Slowing of EEG waves correlates with striatal [18F]fluorodopa PET/CT uptake and executive dysfunction in Parkinson's disease

Karolina Lorek[1], Joanna Mączewska[2], Leszek Królicki[2], Magdalena Siemiatycka[3], Małgorzata Chalimoniuk[4], Katarzyna Kisiel-Sajewicz[3], and Jarosław Marusiak[3]

[1]Wroclaw University of Health and Sport Sciences
[2]Medical University of Warsaw
[3]Wroclaw University of Health and Sport Science
[4]Józef Piłsudski University of Physical Education in Warsaw

May 5, 2023

Abstract

Multimodal studies evaluating associations between specific for Parkinson's disease (PD) neuroimaging and neurophysiological biomarkers in revealing executive dysfunction mechanisms are scarce and needed to be validated. Hence, our study aimed to evaluate associations between electroencephalographic power spectral density (PSD-EEG), striatal [18F]Fluorodopa uptake and neuropsychological testing parameters in PD. Additional aim was to estimate PD diagnostic accuracy of the PSD-EEG parameters. We compared resting PSD-EEG, striatal [18F]Fluorodopa uptake ratio with positron emission computed tomography ([18F]FDOPA PET/CT), and neuropsychological test outcomes between PD patients and healthy controls, and then calculated correlations among these outcomes. Additionally we estimated PD diagnostic sensitivity and specificity (with the receiver operating characteristic curves) of the PSD-EEG parameters in reference to the gold diagnostic standard of the striatal [18F]FDOPA PET/CT uptake ratio.PD patients exhibited (i) increased power of the EEG theta and lower-alpha bands in the frontal lobe areas, (ii) decreased putaminal and caudate nuclei [18F]FDOPA PET/CT uptake ratios and (iii) longer performance times of part A and B of the Trail Making Test (TMT-A and TMT-B). Most of the PSD-EEG parameters negatively correlated with striatal [18F]FDOPA PET/CT uptake ratios and positively correlated with TMT-A and TMT-B. Furthermore, [18F]FDOPA PET/CT uptake ratios positively correlated with TMT-A and TMT-B. Theta and lower-alpha bands PSD-EEG were found to have high diagnostic accuracy. Our findings showed that slowing of EEG waves in the frontal lobe was correlated with striatal dopaminergic deficiency and executive dysfunction in mild PD patients, and appears to be a promising biomarker of PD-related executive dysfunction.

Slowing of EEG waves correlates with striatal [^{18}F]fluorodopa PET/CT uptake and executive dysfunction in Parkinson's disease

Running title: Neural bases of executive dysfunction in PD

Karolina Lorek, MSc, Eng,[1*] Joanna Mączewska, MD, PhD,[2] Leszek Królicki, MD, PhD,[2]Magdalena Siemiatycka, MSc,[1] Małgorzata Chalimoniuk, PhD,[3] Katarzyna Kisiel-Sajewicz, PhD,[1] Jarosław Marusiak, PhD[1*]

1– Department of Kinesiology, Faculty of Physiotherapy, Wroclaw University of Health and Sport Science, Wroclaw, Poland.

2 – Nuclear Medicine Department, Medical University of Warsaw, Warsaw, Poland.

3 – Department of Physical Education and Health in Biala Podlaska, Jozef Pilsudski University of Physical Education in Warsaw, Faculty in Biala Podlaska, Biala Podlaska, Poland.

ORCID numbers of all authors :

Karolina Lorek, 0000-0003-4823-7042; Joanna Mączewska, 0000-0002-3522-8633; Leszek Królicki, 0000-0002-7117-9621; Magdalena Siemiatycka, 0000-0001-8865-0320; Małgorzata Chalimoniuk, 0000-0003-0361-8626; Katarzyna Kisiel-Sajewicz, 0000-0002-3137-2646; Jarosław Marusiak. 0000-0001-6412-5943

Correspondence:

Lorek Karolina,

address: Department of Kinesiology, Faculty of Physiotherapy, Wroclaw University of Health and Sport Science, Wroclaw, Poland; 51-612 Wroclaw, Al. Paderewskiego 35, building P4 telephone number: (+48) 71 347 3532; fax number: (+48) 71 347 3431e-mail address: karolina.lorek@awf.wroc.pl

Jarosław Marusiak,

address: Department of Kinesiology, Faculty of Physiotherapy, Wroclaw University of Health and Sport Science, Wroclaw, Poland; 51-612 Wroclaw, Al. Paderewskiego 35, building P4 telephone number: (+48) 71 347 3057; fax number: (+48) 71 347 3431e-mail address: jaroslaw.marusiak@awf.wroc.pl

Word count Number of used words in the main text: 2497; Number of used words in abstract: 250

Financial Disclosure/Conflict of Interest

No author has a financial relationship with any company that manufactures products or equipment discussed in this manuscript, or any other apparent conflict of interest.

