Clinical Neurophysiology

Resting-state qEEG Alpha/Theta ratio related to neuropsychological test performance in Parkinson's Disease

--Manuscript Draft--

Manuscript Number:	CLINPH-D-20-13700R1
Article Type:	Full Length Article
Section/Category:	Aging, Alzheimer's Disease, other Dementias, Psychiatric Disorders
Keywords:	electroencephalography; Parkinson's disease; Alpha rhythm; Theta rhythm; Neuropsychological tests
Corresponding Author:	Alberto Jaramillo-Jimenez, M.D. Helse Stavanger HF Stavanger, Rogaland NORWAY
First Author:	Alberto Jaramillo-Jimenez, M.D.
Order of Authors:	Alberto Jaramillo-Jimenez, M.D.
	Jazmin Ximena Suarez-Revelo, B.A. M.Sc.
	John Fredy Ochoa-Gomez, Ph.D.
	Jairo Alexander Carmona, M.D. M.Sc.
	Yamile Bocanegra, Ph.D.
	Francisco Lopera, M.D.
	Omar Buriticá, M.D.
	David Antonio Pineda Salazar, M.D. Ph.D.
	Leonardo Moreno Gómez, M.D. M.Sc.
	Carlos Andrés Tobón Quintero, M.D. Ph.D.
	Miguel Germán Borda, M.D. M.Sc.
	Laura Bonanni, M.D. Ph.D.
	Dominic Hannes Ffytche, M.D. Ph.D.
	Kolbjørn Brønnick, Ph.D.
	Dag Aarsland, M.D. Ph.D.
Abstract:	Objective: To determine possible associations of hemispheric-regional alpha/theta ratio (α/θ) with neuropsychological test performance in Parkinson's Disease non-demented patients (PD). Methods: 36 PD were matched to 36 Healthy Controls (HC). Resting-state quantitative electroencephalograms (qEEG) were recorded, the α/θ in eight hemispheric regions were computed from relative power spectral densities. 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.

SESAM
Regionalt kompetansesenter for eldremedisin og samhandling

Centre for Age-Related Medicine (SESAM), Stavanger University Hospital. Stavanger, Norway.

October 11th, 2020

Clinical Neurophysiology
Editor-in-Chief
Dr. Ulf Ziemann

We are re-submitting the manuscript entitled "**Resting qEEG Alpha/Theta ratio related to neuropsychological test performance in Parkinson's Disease"**, by Alberto Jaramillo-Jimenez, Jazmin Ximena Suarez-Revelo, John Fredy Ochoa-Gomez, Jairo Alexander Carmona, Yamile Bocanegra, Francisco Lopera, Omar Buriticá, David Antonio Pineda Salazar, Leonardo Moreno Gómez, Carlos Andrés Tobón Quintero, Miguel Germán Borda, Laura Bonanni, Dominic H. Ffytche, Kolbjørn Brønnick, Dag Aarsland, for your consideration and publication in Clinical Neurophysiology. All authors have reviewed and accepted the changes in this new version.

We thank you in advance for your time.

Kind regards,

Alberto Jaramillo-Jimenez
Centre for Age-Related Medicine (SESAM), Stavanger University Hospital, PB 8100, N-4068. Stavanger, Norway.
alberto.jaramilloj@udea.edu.co

Reviewer #1:

Comment 1: Overall, the topic is relevant .But, given major statistical issues there is no further results supported by the current study. I am not convinced by many of the findings and data presentation.The main issue is the multiple comparisons: The authors selected 8 ROI and ran independent t-test but didn't correct for multiple comparison in both power (alpha/theta) and correlation analysis.

> **Answer 1:** Thank you for your valuable comments. We have made various changes in our manuscript according to your suggestions about multiple testing. Now we have included false discovery rate (FDR) values for the independent t-test comparing the relative power (alpha/theta) and the neuropsychological tests, please see Table 2. Given the exploratory nature of the correlations between the alpha/theta ratio in 8 ROIs and the neuropsychological tests, we did not correct for multiple testing in that step, but we have done FDR correction in the group comparisons as well as in the final moderation analysis. Therefore, once we identified the target neuropsychological and qEEG variables (JLOT and the RP, RO, LO) in the exploratory correlations, we corrected the p-values of the three moderation models (one model for each ROI associated with JLOT performance) with the FDR estimations, obtaining significant results, after correction, for the moderation effect of the right occipital alpha/theta over the JLOT performance.

Comment 2: Statistical report and data presentation needs a major revision (i.e., please use boxplot for cognitive results, 2D-plot and the fitted line for correlation, topoplot for power spectrum distribution,…)

> **Answer 2:** Thanks for your suggestions. We have checked and made substantial changes in the statistical report to make it more clear as suggested by the reviewer. Also, we have added boxplots for the cognitive results (Figure 1), the 2D-plot for correlations between the ROIs and JLOT performance (Figure 3), and the topoplot with the relative power spectrum distribution (Figure 2A).

Reviewer #2:

Overall this is an interesting article and focused on an important neuroscientific area, i.e. neurophysiological correlates of cognitive functions in neurodegenerative disorders. In particular, the Authors compare the α/θ ratio in eight ROIs in patients with PD vs HC. Then they correlate this index with scores from tests evaluating neuropsychological functions. They show that α/θ ratio in the right occipital region is associated with an impairment in visuospatial functions and it may represent an early marker of cognitive impairment in PD.

I have few minor flaws to highlight:

Comment 1: The authors checked the association between α/θ ratio and confounders such as LEDD (in PD group) and age (in HC) before performing the correlations between α/θ ratio and neuropsychological tests. However, even though age was not associated with α/θ ratio from many posterior ROIs, it was associated with α/θ ratio from frontal, temporal and parietal ROIs (Supplementary Table 3). I would suggest adding also the results of correlations between α/θ ratio and neuropsychological tests including age as covariate.

> **Answer 1:** Thank you for your suggestion. Now we have conducted non-parametric partial correlations controlling for age. The relationships between the JLOT performance and right parietal, right occipital, and left occipital alpha/theta ratios are still significant and the correlations coefficients are slightly lower but similar to the previous ones (age-unadjusted), please see Table 5 - Supplementary materials.

Comment 2: The authors combine the group of PD-nMCI with the group of PD-MCI since they did not differ in α/θ ratio. This group include both patients with and without a global cognitive impairment as measured by the MoCA test. It could be helpful including in Supplementary Materials a table showing the MoCA and neuropsychological test scores (mean and SD) in PD-nMCI and PD-MCI patients.

> **Answer 2:** Thank you. We have added a table in the supplementary materials including this information, please see Table 2 - Supplementary materials.

Comment 3: The authors perform a moderator analysis to test whether cognitive performances related to the PD diagnosis were influenced by the α/θ ratio in specific regions. I would propose to use words such as "influence" or "modulate" instead of "modify" to better express the clinical meaning (rather than statistical) of this analysis.

> **Answer 3:** Thank you for this valuable suggestion. Now we have adjusted our manuscript avoiding the use of the word “modify”.

Comment 4: The authors found that a decreased right occipital α/θ ratio was associated with an impairment in visuospatial functions measured by JLOT. The JLOT test is a complex measure of visuo-perceptual abilities that encompasses visual processing from more basic visual functions to more high elaborated visual processing to judge the lines orientation. In this study the clock drawing test was also used to measure the visuospatial functions but the performances in this test did not correlate with α/θ ratio. The clock test evaluates a complex process including also visuo spatial and visuo constructive skills. I would suggest to extend the discussion on this point and also to formulate an hypothesis about the reason why the α/θ ratio in posterior regions is associated with JLOT but not with the clock drawing test performances.

> **Answer 4:** Now, we have added a paragraph considering these important issues that you have remarked (please see page 9, paragraphs 1, and 2).

Comment 5: In the Table 2 footnotes the letter d indicates the Chi square test. Since the table does not show results from Chi square test, it can be deleted.

> **Answer 5:** Thank you, we have corrected that in the revised version of the manuscript.

Please note: In addition to the suggestions of the reviewers, we have made a minor change in the title of the manuscript.

Centre for Age-Related Medicine (SESAM)
Stavanger University Hospital, PB 8100, N-4068. Stavanger, Norway.
Telephone: +47 93269946

Resting-state qEEG Alpha/Theta ratio related to neuropsychological test performance in Parkinson's Disease

Alberto Jaramillo-Jimenez[1,2,3,4,5,6*]; Jazmin Ximena Suarez-Revelo[3,4]; John Fredy Ochoa-Gomez[3,4]; Jairo Alexander Carmona[3,4]; Yamile Bocanegra[3,4]; Francisco Lopera[3]; Omar Buriticá[3]; David Antonio Pineda Salazar[3,4]; Leonardo Moreno Gómez[7]; Carlos Andrés Tobón Quintero[3,4]; Miguel Germán Borda[1,2,8]; Laura Bonanni[9]; Dominic H. Ffytche[10,11]; Kolbjørn Brønnick[1,2]; Dag Aarsland[1,11].

