Acta Scientific MEDICAL SCIENCES (ISSN: 2582-0931)

Volume 9 Issue 5 May 2025

Research Article

Analysis of Structural Connectome in Patients with Parkinson's Disease and Mild Cognitive Impairment

Popovska H[1]*, Boshkovski T[2], Petrov I[1] and Popevski – Dimovski R[3]

[1]University "Ss. Cyril and Methodius", Medical Faculty, Skopje, Macedonia

[2]Brainster Next College, Skopje, Macedonia

[3]University "Ss. Cyril and Methodius", Faculty of Natural Sciences and Mathematics, Skopje, Macedonia

***Corresponding Author:** Popovska H, University "Ss. Cyril and Methodius", Medical Faculty, Skopje, Macedonia.

Received: March 27, 2025

Published: April 04, 2025

Abstract

Objective: This study aims to investigate the alterations in structural and functional connectivity within the brains of patients with Parkinson's Disease (PD), particularly focusing on the differences between patients with and without mild cognitive impairment (MCI).

Methods: Using graph theory, we analyzed MRI data to assess network efficiency and clustering coefficients in a cohort of healthy controls (HC), PD patients with MCI (PD-MCI), and PD patients without MCI (PD-non-MCI). Statistical significance of differences in network properties was determined using Mann-Whitney U tests.

Results: Significant reductions in network efficiency and clustering coefficients were observed in PD-MCI compared to HC, particularly in regions such as the Thalamus, Caudate, and Right superiorfrontal. These alterations indicate substantial disruptions in the local and global network connectivity. PD patients without MCI also showed significant changes but were less pronounced than in PD-MCI, suggesting a gradient of connectivity loss correlating with cognitive decline. Comparisons between PD-MCI and PD-non-MCI highlighted specific regions like the Right entorhinal and Left parahippocampal, further associating structural network changes with cognitive impairment progression within PD.

Conclusion: The findings underscore the utility of graph theory metrics in elucidating the extent and pattern of neural disruption in Parkinson's Disease. They also suggest potential biomarkers for early detection and progression of cognitive impairment in PD, offering insights for targeted therapeutic interventions aimed at preserving neural function and mitigating disease progression.

Keywords: Parkinson's Disease; Cognitive Impairment; Graph Theory; MRI; Network Efficiency; Clustering Coefficient

Introduction

Parkinson's Disease (PD) is a progressive neurodegenerative disorder that predominantly affects motor function, but also frequently entails significant non-motor symptoms, including cognitive impairments. Mild Cognitive Impairment (MCI) in Parkinson's patients presents a critical intermediary stage that may eventually progress to Parkinson's Disease Dementia (PDD). Understanding the neural substrates of cognitive decline in PD is paramount for early diagnosis and effective intervention [1].

Recent advances in neuroimaging have enabled a more precise exploration of the brain's structural connectivity, providing insights into the complex neural networks impacted by various pathologies. The concept of the connectome, which maps the comprehensive network of neural connections in the brain, has emerged as a powerful tool to understand the structural underpinnings of neurological disorders. In PD patients exhibiting MCI, changes in the structural connectome may elucidate the mechanisms driving cognitive decline and differentiate them from typical aging processes [2].

This article aims to delineate the alterations in the structural connectome observed in Parkinson's patients with mild cognitive impairment. By leveraging advanced imaging techniques and network analysis, we seek to uncover the specific pathways and network disruptions that correlate with cognitive deficits in this population. The findings may offer potential biomarkers for early detection and progression of cognitive impairment in Parkinson's Disease, ultimately contributing to tailored therapeutic strategies that address both motor and cognitive symptoms.

Methods and Material

This is a pilot study that was done after approval of the ethics committee of the Faculty of Medicine, University "Ss. Cyril and Methodius", Skopje. The pilot study included 30 patients divided into three groups. Group (PD-nonMCI) included 10 patients with Parkinson's disease without mild cognitive impairment, group (PD-MCI) * included 10 patients with Parkinson's disease with mild cognitive impairment and control group consisted of 10 healthy individuals. All patients were recruited from the Neurology Clinic in Skopje, while the healthy individuals volunteered to participate in the study. All subjects have signed an informed consent to participate. To be included in the PD groups, patients had to had occurrence of Parkinson's disease starting after the age of 50, stage 1 and 2 of the disease according to the scale of Hoehn and Yahr [3], antiparkinsonian treatment** [4] started at least 4 weeks before entering the study. Patients with Parkinson's disease with diagnosed dementia, psychiatric diseases, medicines that potentially interfere with cognition, including psychotropic substances and anticholinergic drugs, and patients with serious cardiovascular or cerebrovascular diseases were excluded from the study.