Funding Sources for study

The work was supported by the National Science Centre, Poland, under research project no 2017/25/B/NZ7/02795, entitled „Effect of high intensity interval training on mechanisms of neuroplasticity and psychomotor behaviours in Parkinson's disease patients: a randomized study with 1-year follow up", awarded to Jaroslaw Marusiak.

Abstract

Multimodal studies evaluating associations of the Parkinson's disease (PD) specific neuroimaging and neurophysiological biomarkers in revealing executive dysfunction mechanisms are scarce and needed to be validated.

Hence, our study aimed to evaluate associations between electroencephalographic power spectral density (PSD-EEG), striatal [^{18}F]Fluorodopa uptake and neuropsychological cognitive testing parameters in PD. Additional aim was to estimate PD diagnostic accuracy of the PSD-EEG parameters.

We compared resting PSD-EEG, striatal [^{18}F]Fluorodopa uptake ratio with positron emission computed tomography ([^{18}F]FDOPA PET/CT), and neuropsychological test outcomes between PD patients and healthy controls, and then calculated correlations among these outcomes. Additionally we estimated PD diagnostic sensitivity and specificity (with the receiver operating characteristic curves) of the PSD-EEG parameters in reference to the gold diagnostic standard of the striatal [^{18}F]FDOPA PET/CT uptake ratio.

PD patients exhibited (i) increased power of the EEG theta and lower-alpha bands in the frontal lobe areas, (ii) decreased putaminal and caudate nuclei [^{18}F]FDOPA PET/CT uptake and (iii) longer performance times of part A and B of the Trail Making Test (TMT-A and TMT-B). Most of the PSD-EEG parameters negatively correlated with striatal [^{18}F]FDOPA PET/CT uptake ratios and positively correlated with TMT-A and TMT-B. Furthermore, striatal [^{18}F]FDOPA PET/CT uptake ratios positively correlated with TMT-A and TMT-B. Theta and lower-alpha bands PSD-EEG were found to have high diagnostic accuracy.

Our findings showed that slowing of EEG waves in the frontal lobe was correlated with striatal dopaminergic deficiency and executive dysfunction in mild PD patients, and appeared to be a promising biomarker of PD-related executive dysfunction.

Key Words: Parkinson's disease, executive dysfunction, EEG, [^{18}F]FDOPA PET/CT, cognitive impairment

Introduction

Previous studies showed that slowing of electroencephalographic (EEG) and magnetoencephalographic (MEG) waves assessed by power spectral density (PSD) may be related to cognitive decline in Parkinson's disease (PD) patients.[1–3] Multimodal studies evaluating associations between PD-specific neuroimaging and neurophysiological biomarkers in revealing executive dysfunction mechanisms in PD are scarce, and especially in studying the association of resting state brain waves (PSD-EEG) with the dopaminergic function imaging methods. Currently, a gold standard diagnostic tool in PD is positron emission computed tomography (PET/CT), particularly using the PD-specific radiotracer, e.g., the [^{18}F]Fluorodopa ([^{18}F]FDOPA) uptake ratio in the striatum, which reflects dopaminergic deficiency in idiopathic PD patients.[4–7] Multimodal studies with usage of the PET/CT, EEG and behavioral testing may have scientific relevance in an understanding of neural mechanisms in PD-related executive dysfunction, but also they may be of great practical importance for PD diagnosis.

Hence, our study aimed to (i) compare the values of resting state PSD-EEG, striatal [^{18}F]FDOPA PET/CT uptake and neuropsychological cognitive testing parameters between mild PD patients and healthy controls, as well as (ii) to evaluate associations between these outcomes. Additional aim was to estimate PD diagnostic accuracy (with receiver operating characteristic [ROC] curves) of the PSD-EEG parameters in reference to the gold diagnostic standard of the striatal [^{18}F]FDOPA PET/CT uptake ratio.

According to the "dual hypothesis",[8] assuming the dopaminergic-mediated striatofrontal executive dysfunction in early-stage PD, we hypothesized that values of (i) the PSD-EEG, striatal [^{18}F]FDOPA PET/CT uptake ratio and neuropsychological parameters would differ between mild PD patients and healthy controls and (ii) that the PD-specific neuroimaging findings (increased PSD-EEG alpha- and theta- waves and decreased striatal [^{18}F]FDOPA PET/CT uptake ratio) would be correlated to each other and with neuropsychological outcomes reflecting executive dysfunction.