1. Centre for Age-Related Medicine (SESAM), Stavanger University Hospital. Stavanger, Norway.
2. Faculty of Health Sciences, University of Stavanger. Stavanger, Norway.
3. Grupo de Neurociencias de Antioquia, Universidad de Antioquia, School of Medicine. Medellín, Colombia.
4. Grupo Neuropsicología y Conducta, Universidad de Antioquia, School of Medicine. Medellín, Colombia.
5. Semillero de Investigación SINAPSIS, Universidad de Antioquia, School of Medicine. Medellín, Colombia.
6. Semillero de Investigación NeuroCo, Universidad de Antioquia, School of Medicine & School of Engenieering. Medellín, Colombia.
7. Neurology Unit, Pablo Tobón Uribe Hospital. Medellín, Colombia.
8. Semillero de Neurociencias y Envejecimiento, Ageing Institute, Medical School, Pontificia Universidad Javeriana. Bogotá, Colombia.
9. Department of Neuroscience, Imaging and Clinical Science, and Aging Research Centre, G. d'Annunzio University. Chieti, Italy.
10. Department of Old Age Psychiatry, Institute of Psychiatry, Psychology, and Neuroscience, King's College London. London, UK.
11. KCL-PARCOG Group, Institute of Psychiatry, Psychology, and Neuroscience, King's College London, London, UK.

* Corresponding author at: Centre for Age-Related Medicine (SESAM), Stavanger University Hospital, PB 8100, N-4068. Stavanger, Norway. Tel: +47 51 51 56 19.
E-mail address: alberto.jaramilloj@udea.edu.co

Keywords: Electroencephalography, Parkinson's Disease, Alpha rhythm, Theta rhythm, Neuropsychological tests.

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 non-demented patients (PD).

Methods: 36 PD were matched to 36 Healthy Controls (HC). Resting-state quantitative electroencephalograms (qEEG) were recorded, the α/θ in eight hemispheric regions were computed from relative power spectral densities. 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.

Resting-state qEEG Alpha/Theta ratio related to neuropsychological test performance in Parkinson's Disease

Alberto Jaramillo-Jimenez[1,2,3,4,5,6*]; Jazmin Ximena Suarez-Revelo[3,4]; John Fredy Ochoa-Gomez[3,4]; Jairo Alexander Carmona[3,4]; Yamile Bocanegra[3,4]; Francisco Lopera[3]; Omar Buriticá[3]; David Antonio Pineda Salazar[3,4]; Leonardo Moreno Gómez[7]; Carlos Andrés Tobón Quintero[3,4]; Miguel Germán Borda[1,2,8]; Laura Bonanni[9]; Dominic H. Ffytche[10,11]; Kolbjørn Brønnick[1,2]; Dag Aarsland[1,11].

1. Centre for Age-Related Medicine (SESAM), Stavanger University Hospital. Stavanger, Norway.
2. Faculty of Health Sciences, University of Stavanger. Stavanger, Norway.
3. Grupo de Neurociencias de Antioquia, Universidad de Antioquia, School of Medicine. Medellín, Colombia.
4. Grupo Neuropsicología y Conducta, Universidad de Antioquia, School of Medicine. Medellín, Colombia.
5. Semillero de Investigación SINAPSIS, Universidad de Antioquia, School of Medicine. Medellín, Colombia.
6. Semillero de Investigación NeuroCo, Universidad de Antioquia, School of Medicine & School of Engenieering. Medellín, Colombia.
7. Neurology Unit, Pablo Tobón Uribe Hospital. Medellín, Colombia.
8. Semillero de Neurociencias y Envejecimiento, Ageing Institute, Medical School, Pontificia Universidad Javeriana. Bogotá, Colombia.
9. Department of Neuroscience, Imaging and Clinical Science, and Aging Research Centre, G. d'Annunzio University. Chieti, Italy.
10. Department of Old Age Psychiatry, Institute of Psychiatry, Psychology, and Neuroscience, King's College London. London, UK.
11. KCL-PARCOG Group, Institute of Psychiatry, Psychology, and Neuroscience, King's College London, London, UK.

* Corresponding author at: Centre for Age-Related Medicine (SESAM), Stavanger University Hospital, PB 8100, N-4068. Stavanger, Norway. Tel: +47 51 51 56 19.
E-mail address: alberto.jaramilloj@udea.edu.co

Keywords: Electroencephalography, Parkinson's Disease, Alpha rhythm, Theta rhythm, Neuropsychological tests.

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 non-demented patients (PD).
Methods: 36 PD were matched to 36 Healthy Controls (HC). Resting-state quantitative electroencephalograms (qEEG) were recorded, the α/θ in eight hemispheric regions were computed from relative power spectral densities. 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.

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 (NMS) including cognitive decline. Cognitive decline is among the most common and important NMS 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.

Quantitative electroencephalogram (qEEG) may reflect cholinergic dysfunction (van der Zande et al. 2018; Massa et al. 2020), and some qEEG features seem to be promising biomarkers for PD and other neurodegenerative dementias (Bonanni et al. 2008, 2016; Geraedts et al. 2018; Babiloni et al. 2020). As a case in point, our group has shown that frontal coherence is related to executive function in PD MCI (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 (Schmidt et al. 2013; Al-Qazzaz et al. 2014), but synoptic PSD indexes such as the ratio between alpha and theta PSD (α/ θ) may enhance the differences between patients and healthy controls (Schmidt et al. 2013; Massa et al. 2020). However, few studies have calculated those indexes in PD, and if so, have computed an average of 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 EEG 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 during 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), no significant cognitive complains or cognition-related functional decline. Besides, PD patients with MCI (PD-MCI, n = 14), defined following level one task force criteria - Movement Disorders Society (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 group

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 (UPDRS) part 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 dementia (exclusion criterion). 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 Semantic fluency of animals (SF) and FAS phonemic fluency tests (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 Benton Judgment of Line Orientation Test (JLOT) (Benton et al. 1978) and the free draw of the clock drawing test (Clock) (Agrell and Dehljn 1998). We included the raw scores of each test in the analysis.

3. qEEG recordings and preprocessing

Resting-state qEEGs in quiet wakefulness with eyes closed were recorded for five minutes 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 (Suárez-Revelo et al. 2018) with proved test-retest reliability (Suarez-Revelo et al. 2016) (See supplementary materials 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 (ROIs), 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 (alpha relative PSD/theta relative PSD) and its logarithmic transformation (i.e. natural log) following previously published methods (Moretti et al. 2004; Schmidt et al. 2013; Massa et al. 2020). Delta and frequencies higher than alpha were excluded from the current analysis.

2.4 Statistical analysis

Statistical analyses were performed using SPSS (version 25). Statistical significance was set at $p < 0.05$. Since α/θ in most of the posterior regions was different when comparing HCs and the two PD groups, but not when PD-MCI and PD-nMCI were compared (Tables 1, 2, and 3 – Supplementary materials), we merged PD-MCI and PD-nMCI in a single PD group to increase our statistical power with a 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 chi-square 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 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 (Table 6 – Supplementary materials), 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 (Table 4 – Supplementary materials), 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 ROIs 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 (Table 5 - Supplementary materials). As JLOT, Clock, and MoCA were non-normally distributed, we performed non-parametric correlations with these variables and Pearson correlations with the remaining, as shown in Table 3. 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 ROIs and neuropsychological tests.

Finally, to test our hypothesis that PD performance in some neuropsychological tests was influenced by the α/θ, those regions (ROIs) 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 10000 Bootstrap sampling. The p-values of the three resulting moderation models were corrected for multiple testing with the FDR method.

3. 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).

Insert here Table 1

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

Insert here Figure 1
Insert here 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 ROIs 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. Figure 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 Figure 2B. To separate PD patients from HC, the cut-off value obtained in ROC analysis for α/θ right occipital 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%).

Insert here Figure 2

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 Figure 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 ROIs (Table 5 – Supplementary materials). These p-values were not corrected given the exploratory nature of these correlations.

Insert here Table 3
Insert here Figure 3

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).

Insert here Figure 4

Figure 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) ROIs as moderators (Figure 3 - Supplementary materials). 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 (Figures 1 and 2 - Supplementary materials). Thus, low α/θ (i.e. slowing-down) in the right occipital region, influenced the JLOT impairment related to PD diagnosis.

4. 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 AD, seems to trigger the global cognitive decline and progression to dementia, and precedes further basal forebrain cell loss (Bohnen et al. 2015; Ballinger et al. 2016). 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 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 HCs and patients with neurodegenerative diseases such as Alzheimer's Disease (AD) (Moretti et al. 2004; Schmidt et al. 2013), dementia with Lewy bodies (Bonanni et al. 2008, 2016) 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 (Williams-Gray et al. 2007; Kehagia et al. 2012). In our study, an α/θ association with MoCA was not observed. Similarly, PSD and 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" 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 (Williams-Gray et al. 2007; Kehagia et al. 2012).

