Gomez J, Duque-Grajales J. Improving test-retest reliability of quantitative electroencephalography using different preprocessing approaches. 38th Annu Int Conf IEEE Eng Med. Biol Soc 2016:961–4. https://doi.org/10.1109/EMBC.2016.7590861.

Suarez-Revelo J, Ochoa-Gómez J, Tobón-Quintero C. Validation of EEG Preprocessing Pipeline by Test-Retest Reliability. Commun Comput Inf Sci 2018;916:290–9. https://doi.org/10.1007/978-3-030-00353-1_26.

Torralva T, Roca M, Gleichgerrcht E, López P, Manes F. INECO Frontal Screening (IFS): A brief, sensitive, and specific tool to assess executive functions in dementia. J Int Neuropsychol Soc 2009;15:777–86. https://doi.org/10.1017/S1355617709990415.

Tranel D, Rudrauf D, Vianna EPM, Damasio H. Does the Clock Drawing Test Have Focal Neuroanatomical Correlates. Neuropsychology 2008;22:553–62. https://doi.org/10.1037/0894-4105.22.5.553.

Tranel D, Vianna E, Manzel K, Damasio H, Grabowski T. Neuroanatomical correlates of the Benton Facial Recognition Test and Judgment of Line Orientation Test. J Clin Exp Neuropsychol 2009;31:219–33. https://doi.org/10.1080/13803390802317542.

Watson G Stennis, Cholerton Brenna A, Gross Rachel G, Weintraub Daniel, Zabetian Cyrus P, Trojanowski John Q, et al. Neuropsychologic assessment in collaborative Parkinson's disease research: A proposal from the National Institute of Neurological Disorders and Stroke Morris K. Udall Centers of Excellence for Parkinson's Disease Research at the University of Pennsylvania and the University of Washington. Alzheimer's and Dementia 2013;9(5):609–14. https://doi.org/10.1016/j.jalz.2012.07.006.

Williams-Gray CH, Foltynie T, Brayne CEG, Robbins TW, Barker RA. Evolution of cognitive dysfunction in an incident Parkinson's disease cohort. Brain 2007;130:1787–98. https://doi.org/10.1093/brain/awm111.

Yuvaraj R, Murugappan M, Mohamed Ibrahim N, Iqbal Omar M, Sundaraj K, Mohamad K, et al. On the analysis of EEG power, frequency and asymmetry in Parkinson's disease during emotion processing. Behav Brain Funct 2014;10. https://doi.org/10.1186/1744-9081-10-12.

van der Zande JJ, Gouw AA, van Steenoven I, Scheltens P, Stam CJ, Lemstra AW. EEG characteristics of dementia with Lewy Bodies, Alzheimer's Disease and mixed pathology. Front Aging Neurosci 2018;10. https://doi.org/10.3389/fnagi.2018.00190.