Materials and methods

Participants

Eleven PD patients (PD; women n = 5, men n = 6; mean age 65.4 ± 4.5 years, body mass 72.2 ± 12.4 kg, height 168.7 ± 8.9 cm) assessed with the Hoehn and Yahr scale (H&Y)[9] to be mildly affected, and 11 healthy age-matched controls (HCO; women n = 6, men n = 5; mean age 63.4 ± 4.6 years, body mass 74.1 ±18.9 kg, height 166.4 ± 8.9 cm) participated in our study (Table 1). All PD and HCO subjects were non-demented (confirmed by a neuropsychologist), right-handed, and the PD patients had an affected dominant side (Table 1). All subjects wrote informed consent prior participation in this study which was approved by the local ethical review board. All study participants underwent EEG recording, PET/CT neuroimaging and neuropsychological cognitive assessment, and PD patients underwent additional clinical neurological evaluation. All PD patients' testing procedures were conducted during their "off-medication" phase, i.e. after an overnight 12-hours withdrawal of anti-parkinsonian drugs (24 hours for extended release medications).

EEG recording and data analysis

EEG data were recorded in an eyes-open resting condition with the BioSemi system (Biosemi Inc., Amsterdam, the Netherlands), using 128 Ag/AgCl electrodes set and analyzed with MATLAB software (version

R2019) running EEGLAB[10] functions and proprietary scripts. Raw data were bandpass filtred (0.5-50 Hz) and manually examined for artifacts. Contaminated segments and bad channels were removed from the analysis and then interpolated. In the next step, EEG data underwent an Independent Component Analysis (ICA) to exclude remaining artifacts. The PSD-EEG was calculated using the MATLAB pwelch function, with a Hamming window of 512 samples and 50% overlap in six frequency bands: delta (1-4 Hz), theta (4-8 Hz), lower alpha (8-10 Hz), upper alpha (10-13 Hz), beta (13-30 Hz) and gamma (30-40 Hz)[3]. Individual maximal peaks in the theta-alpha band were detected using the "findpeaks" function in the 4-13 Hz frequency range. For all channels and frequency bands, we constructed topographic maps of significant inter-group differences. These statistical maps revealed clusters of significant electrodes over midline frontal and left frontal lobe. Based on the polar coordination system, and according to literature data,[11–13] we matched the electrodes to three Regions of Interest (ROIs): the supplementary motor area (SMA - C14, C18, C19, C20, C27), the prefrontal motor cortex (PFC - D04, D05, D06, C31, C32), and the primary motor cortex (M1 - D10, D11, D12, D19, D20). Finally, from each crucial region, we selected one representative electrode, i.e. an electrode with the most significant inter-group difference: C21 (SMA), D05 (PFC) and D10 (M1) (Figure 1A) for further analysis.

PET imaging and data analysis

A standard protocol was used for all [^{18}F]FDOPA PET/CT scans. All patients were instructed to adhere to a low protein diet for 24 hours, fast at least 4 hours before tracer injection, and withhold anti-parkinsonian medications (L-dopa and dopamine agonists) that could interfere with [^{18}F]FDOPA uptake. Patients were premedicated orally with 150 mg of carbidopa 1 hour prior to injection with 250 MBq [^{18}F]FDOPA, and imaging started 110 minutes post-injection. [^{18}F]FDOPA scanning was performed using a Biograph 64 PET/CT scanner (Siemens Medical Solutions, Malvern, PA, USA, Inc.) operating with the Somaris/5 SyngoCT 2006 software, having a 3-dimensional acquisition mode. PET images were fused to magnetic resonance T1-weighted images (MRI scanner model: 3T Siemens Trio scanner; Siemens, Munich Germany), that were performed before PET/CT scans. Semi-quantitative striatal dopaminergic function analysis was performed using the VE30 software (Siemens Medical Solutions, Malvern, PA, USA, Inc.). Interpretation was based on analysis of [^{18}F]FDOPA uptake ratios for the putamen and caudate nucleus versus the occipital cortex as a reference.

Clinical and neuropsychological assessment

The H&Y scale, the Unified Parkinson's Disease Rating Scale (UPDRS)[9] and Schwab & England scale (S&E)[14] were used to evaluate the severity of PD. Cognitive assessments were performed using the Trail Making Test, parts A and B (TMT-A, TMT-B),[15,16] and Stroop test, parts I and II (ST-I, ST-II)[17,18] in the PD and HCO groups.