4.1. **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 6 – Supplementary materials), 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. 2016; Suárez-Revelo et al. 2018). 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 (Williams-Gray et al. 2007; Kehagia et al. 2012; Aarsland et al. 2017), 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).

5. Conclusion

Slowing-down in the right occipital α/θ seems to be associated to, 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 (Williams-Gray et al. 2007; Kehagia et al. 2012).

Acknowledgments: We want to thank all the participants, researchers that collaborated, the Research Development Committee (CODI) at Universidad de Antioquia, as well as the staff and facilities provided by Grupo de Neurociencias de Antioquia (GNA), Grupo Neuropsicología y Conducta (GRUNECO), Semillero SINAPSIS (research incubator program) and the School of Medicine at the Universidad de Antioquia in Colombia, as well to the Centre for age-related medicine (SESAM) in Norway.
Declaration of Competing Interest: The authors have no conflicts of interest to declare. The sponsor has no role in the collection, analysis, interpretation of the data, and writing of the final manuscript.
Funding: This work was supported by the Research Development Committee (CODI) - Universidad de Antioquia (University of Antioquia), Colombia, under the research project: “Procesamiento del lenguaje de acción en pacientes con enfermedad ganglio-basal desde una perspectiva neuropsicológica y neurofisiológica” (grant reference PRG-2014-768). In addition, this paper represents independent research supported by the Norwegian government, through hospital owner Helse Vest (Western Norway Regional Health Authority).

Author contributions:

A: conception and design; **B:** execution of the project and data collection; **C:** data analysis; **D:** interpretation of data; **E:** writing the first draft, **F:** review of the manuscript.

Alberto Jaramillo-Jimenez: A, B, C, D, E, F.
Jazmin Ximena Suarez-Revelo: B, C, F.
John Fredy Ochoa-Gomez: A, B, C, F.
Jairo Alexander Carmona: A, B, C, F.
Yamile Bocanegra: A, B, C, F.
Francisco Lopera: A, B, F.
Omar Buriticá: A, B, F.
David Antonio Pineda Salazar: A, B, F.
Leonardo Moreno Gómez: A, B, F.
Carlos Andrés Tobón Quintero: A, B, F.
Kolbjørn Brønnick: A, C, E, F.
Laura Bonanni: D, E, F.
Miguel Germán Borda: D, E, F.
Dominic H Ffytche: D, F.
Dag Aarsland: A, D, E, F.

References

Aarsland D, Creese B, Politis M, Chaudhuri KR, Ffytche DH, Weintraub D, et al. Cognitive decline in Parkinson disease. Vol. 13, Nature Reviews Neurology. Nature Publishing Group; 2017. p. 217–31. 10.1038/nrneurol.2017.27

Agrell B, Dehljn O. The clock-drawing test [Internet]. Vol. 27, Age and Ageing. 1998.

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;2014. 10.1155/2014/906038

Armstrong MJ. Lewy Body Dementias. Contin Lifelong Learn Neurol. 2019 Feb;25(1):128–46. 10.1212/CON.0000000000000685

Babadi B, Brown EN. A review of multitaper spectral analysis. IEEE Trans Biomed Eng. 2014;61(5):1555–64. 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 [Internet]. Vol. 85, Neurobiology of Aging. Elsevier Inc.; 2020. p. 58–73. 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 Jan 1;73:9–20. 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 [Internet]. Vol. 91, Neuron. Cell Press; 2016. p. 1199–218. 10.1016/j.neuron.2016.09.006

Benton AL, Varney NR, Hamsher K Des. Visuospatial Judgment: A Clinical Test. Arch Neurol. 1978;35(6):364–7. 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 Jun 18;9. 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 Feb 1;72(2):194–200. 10.1001/jamaneurol.2014.2757
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 Mar;131(3):690–705. 10.1093/brain/awm322
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 Oct 18;54(4):1649–57. 10.3233/JAD-160435
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 Nov;1(11):884–90. 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 May 24;14(2):FNL18. 10.2217/fnl-2018-0048
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. Neurol (English Ed. 2013 Jan 1;28(1):33–40. 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 Feb;23(2):387–92. 10.1111/ene.12878
Cozac V V., Gschwandtner U, Hatz F, Hardmeier M, Rüegg S, Fuhr P. Quantitative EEG and cognitive decline in Parkinson's disease. Vol. 2016, Parkinson's Disease. Hindawi Limited; 2016. 10.1155/2016/9060649
Delorme A, Makeig S. EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis [Internet]. Vol. 134, Journal of Neuroscience Methods. 2004.
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. Bodis-Wollner I, editor. Parkinsons Dis. 2017;2017:3659784. 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. Vol. 22, Movement Disorders. 2007. p. 1689–707. 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 Apr 1;88(4):325–31. 10.1136/jnnp-2016-314832
Franciotti R, Pilotto A, Moretti D V., 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 Sep 1;93:55–60. 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 Jan 1;3:261–70. 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 Nov 6;91(19):871–83. 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 Jun 1;30(6):655–62. 10.1002/gps.4199
Goetz CC. The Unified Parkinson's Disease Rating Scale (UPDRS): Status and recommendations [Internet]. Vol. 18, Movement Disorders. John Wiley & Sons, Ltd; 2003. p. 738–50. 10.1002/mds.10473
Golden C, Freshwater S. Stroop color and word test. 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 Sep;118(9):1931–9. 10.1016/j.clinph.2007.05.070
Hoehn MM, Yahr MD. Parkinsonism: Onset, progression, and mortality. Neurology. 1967;17(5):427–42. 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 Nov;11(2):79–92. 10.1159/000341998
Lawton MP, Brody EM. Assessment of Older People: Self-Maintaining and Instrumental Activities of Daily Living1. Gerontologist. 1969 Oct 1;9(3_Part_1):179–86. 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 Mar;27(3):349–56. 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 Dec 21;96(26):15222–7. 10.1073/pnas.96.26.15222
Mahoney FI, Barthel DW. Functional Evaluation: The Barthel Index. Md State Med J. 1965 Feb;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 Jun

1;75:70–5. 10.1016/j.parkreldis.2020.05.007
Mitra PP, Bokil H. Observed Brain Dynamics [Internet]. New York: Oxford University Press; 2007. 10.1093/acprof:oso/9780195178081.003.0012
Moretti D V, 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 Feb;115(2):299–308.
Postuma RB, Berg D, Stern M, Poewe W, Olanow CW, Oertel W, et al. MDS clinical diagnostic criteria for Parkinson's disease [Internet]. Vol. 30, Movement Disorders. John Wiley and Sons Inc.; 2015. p. 1591–601. 10.1002/mds.26424
Preacher KJ, Hayes AF. SPSS and SAS procedures for estimating indirect effects in simple mediation models. Behav Res Methods, Instruments, Comput. 2004;36(4):717–31. 10.3758/BF03206553
Prerau MJ, Brown RE, Bianchi MT, Ellenbogen JM, Purdon PL. Sleep neurophysiological dynamics through the lens of multitaper spectral analysis. Vol. 32, Physiology. American Physiological Society; 2017. p. 60–92. 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 Mar;67(3):353–64. 10.1002/ana.21904
Roberts JA, Breakspear M. Synaptic assays: using biophysical models to infer neuronal dysfunction from non-invasive EEG. Brain. 2018 May 25;141(6):1583. 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. 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. In: 2016 38th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC). 2016. p. 961–4. 10.1109/EMBC.2016.7590861
Suárez-Revelo JX, Ochoa-Gómez JF, Tobón-Quintero CA. Validation of EEG Pre-processing Pipeline by Test-Retest Reliability. In: Communications in Computer and Information Science. Springer Verlag; 2018. p. 290–9. 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(5):777–86. 10.1017/S1355617709990415
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(2):219–33. 10.1080/13803390802317542
Watson GS, Cholerton BA, Gross RG, Weintraub D, Zabetian CP, Trojanowski JQ, 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. Vol. 9, Alzheimer's and Dementia. Elsevier Inc.; 2013. p. 609–14. 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 May 29;130(7):1787–98. 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(1). 10.1186/1744-9081-10-12

van der Zande JJ, Gouw AA, Steenoven I van, Scheltens P, Stam CJ, Lemstra AW. EEG characteristics of dementia with Lewy Bodies, Alzheimer's Disease and mixed pathology. Front Aging Neurosci. 2018 Jul 3;10(JUL). 10.3389/fnagi.2018.00190

Tables and Figures

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)

Values presented in the table are means with Standard Deviation (S.D)
[a] The marked situations show median (interquartile range)

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**

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
p-values were FDR corrected. FDR values < 0.05 are printed in bold

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

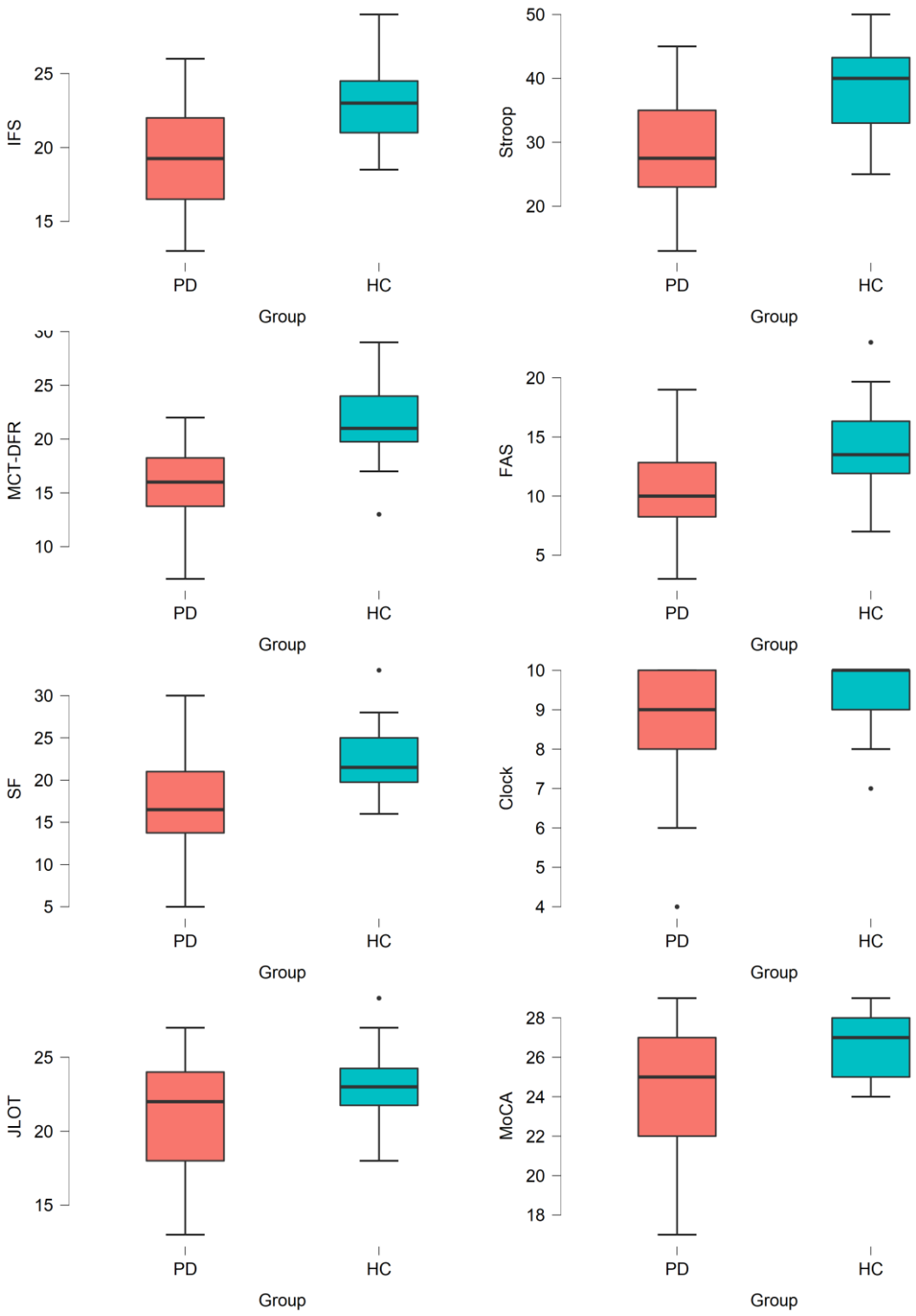
Log (α/θ)	IFS [a]	Stroop [a]	MCT-DFR [a]	FAS [a]	SF [a]	Clock [b]	JLOT [b]	MoCA [b]
R. Frontal	-0.182	0.093	-0.072	-0.202	0.032	-0.064	0.315	-0.174
L. Frontal	-0.135	0.135	-0.070	-0.194	0.047	-0.092	0.321	-0.177
R. Temporal	-0.122	0.027	0.052	-0.118	0.034	-0.014	0.254	-0.044
L. Temporal	-0.163	0.011	-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

R: Right; L: Left

[a] Pearson correlation [b] Spearman correlation

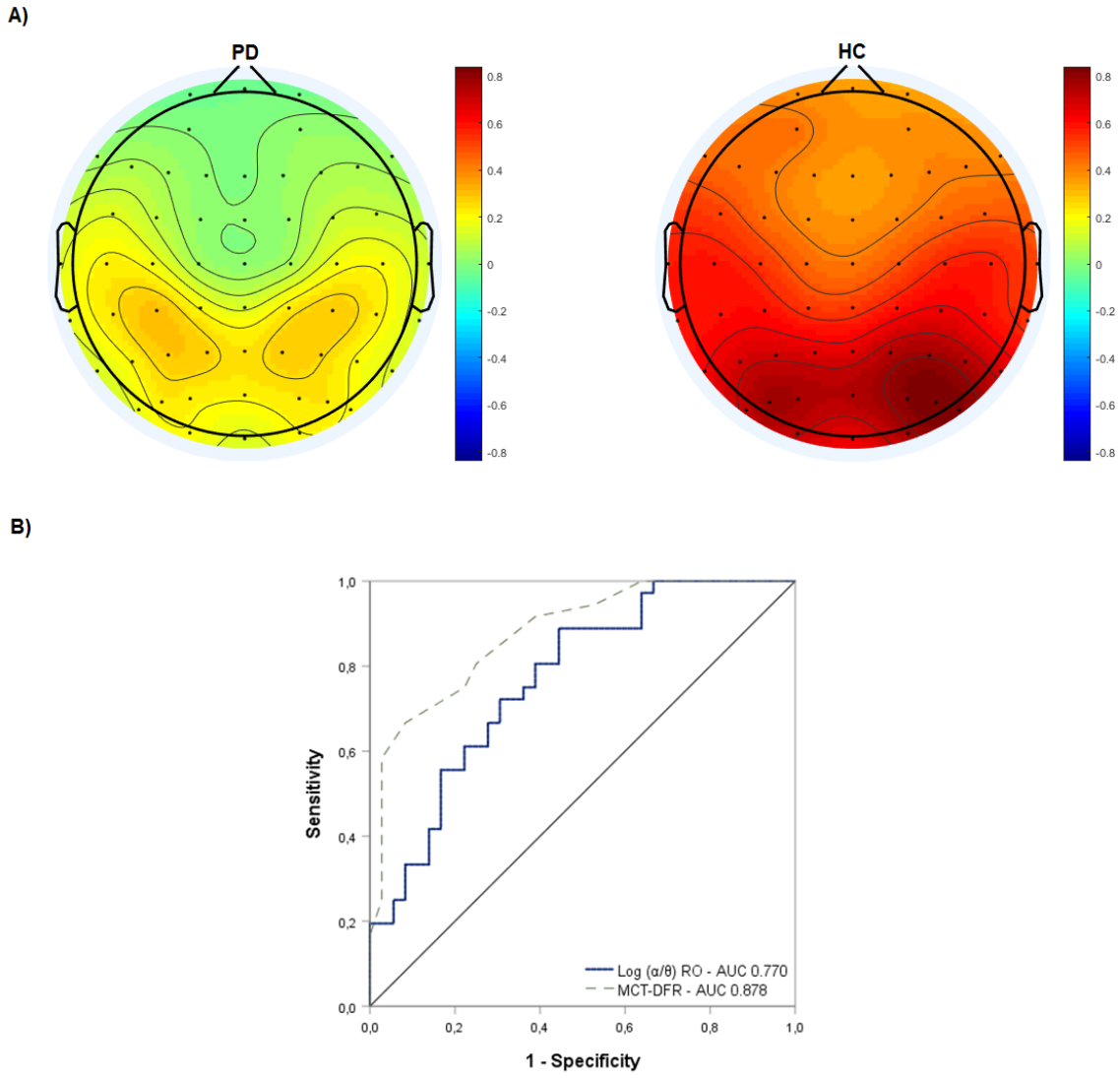
Coefficients with unadjusted $p < 0.05$ are printed in bold