Statistical Analysis

Student's t-test was used to examine the statistical significance of inter-group (PD vs HCO) differences for values of the PSD-EEG, striatal [18F]FDOPA PET/CT uptake ratios and cognitive tests parameters. When comparing PSD-EEG parameters the inter-group comparisons' p-values were adjusted according to the Bonferroni correction to avoid the type I error derived from multiple comparisons. Pearson's correlation coefficient (r) or Spearman's correlation coefficient (ρ - rho) was calculated to evaluate the associations of the PSD-EEG parameters revealing statistically significant inter-group differences with the striatal [18F]FDOPA PET/CT uptake ratios and neuropsychological parameters. Additionally, to assess the diagnostic accuracy (sensitivity and specificity) of the PSD-EEG and striatal [18F]FDOPA PET/CT uptake ratio parameters, the ROC curves were estimated and the area under the curve (AUC) values were calculated. All statistical analyses were performed with Statistica version 13.1 software, and the significance level was set at $\alpha = 0.05$.

Results

Inter-group comparisons for anthropometric, PSD-EEG, PET/CT and neuropsychological parameters

There was no significant difference between the PD and HCO group in age 65.4 ± 4.5 vs. 63.4 ± 4.6 years ($p = 0.337$, $t = 0.983$), body mass 72.2 ± 12.4 vs. 74.1 ± 18.9 kg ($p = 0.792$, t = -0.267) and height 168.7 ± 8.9 vs. 166.4 ± 8.9 cm ($p = 0.558$,$t = 0.595$) (Table 1), respectively.

Compared with the HCO group, the PD group exhibited: (i) significantly higher PSD-EEG theta and lower-alpha band and maximal peaks values for: C21 (SMA), D05 (PFC), and D10 (M1) ($p < 0.05$) (Figure 1A and Figure 1B); and (ii) significantly lower values of [^{18}F]FDOPA PET/CT uptake ratio in the putamen ($p < 0.001$, t = -10.14; Figure 2A), and caudate nucleus ($p < 0.001$, t = -6.16; Figure 2B).

Inter-group comparison of cognitive tests parameters in PD vs. HCO showed (i) significantly worse executive function reflected in longer performance times of TMT-A ($p = 0.012$, $t = 2.75$; Figure 2C) and TMT-B ($p = 0.004$, $t = 3.22$; Figure 2D), and (ii) a lack of significant inter-group differences for the ST-I ($p = 0.864$, $t = 0.173$; Figure 2E) and ST-II ($p = 0.074$,$t = 1.89$; Figure 2F), although there was a clear tendency of longer (19% inter-group difference) ST-II performance time in PD group (Figure 2F).

Correlations among the PSD-EEG, striatal [^{18}F]FDOPA PET/CT uptake ratio and neuropsychological parameters

Almost all of the PSD-EEG parameters significantly negatively correlated with the [^{18}F]FDOPA PET/CT uptake ratio in the putamen ($p < 0.05$; Table 2), excluding only the PSD-EEG theta band of the C21 (SMA) and D10 (M1) ($p > 0.05$; Table 2). The significant negative correlations between PSD-EEG and [^{18}F]FDOPA PET/CT uptake ratio in the caudate nucleus were found for the PSD-EEG of the: (i) lower-alpha band of the C21 (SMA) and D05 (PFC), (ii) maximal peak of the C21 (SMA) and D10 (M1), as well as for (iii) theta band of the D05 (PFC) ($p< 0.05$; Table 2).

Almost all the PDS-EEG parameters positively significantly correlated with the TMT-A and TMT-B ($p < 0.05$; Table 2), excluding only correlations of the lower-alpha band and maximal peak of the D10 (M1) with TMT-A ($p > 0.05$; Table 2). Furthermore, the PSD-EEG theta band of the C21 (SMA) and D05 (PFC) was positively significantly correlated with the ST-II ($p < 0.05$; Table 2).

Moreover, the [^{18}F]FDOPA PET/CT uptake ratio in the putamen and caudate nucleus negatively significantly correlated with the TMT-B, as well as the caudate nuclei [^{18}F]FDOPA PET/CT uptake ratio negatively significantly correlated with the TMT-A ($p < 0.05$; Table 2).