Figure 1. Performance of PD patients and HC in neuropsychological tests



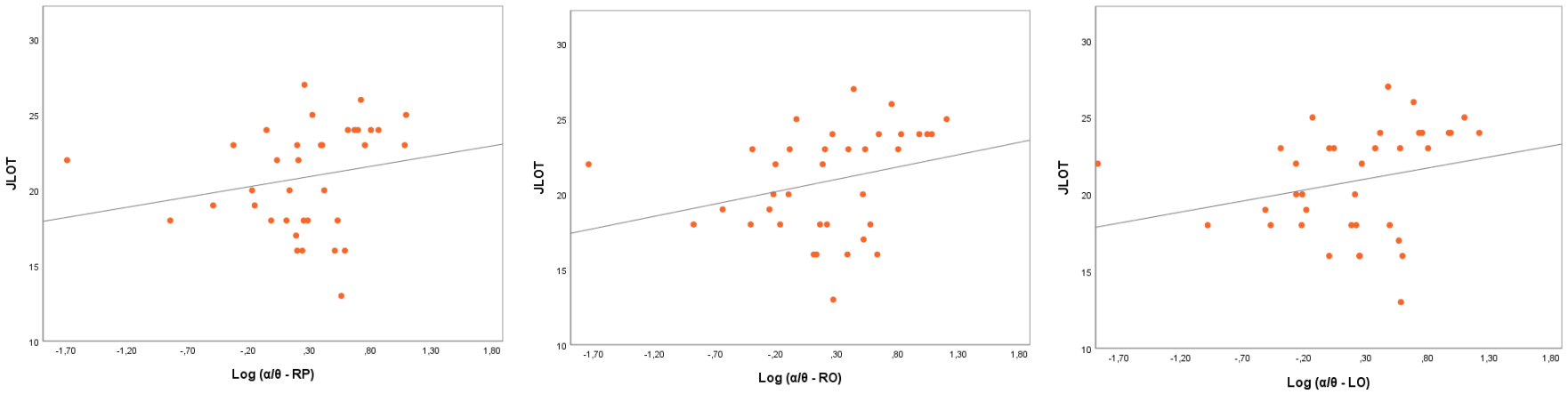
PD: Parkinson's Disease; HC: Healthy Controls; IFS: INECO Frontal Screening Test; Stroop: Stroop test interference score; MCT - DFR: Memory Capacity Test - Delayed Free Recall; FAS: FAS verbal fluency test; SF: Animals semantic fluency; Clock: Free draw of the Clock drawing test; JLOT: Judgement of Line Orientation Test; MoCA: Montreal Cognitive Assessment.

Figure 2. Log (α/θ) values and its accuracy to separate PD patients from HC



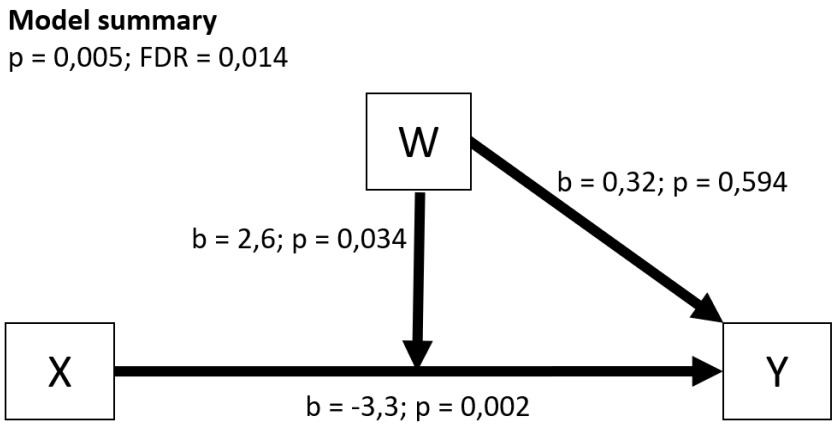
A. Mean of Log (α/θ) by ROI in PD and HC group; B. ROC curves for right occipital α/θ and MCT-DFR
R: Right; L: Left; CI: Confidence Interval; RO: Right occipital; AUC: Area Under Curve.
For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.

Figure 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: Benton Judgement of Line Orientation Test.

Figure 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.

Figure 1

Click here to access/download;Figure;Figure 1.tif

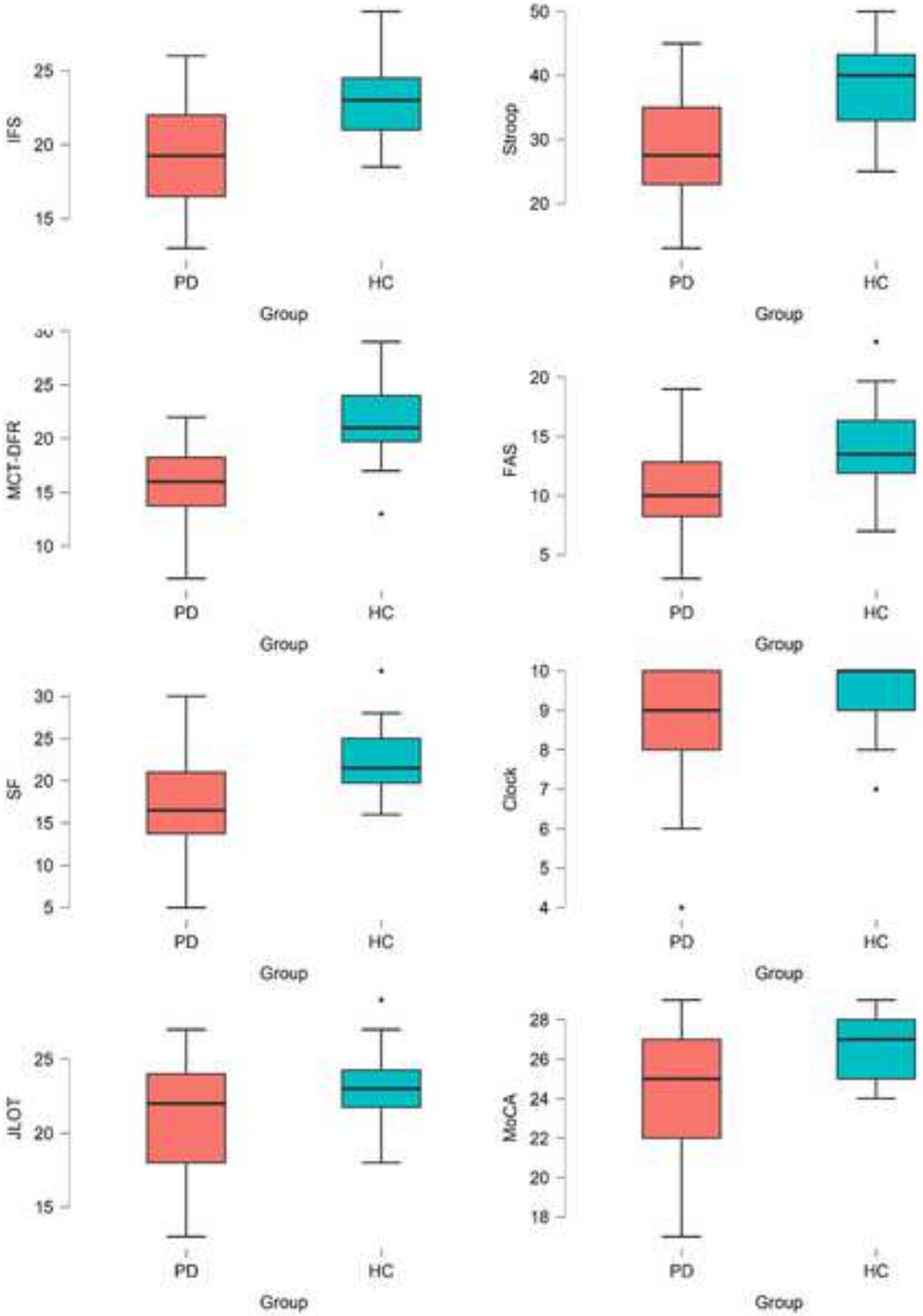


Figure 2

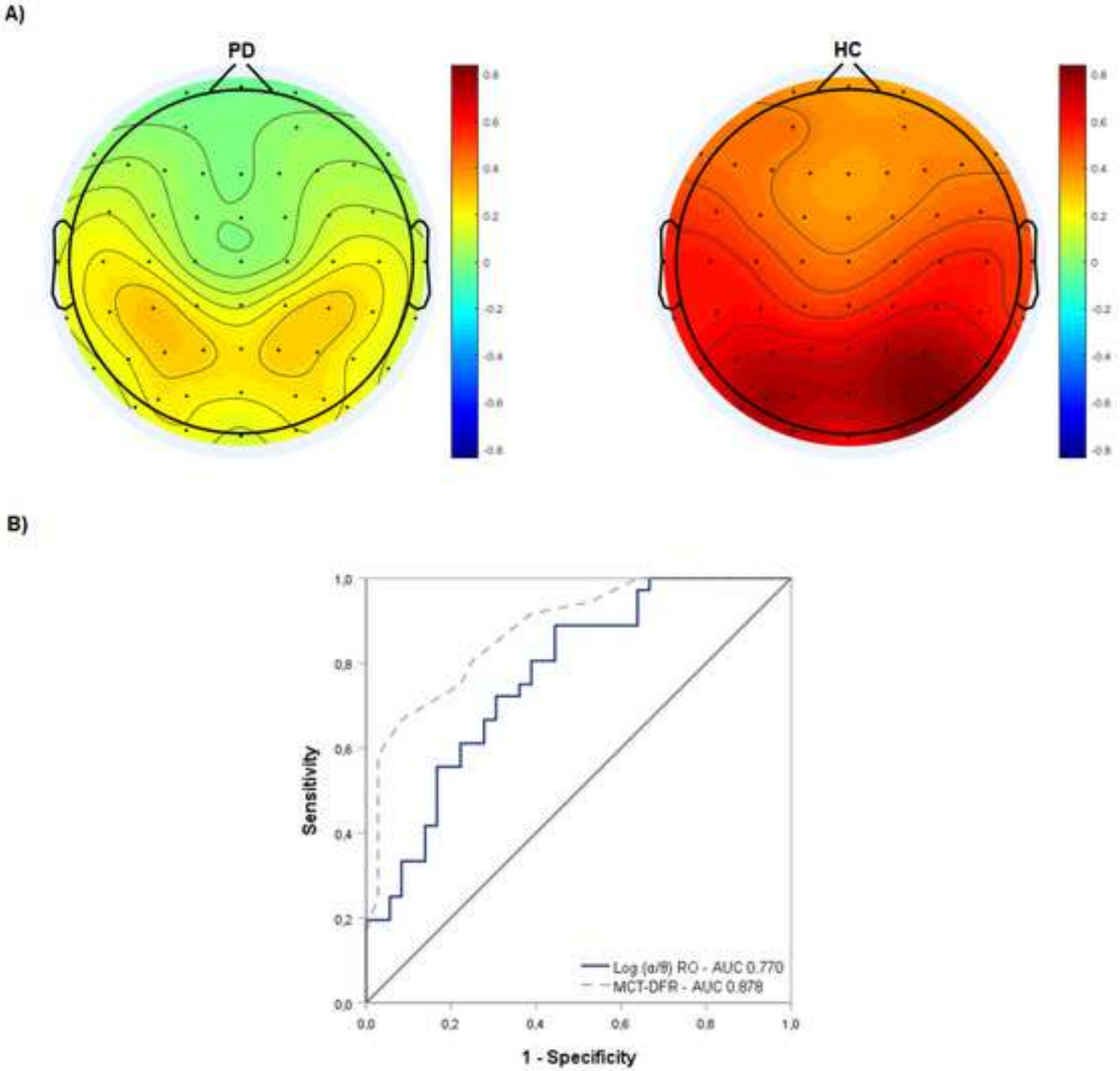
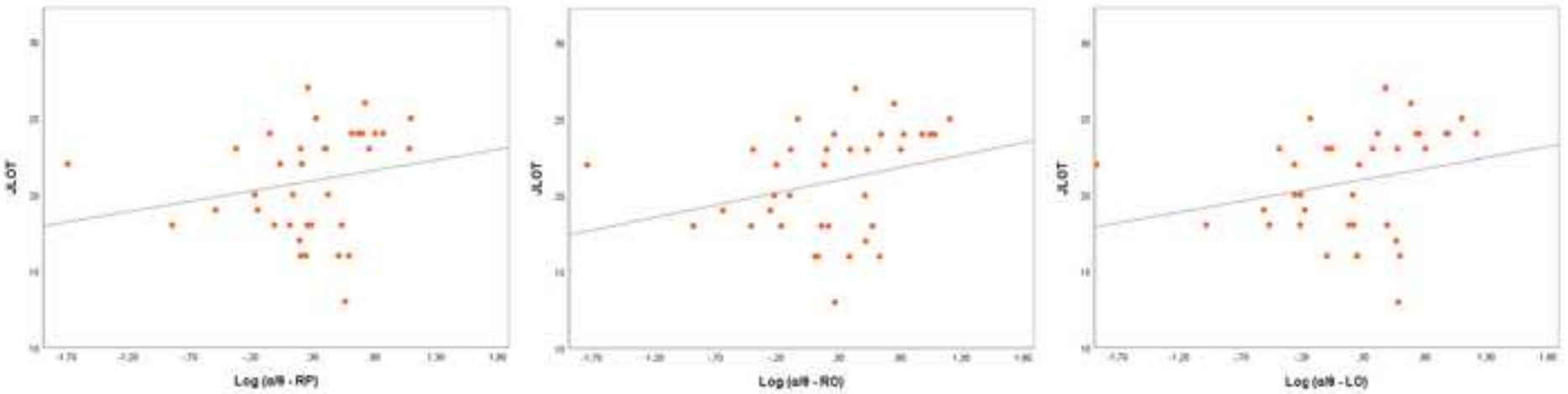


Figure 3

Click here to access/download;Figure;Figure 3.tif



EEG pre-processing methods: PREP pipeline

The pipeline consists on: data importation, removing of artifactual epochs by visual inspection, PREP pipeline with robust re-reference to average, detection and interpolation of defective channels, high pass FIR filtering at 1 Hz, independent component analysis (ICA INFOMAX), 2 seconds epoch segmentation, filtering of muscular and eye artifacts independent components using wavelets (wICA), low-pass FIR filtering at 30 Hz, and rejection of remaining deficient epochs by a procedure based on linear trend, joint probability, and kurtosis approach. For each subject, the average amount of interpolated channels was 4.96 (±3.66), 9.0 (±3.09) epochs were rejected, and 164.38 (±20.01) epochs were considered for randomized epoch selection.

Table 1 - Supplementary materials. Clinical and demographic characteristics of HC, PD-nMCI and PD-MCI groups

	HC (n = 36)	**PD – nMCI (n = 22)**	**PD-MCI (n = 14)**	**p Value**	**Multiple comparisons**
Age, mean (S.D)	63.3 (6.2)	61.8 (8)	66.1 (7.4)	0.218	PDnMCI: 0.662 [c] PD-MCI: 0.382 [c] PDnMCI vs. PD-MCI:0.247 [d]
Sex (F/M)	12/24	8/14	4/10	0.946 [a]	-
Education - years, mean (S.D)	12.4 (4.8)	11.5 (5)	11.9 (5.6)	0.800	PDnMCI: 0.752 [c] PD-MCI: 0.927 [c] PDnMCI vs. PD-MCI:1 [d]
Years from diagnosis of PD, mean (S.D)	-	4.4 (2.7)	6.2 (3.5)	0.129 [b]	-
Hoehn & Yahr, mean (S.D)	-	2.1 (0.4)	2.1 (0.3)	0.745 [b]	-
UPDRS-III, mean (S.D)	-	28.3 (12.6)	34.6 (10.3)	0.057 [b]	-
LEDD (mg), mean (S.D)	-	586.7 (304.8)	748.5 (396.9)	0.176 [b]	-

[a] p Values for Fisher exact
[b] p Values for Mann-Whitney U
[c] p Values for Dunnet t (2-sided), treating HC as the control group and comparing all other groups against HC.
[d] p Values for Bonferroni test

After conducting a one-way ANOVA, non-significant differences were obtained for age, gender, years of education, years from PD diagnosis, Hoehn & Yahr stage, UPDRS – III or Levodopa Equivalent Daily Dose (LEDD), even after correcting for multiple comparisons using Dunnett and Bonferroni tests. See Table 1 – Supplementary materials.

Table 2 - Supplementary materials. Neuropsychological performance in PD subgroups (PD-nMCI & PD-MCI) and HC.

	Healthy Controls (n = 36)	**PD – nMCI (n = 22)**	**PD-MCI (n = 14)**
Executive Function			
IFS	22.8 (2.5)	20.7 (2.4) *	16.6 (3.5) ** ††
Stroop	38.7 (6.9)	29.5 (6.9) **	28.2 (8.5) **
Language			
FAS	14.0 (3.3)	11.5 (3.4) *	8.9 (3.4) **
SF	22.1 (3.9)	19 (5.0) *	14.8 (4.7) ** †
Memory			
MCT-DFR	21.4 (3.3)	17.7 (2.7) **	12.8 (2.9) ** ††
Visuospatial abilities			
Clock [a]	10 (1.0)	10 (1.0)	9 (3) ** ††
JLOT	23.0 (2.5)	21.1 (3.0)	20.6 (4.2) *
Global Cognition			
MoCA	26.6 (1.)	26.4 (1.5)	20.9 (1.5) ** ††

Values presented in the table are means with Standard Deviation (S.D).
[a] The marked situations show median (interquartile range)
*Differs from Healthy Controls ($p<0.05$) **Differs from Healthy controls ($p<0.005$). †Differs from PD-nMCI ($p<0.05$) †† Differs from PD-nMCI ($p<0.005$).

Table 2 – Supplementary materials, shows the neuropsychological characteristics of the three subgroups. All the neuropsychological tests exhibited significant differences between cognitively normal subjects and patients of the PD-MCI group. The Stroop interference and the JLOT did not show significant differences between the two PD subgroups (PD-MCI and PD-nMCI) suggesting similar performances in those patients, but different when compared to the HC subgroup.