Diagnostic accuracy analysis for the PSD-EEG and striatal [18F]FDOPA PET/CT uptake parameters

ROC-AUC values indicated an excellent diagnostic model of PD based on the results of the [^{18}F]FDOPA PET/CT uptake ratio in the putamen, caudate nucleus, and PSD-EEG theta band for the D05 (PFC) (AUC values: 1.000, 0.979, 0.950; respectively) (Figure 1C). Good diagnostic model was confirmed based on PSD-EEG lower-alpha band for the D05 (PFC) and maximal peak of the following: D05 (PFC), C21 (SMA) and D10 (M1) (AUC values: 0.909, 0.946, 0.835, 851; respectively) (Figure 1C).

Fair diagnostic accuracy was found for the PSD-EEG lower-alpha band of the C21 (SMA) and D10 (M1) (AUC values: 0.810, 0.810; respectively). However, poor accuracy of the model was achieved based on the PSD-EEG theta band for the: C21 (SMA) and D10 (M1) (AUC values: 0.674, 0.678; respectively) (Figure 1C).

Discussion

Our findings of the EEG waves slowing in frontal lobe areas and the association of this phenomenon with the executive function decline in PD patients (revealed with neuropsychological assessment using TMT-A and TMT-B) is in line with the previous literature data describing the mechanisms of PD-specific frontal dysfunction.[1,7,8]Furthermore, lower values of putamen and caudate nuclei [^{18}F]Fluorodopa PET/CT uptake ratios in our PD patients are consistent with the current state of knowledge and describe PD-related dopaminergic deficits.[4–8,19,20] Thus, taking into account the concept of the "dual hypothesis",[8] which assumes the dopaminergic-mediated striatofrontal executive dysfunction in early-stage PD (and cholinergic-based cognitive impairment, especially in later demented PD patients), we hypothesized a significant correlation of the frontal lobe EEG waves slowing with the dopaminergic deficiency and the executive dysfunction measures in mild non-demented PD patients tested in the present study. Indeed, our results confirmed almost completely this hypothesis as for the negative correlation between the PSD-EEG and striatal [^{18}F]Fluorodopa PET/CT uptake ratios. However, with regard to consideration on the associations of the EEG waves slowing in frontal lobe and striatal dopaminergic deficiency with neuropsychological outcomes describing the executive dysfunction (i.e. TMT and and ST), one should point out that in majority of our results these associations were confirmed only with the Trail Making Test but not with the Stroop Test. The TMT consists of two parts (TMT-A and TMT-B). In TMT-A part a subject connects (by drawing a line) numbers in sequential order, but in the TMT-B the subject alternates between numbers and letters (1, A, 2, B, etc.). The former is used to examine cognitive processing speed, while the latter assesses executive function.[15,16] The ST also consists of two parts: ST-I, in which a subject reads a list of 40 words, which are names of colors printed in the color itself; and ST-II, where color names are printed in an incongruent color and the subject is required to ignore the word and correctly name the ink color. The former is used as a measure of processing speed and the latter to test selective attention and inhibition.[17,18] Thus, both of these tests (TMT and ST) evaluate an executive function, but the TMT is more related to motor skills (due to line's hand drawing task), and therefore a disordered performance of this test in PD patients might be partly related to pathological neural networks causing bradykinesia. According to the triadic subdivision of the parallel striatal projections in the dopaminergic system (mesostriatal, mesocortical and mesolimbic pathways) the mesostriatal component is responsible for the bradykinesia in the hypodopaminergic conditions [21] as in our PD patients. At the same time, it is important to note that the mesocortical system is responsible for executive function.[21] It is necessary take into account that the mesostriatal dopaminergic circuit is most prominently affected, also on the early stage of PD, whereas the mesocortical and mesolimbic dopaminergic circuits are relatively preserved in the early stage of the disease.[22,23]Therefore in our mild PD patients (being on early stage of disease) the mesostriatal component of the triadic striatal projections in the dopaminergic system might be more affected by stated in our study dopaminergic deficiency. In consequence, this may be a reason of stated by us significant correlations of the PD-specific slowing of brain waves and dopaminergic deficiency with the Trail Making Test, with simultaneous lack of significant correlations with the Stroop Test.

Our diagnostic accuracy analyses showed that some of the PSD-EEG parameters might be potentially a good alternative for expensive PET/CT diagnostics in PD. Particularly, the PSD-EEG theta-alpha maximal peak and lower-alpha band for the SMA and PFC regions seemed to be promising PD-related executive dysfunction biomarkers, since they presented high diagnostic sensitivity and specificity, significantly differentiated mild PD patients from healthy controls, as well as they were correlated with dopaminergic deficiency and executive dysfunction parameters.