Table 3 – Supplementary materials. Differences in Log α/θ between the three groups

Log (α/θ)	HC (n = 36)	PD – nMCI (n = 22)	PD-MCI (n = 14)	F (p Value)	Multiple Comparisons
Right Frontal	0.400 (0.49)	-0.003 (0.60)	0.125 (0.35)	**4.71 (0.012)**	**PDnMCI: 0.008** [a] PD-MCI: 0.161 [a] PDnMCI vs. PD-MCI:1 [b]
Left Frontal	0.408 (0.51)	-0.017 (0.58)	0.112 (0.38)	**5.04 (0.009)**	**PDnMCI: 0.006** [a] PD-MCI: 0.132 [a] PDnMCI vs. PD-MCI: 1 [b]
Right Temporal	0.540 (0.38)	0.160 (0.52)	0.135 (0.42)	**7.20 (0.001)**	**PDnMCI: 0.004** [a] **PD-MCI: 0.009** [a] PDnMCI vs. PD-MCI:1 [b]
Left Temporal	0.574 (0.37)	0.154 (0.52)	0.229 (0.42)	**7.57 (0.001)**	**PDnMCI: 0.001** [a] **PD-MCI: 0.025** [a] PDnMCI vs. PD-MCI:1 [b]
Right Parietal	0.692 (0.47)	0.220 (0.60)	0.330 (0.43)	**6.78 (0.002)**	**PDnMCI: 0.002** [a] **PD-MCI: 0.048** [a] PDnMCI vs. PD-MCI:1 [b]
Left Parietal	0.630 (0.50)	0.250 (0.58)	0.291 (0.44)	**4.45 (0.015)**	**PDnMCI: 0.017** [a] PD-MCI: 0.080 [a] PDnMCI vs. PD-MCI:1 [b]
Right Occipital	0.813 (0.58)	0.199 (0.68)	0.243 (0.40)	**9.26 (<0.001)**	**PDnMCI: 0.001** [a] **PD-MCI: 0.006** [a] PDnMCI vs. PD-MCI:1 [b]
Left Occipital	0.740 (0.56)	0.190 (0.69)	0.222 (0.49)	**7.48 (0.001)**	**PDnMCI: 0.002** [a] **PD-MCI: 0.013** [a]

					PDnMCI vs. PD-MCI:1 [b]

[a] p Values for Dunnet t (2-sided), treating HC as control group and comparing each PD group against HC.
[b] p Values for Bonferroni test
Significant differences are printed in bold (p<0.05)

Before merging PD-nMCI and PD-MCI groups, we conducted Dunnett t-test, to adjust for multiple comparisons (i.e. comparing PD-MCI vs. HC, and PD-nMCI vs. HCs). We found significant differences between the two PD groups and HCs in all the ROIs except for frontal regions and left parietal. In addition, we checked for differences in Log (α/θ) between PD-MCI and PD-nMCI groups using Bonferroni and Hochberg tests but we did not find significant differences, as shown in Table 3 - Supplementary materials. Thus, we hypothesized that our findings in α/θ seem to be related to PD rather than PD-MCI diagnosis. Similarly, significant differences in JLOT scores between PD and HCs groups were found after adjusting for multiple comparisons using Dunnett t-test (HC vs. PD-nMCI = 0.044; HC vs. PD-MCI: 0.029). Besides, non-significant differences were founded when comparing PD-nMCI and PD-MCI groups using both Bonferroni and Hochberg tests ($p > 0.05$). Then, we merged PD-MCI and PD-nMCI groups into a single PD group to increase our statistical power and include a wider spectrum of PD.

Table 4 – Supplementary materials. Correlations between Age and Log α/θ in HCs

Log (α/θ)		Age
Right Frontal	r	0.426**
	p-Value	0.010
Left Frontal	r	0.391*
	p-Value	0.019
Right Temporal	r	0.324
	p-Value	0.054
Left Temporal	r	0.333*
	p-Value	0.047
Right Parietal	r	0.328
	p-Value	0.051
Left Parietal	r	0.362*
	p-Value	0.030
Right Occipital	r	0.170
	p-Value	0.323
Left Occipital	r	0.232
	p-Value	0.172

** Pearson Correlation is significant at the 0.01 level (2-tailed).
* Pearson Correlation is significant at the 0.05 level (2-tailed).

The correlation between α/θ and age was evaluated in our HC group using Pearson correlations to explore possible confounding effects for subsequent analyses. As non-significant correlations were found in HCs between age and most of the α/θ in posterior regions, then we chose to perform bivariate correlations in those regions where age was not correlated (i.e. right and left occipital, and right parietal). See Table 4 – Supplementary materials.

Table 5 – Supplementary materials. Exploratory non-parametric partial correlations between α/θ and neuropsychological performance in PD patients, controlling for Age.

Log (α/θ)	IFS [a]	Stroop [a]	MCT-DFR [a]	FAS [a]	SF [a]	Clock [a]	JLOT [a]	MoCA [a]
R. Frontal	-0.060	0.113	-0.102	-0.240	0.060	-0.117	0.308	-0.267
L. Frontal	-0.045	0.168	-0.127	-0.231	0.072	-0.145	0.314	-0.269
R. Temporal	-0.020	0.099	0.022	-0.150	0.061	-0.072	0.245	-0.138
L. Temporal	-0.060	0.104	-0.112	-0.156	0.073	-0.082	0.318	-0.232
R. Parietal	-0.093	0.073	-0.129	-0.175	0.111	-0.182	**0.356**	-0.289
L. Parietal	-0.061	0.107	-0.100	-0.189	0.116	-0.147	0.227	-0.282
R. Occipital	0.011	0.155	-0.017	-0.231	0.198	-0.163	**0.404**	-0.192
L. Occipital	0.028	0.139	0.029	-0.229	0.128	-0.115	**0.377**	-0.181

R: Right; L: Left
[a] Spearman correlation
Coefficients with $p < 0.05$ are printed in bold

Even if the α/θ in most of the posterior ROIs did not show correlations with age, some other regions exhibited an association with age. Therefore, to confirm our exploratory results, we conducted additional non-parametric partial correlations between the α/θ in the eight ROIs and the neuropsychological tests. Table 5 – Supplementary materials, shows the significant exploratory correlation between JLOT and the same ROIs obtained without controlling for age (i.e. the right parietal, and the right and left occipital α/θ). The correlation coefficients were slightly reduced after controlling for age but remained above 0.4 in the right occipital α/θ.

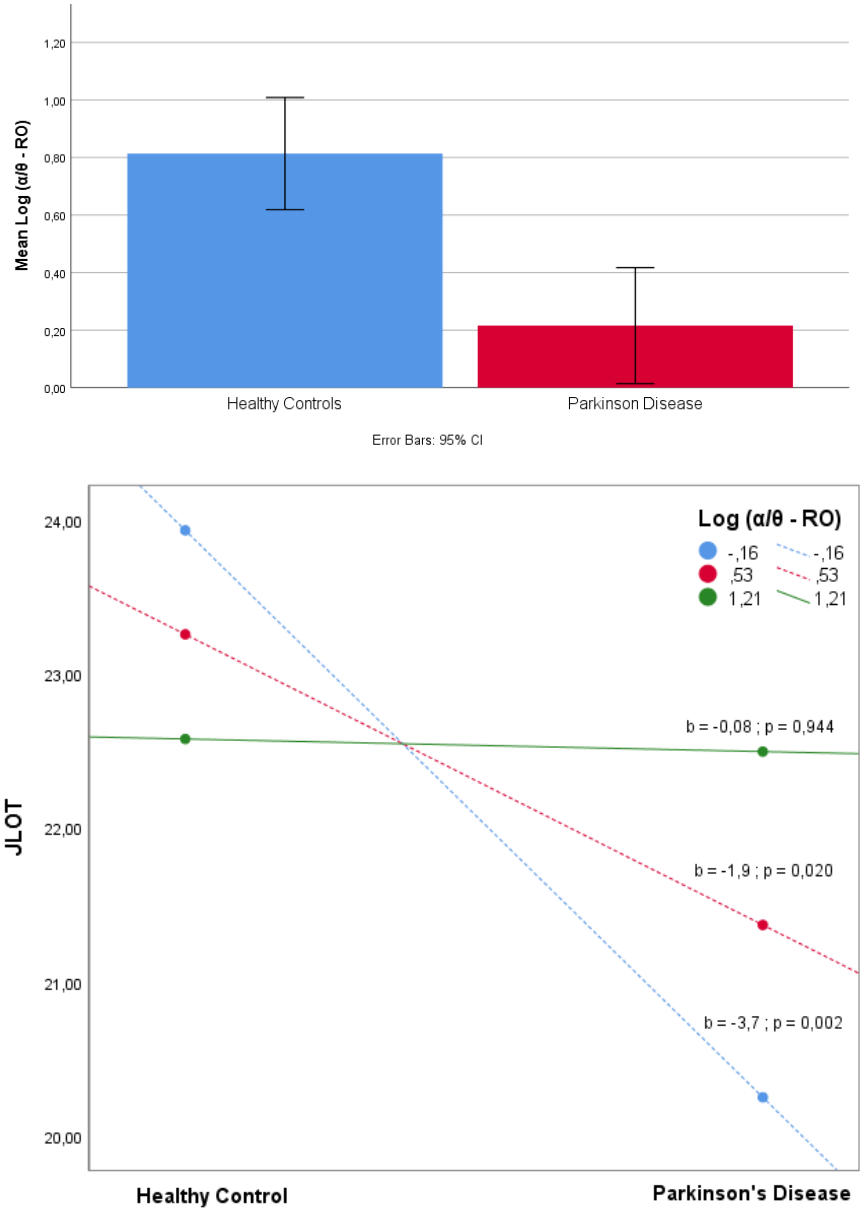
Table 6 – Supplementary Materials. Correlations between Levodopa Equivalent Daily Dose (LEDD) and Log α/θ in the PD group.