Limitations of the study and future directions

An important limitation of this study is the relatively small sample size. Nevertheless, an appropriate statistical analysis applied by us (for inter-group comparisons and for correlations calculations) was able to reveal an effect of dopaminergic system pathophysiology in PD PET/CT neuroimaging, PSD-EEG and neuropsychological parameters outcomes even in this relatively small sample size. However, due to this relatively small sample size, the results of this study cannot be generalized for the whole PD patients population. Another important limitation of our study is the choice of only two neuropsychological cognitive tests (TMT and ST).

This choice narrowed down a range of our considerations on associations of the PD-specific EEG brain waves slowing and dopaminergic deficiency with disordered executive functions in tested by us PD patients. Hence, further studies are needed using multimodal scientific approach, with an application of electroencephalography (using EEG recordings with resting and cognitive paradigms), PET/CT neuroimaging methods (using dopaminergic and other PD-specific radiotracers) and broad PD-specific battery of cognitive tests.

Conclusion

Our findings showed that slowing of EEG waves in the frontal lobe was correlated with striatal dopaminergic deficiency and executive dysfunction in mild PD patients, and appears to be a promising biomarker of PD-related executive dysfunction.

Acknowledgements

We thank the patients with Parkinson's disease and healthy individuals for participation in our study. Also, we would like to thank M.Sc. Eng. Łukasz Szumowski for his technical assistance and the following PhD and Master's Students (stipendists in this grant) who helped by the data collection: Bartosz Kamiński, Aleksandra Pawłowska, Katarzyna Śpik, Marcin Zawisza and Katarzyna Moczulska.

Data Sharing

The data that support the findings of this study are available from the corresponding author upon reasonable request.

REFERENCES

1. Kamei S, Morita A, Serizawa K, Mizutani T, Hirayanagi K. Quantitative EEG analysis of executive dysfunction in Parkinson disease. J Clin Neurophysiol Off Publ Am Electroencephalogr Soc 2010; 27(3): 193–7.

2. Caviness JN, Hentz JG, Evidente VG, et al. Both early and late cognitive dysfunction affects the electroencephalogram in Parkinson's disease. Parkinsonism Relat Disord 2007; 13(6): 348–54.

3. Stoffers D, Bosboom JLW, Deijen JB, Wolters EC, Berendse HW, Stam CJ. Slowing of oscillatory brain activity is a stable characteristic of Parkinson's disease without dementia. Brain 2007; 130(7): 1847–60.

4. Darcourt J, Schiazza A, Sapin N, et al. 18F-FDOPA PET for the diagnosis of parkinsonian syndromes. Q J Nucl Med Mol Imaging Off Publ Ital Assoc Nucl Med [and] Int Assoc Radiopharmacol (IAR), [and] Sect Soc of. 2014; 58(4): 355–65.

5. Ibrahim N, Kusmirek J, Struck AF, et al. The sensitivity and specificity of F-DOPA PET in a movement disorder clinic. Am J Nucl Med Mol Imaging 2016; 6(1): 102–9.

6. Morrish PK, Sawle G V, Brooks DJ. Clinical and [18F] dopa PET findings in early Parkinson's disease. J Neurol Neurosurg Psychiatry 199; 59(6): 597–600.

7. Strafella AP, Bohnen NI, Perlmutter JS, et. al. Molecular imaging to track Parkinson's disease and atypical parkinsonisms: New imaging frontiers. Mov Disord. 2017 Feb; 32(2): 181–192.

8. Kehagia AA, Barker RA, Robbins TW. Cognitive Impairment in Parkinson's Disease: The Dual Syndrome Hypothesis. Neurodegener Dis 2013; 11(2): 79–92.

9. Martinez-Martin P, Rodriguez-Blazquez C, Alvarez-Sanchez M, et al. Expanded and independent validation of the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS). J Neurol. 2013; 260(1): 228–36.

10. Delorme A, Mullen T, Kothe C, et al. EEGLAB, SIFT, NFT, BCILAB, and ERICA: New tools for advanced EEG processing. Comput Intell Neurosci. 2011.

11. Koessler L, Maillard L, Benhadid A, et al. Automated cortical projection of EEG sensors: Anatomical correlation via the international 10–10 system. Neuroimage 2009; 46(1): 64–72.

12. Siemionow V, Yue GH, Ranganathan VK, Liu JZ, Sahgal V. Relationship between motor activity-related cortical potential and voluntary muscle activation. Exp brain Res. 2000; 133(3): 303–11.

13. Yao WX, Ranganathan VK, Allexandre D, Siemionow V, Yue GH. Kinesthetic imagery training of forceful muscle contractions increases brain signal and muscle strength. Front Hum Neurosci. 2013; 7(SEP): 1–6.

14. Siderowf A. Schwab and England Activities of Daily Living Scale. In: Kompoliti K, Metman LVBT-E of MD, editors. Oxford: Academic Press, 2010, pp 99–100.

15. Arbuthnott K, Frank J. Trail making test, part B as a measure of executive control: validation using a set-switching paradigm. J Clin Exp Neuropsychol. 2000; 22(4): 518–28.

16. Sánchez-Cubillo I, Periáñez JA, Adrover-Roig D, et al. Construct validity of the Trail Making Test: role of task-switching, working memory, inhibition/interference control, and visuomotor abilities. J Int Neuropsychol Soc. 2009; 15(3): 438–50.

17. Zalonis I, Christidi F, Bonakis A, et al. The stroop effect in Greek healthy population: normative data for the Stroop Neuropsychological Screening Test. Arch Clin Neuropsychol Off J Natl Acad Neuropsychol. 2009; 24(1): 81–8.

18. Egner T, Hirsch J. The neural correlates and functional integration of cognitive control in a Stroop task. Neuroimage. 2005; 24(2): 539–47.

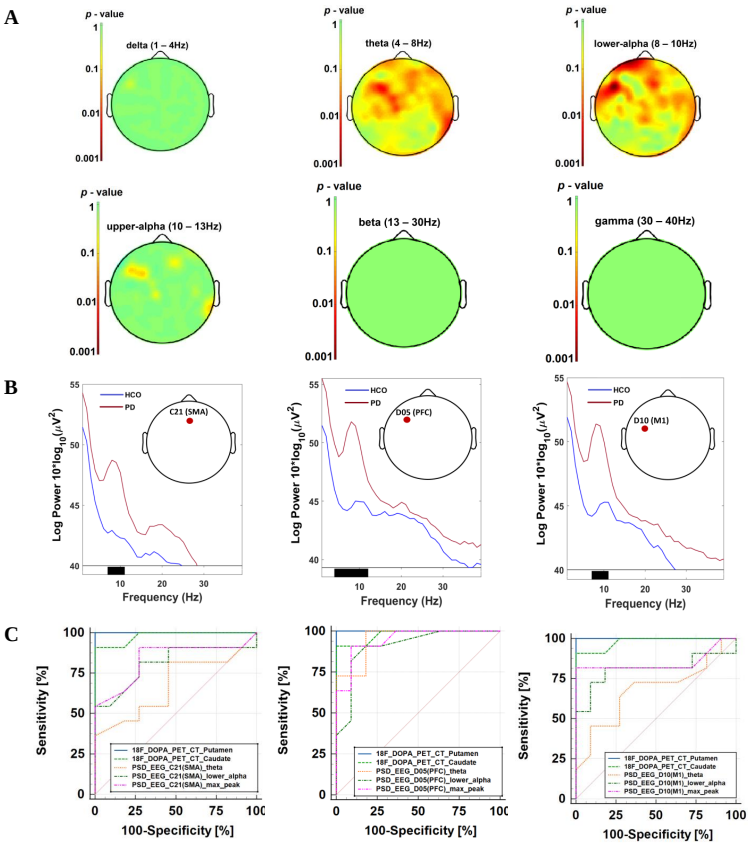
19. Rinne OJ, Nurmi E, Ruottinen HM, Bergman J, Eskola O, Solin O. [(18)F]FDOPA and [(18)F]CFT are both sensitive PET markers to detect presynaptic dopaminergic hypofunction in early Parkinson's disease. Synapse. 2001; 40(3): 193–200.