Log α/θ		LEDD
Right Frontal	r	0.099
	p-Value	0.573
Left Frontal	r	0.119
	p-Value	0.495
Right Temporal	r	0.093
	p-Value	0.595
Left Temporal	r	0.045
	p-Value	0.796
Right Parietal	r	0.119
	p-Value	0.495
Left Parietal	r	0.091
	p-Value	0.605
Right Occipital	r	0.093
	p-Value	0.596
Left Occipital	r	0.131
	p-Value	0.453

LEDD: Levodopa Equivalent Daily Dose

The correlation between α/θ and Levodopa Equivalent Daily Dose was evaluated in the PD group. We computed LEDD in 35 PD patients (except for one PD-MCI patient due to loss of data regarding medication). Since LEDD was normally distributed, Pearson correlations were used to explore the effect of LEDD on α/θ for adjusting subsequent correlation and moderation analyses. However, no significant correlations were found between LEDD and any of the α/θ, then we did not conduct LEDD-adjusted analyses. See Table 6 – Supplementary materials.

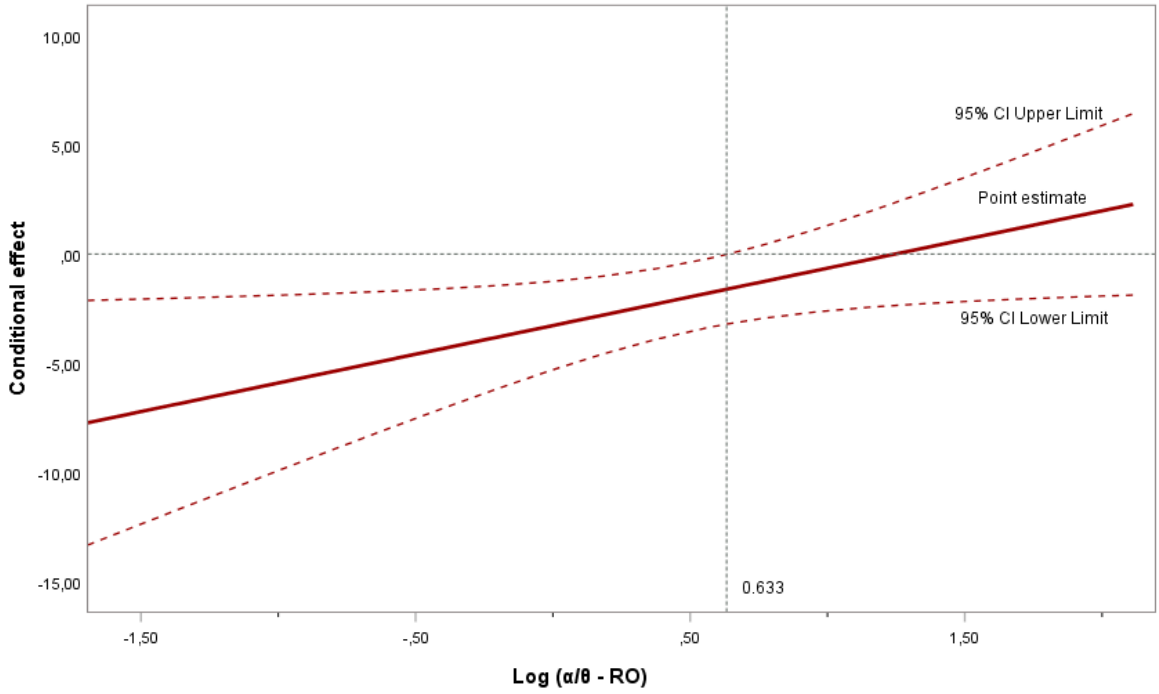
Figure 1 – Supplementary Materials. The mean value of α/θ– right occipital in HCs and PD groups (up) and its conditional effects on JLOT performance (down).



RO: right occipital; CI: Confidence Interval; JLOT: Benton Judgement on Line Orientation Test.

Figure 1 – Supplementary materials, depicts the mean values of α/θ – right occipital for HC and PD groups (up). Also, beta coefficients for the conditioned effects of low (blue), medium (red), and high (green) values of the α/θ – right occipital in HC and PD groups are presented (down). Dotted lines indicate statistically significant conditional effects of lower and medium values of α/θ – right occipital on the relationship between PD diagnosis and JLOT performance.

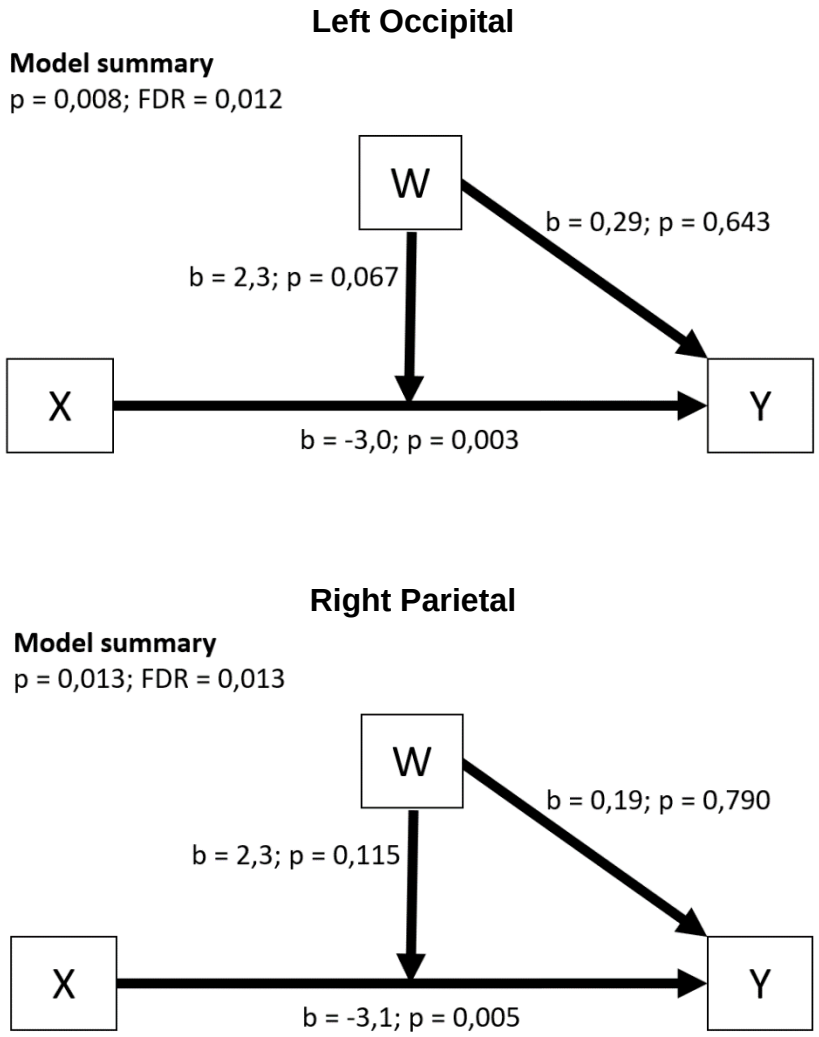
Figure 2 – Supplementary Materials. Conditional effects of α/θ values in the right occipital region on the relationship between PD diagnosis and JLOT performance.



RO: right occipital; CI: Confidence Interval; JLOT: Benton Judgement on Line Orientation Test.

Estimations of α/θ – right occipital significance region was defined using Johnson – Neyman method. All the values of Log (α/θ – right occipital) below 0.633 ($p \leq 0.05$) showed a significant conditional effect on the relationship between PD diagnosis and JLOT performance (left inferior quadrant).

Figure 3 – Supplementary materials. Moderation effects of the α/θ - left occipital (up) and right parietal (down) 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 independently of PD diagnosis (W) over JLOT performance was examined. The moderation effect of W (α/θ) on the PD-related JLOT performance (X to Y) was also evaluated.

This piece of the submission is being sent via mail.