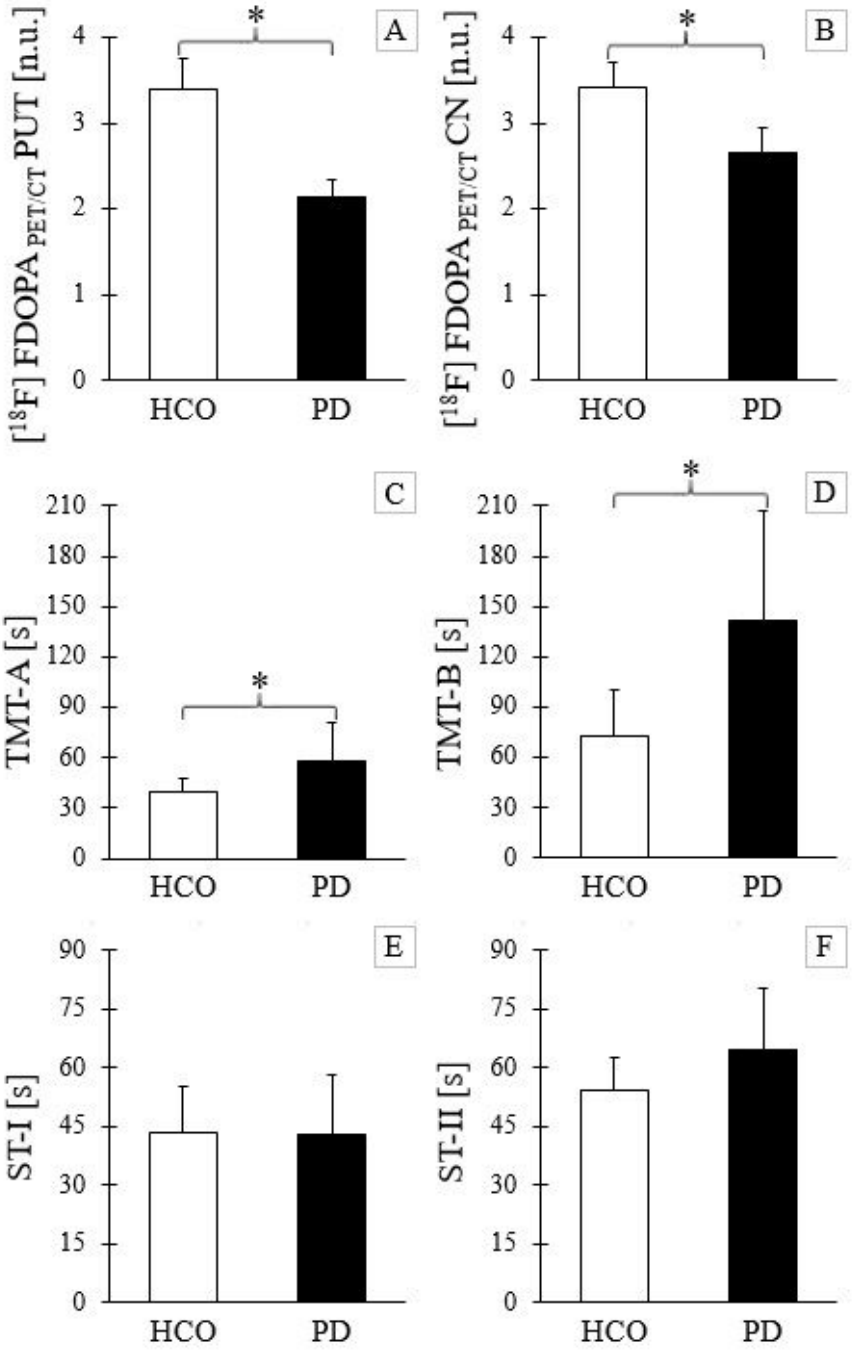
20. Stormezand GN, Chaves LT, Vállez García D, et al. Intrastriatal gradient analyses of 18F-FDOPA PET scans for differentiation of Parkinsonian disorders. NeuroImage Clin. 2020; 25: 102161.

21. Hirano S. Clinical implications for dopaminergic and functional neuroimage research in cognitive symptoms of Parkinson's disease. Mol Med. 2021 Apr 15;27(1):40. doi: 10.1186/s10020-021-00301-7. PMID: 33858320; PMCID: PMC8048076.

22. Ma Y, Dhawan V, Mentis M, Chaly T, Spetsieris PG, Eidelberg D. Parametric mapping of [18F]FPCIT binding in early stage Parkinson's disease: a PET study. Synapse. 2002 Aug;45(2):125-33. doi: 10.1002/syn.10090. PMID: 12112405.

23. Rinne JO, Portin R, Ruottinen H, Nurmi E, Bergman J, Haaparanta M, Solin O. Cognitive impairment and the brain dopaminergic system in Parkinson disease: [18F]fluorodopa positron emission tomographic study. Arch Neurol. 2000 Apr;57(4):470-5. doi 10.1001/archneur.57.4.470. PMID: 10768619.





Hosted file

4) Table_1.docx available at https://authorea.com/users/614786/articles/641495-slowing-of-eeg-waves-correlates-with-striatal-18f-fluorodopa-pet-ct-uptake-and-executive-dysfunction-in-parkinson-s-disease

Hosted file

5) Table_2.docx available at https://authorea.com/users/614786/articles/641495-slowing-

of-eeg-waves-correlates-with-striatal-18f-fluorodopa-pet-ct-uptake-and-executive-dysfunction-in-parkinson-s-disease