- **Study protocol:** All study's subjects underwent standardized study protocol (neuropsychological assessment and Magnetic Resonance Imaging MRI).
- **Neuropsychological assessment:** The same psychological tests were administered to all subjects with Parkinson's disease. The neuropsychological tests were grouped according to cognitive function as follows: 1. Episodic memory - Rey auditory test for remembering 15 words, with immediate recall and with delayed recall; [5] 2. Execution - Frontal Assessment Battery (FAB), 6v Stroop-color-word test; [7] 3. Attention-matrices for attention [8] and 4. Visuo-spatial domain redrawing of the Rey–Osterrieth complex figure, [9] the clock test [10]. All participants were assessed with the Mini Mental State Examination (MMSE) [11].
- **MRI protocol:** All participants were scanned with a 3T SIEMENS Prisma Scanner, using the following multimodal protocol: 1. DTI sequence (TR = 12.5 ms, TE = 89 ms, voxel size = 2x2x2 mm^3, gradient direction = 30, maximum b value = 1000 s/mm^2), 2. MPRAGE sequence (TR = 2200 ms, TE = 2.26 ms, flip angle = 8 degrees, TI = 950 ms, FOV = 256x256 mm, voxel size = 1x1x1 mm^3).

Once the images for all subjects were acquired, a quality check was performed by a trained neuroscientist, and only the images that have passed the QC were analyzed. After the QC, the images were preprocessed. The T1w image was processed with free surfer (ref) to parcellate the brain into 68 cortical and 14 subcortical cerebral gray matter regions using the Desikan-Killiany Atlas [12]. e individual brain network was defined with 68 cortical and 14 subcortical brain regions as nodes and 3,362 unique interconnection links. To obtain characterization of connectome

differences between groups, we looked at the topological organization of the brain network [13,14].

- * Patients were evaluated according to diagnostic criteria for PD (MDS-PD), as well as with neuropsychological assessment for their cognitive status, using multiple neuropsychological tests for different domains of cognition.
- ** For antiparkinsonian treatment was considered antiparkinsonian drugs, various combinations of levodopa, dopamine agonists, catechol-O-methyl transferase inhibitors, monoamine oxidase inhibitors, amantadine. Levodopa equivalent daily dose (LEDD) was estimated in a way suggested by Tomlison., *et al*. [4].

Analysis of structural MRI data

Before starting the analysis of MRI data, it is necessary to preprocess it to remove noise, motion artifacts, and artifacts from magnetic field inhomogeneity, which affect the MRI data. The preprocessing of anatomical/structural T1 images was performed using the software tool FreeSurfer (version 6.0; http://surfer.nmr.mgh.harvard.edu/). The entire process is automated and reduces the level of error in further analyses [15-17].

DWI images were preprocessed using MRtrix (version 3.0; https://www.mrtrix.org/) and FSL (version 5.08; http://www.fmrib.ox.ac.uk/fsl/). Probabilistic diffusion tractography was obtained using MRtrix, aimed at performing voxel-based analysis of diffusion MRI data.

Construction of the structural network - An individual brain network was obtained for each subject included in the study. Using the tool Free Surfer (version 6.0), segmentation and parcellation of the cerebral cortex into 68 cortical and 14 subcortical regions of interest (ROIs), (appendix 1), were performed using the Desikan-Killiany Atlas [12]. A weight measure was given for each connection in the connectome. The weight measure was calculated as the average FA and MD value of the tract between each pair of regions. Then, for each group, a group connectome was reconstructed by taking the average of the weight metrics on the connections present in at least 50% of the subjects [18]. Subsequently, a PLS (Partial Least Square) statistical analysis was conducted to determine the group of connections in the connectomes that maximally covary between different groups (i.e., differentiating between groups) [19].

Analysis of structural connectome

The analysis and modeling of each group structural connectome was performed according to the principles of graph theory. Accordingly, the properties of the global topological network were obtained for each group using the Brain Connectivity Toolbox (https://sites.google.com/site/bctnet/) from MATLAB. The following network measures/parameters were examined: clustering coefficient, network efficiency, and node strength. The Mann-Whitney U test was used to compare these parameters between groups. Results were corrected for False Discovery Rate (FDR).

Results

Demographic and neurocognitive characteristic

The subjects were evaluated using the MDS-UPDRS. Also, the subjects were assessed for their cognitive abilities using the already named neuropsychological tests. By using the Kruskal-Wallis nonparametric test, we compared the demographic and the clinical scores (Table 1). With a $\chi 2$ test, the gender was compared.

In all three groups, there was no significant difference in demographic characteristics ($p > 0.05$). However, there was observed a significant difference between the groups for the MMSE, the tests of episodic memory, executive function and visuospatial abilities, whereas the group with PD and with mild cognitive decline had significant lower scores (Table 1).

	Control group (n=10)	PD-nonMCI (n=10)	PD-MCI (n=10)	p-value
Age	63.3 (10.3)	63.6 (9.5)	66.5 (11.1)	0.404
Gender (female)	7	9	9	0.796
Hand dominance (right)	10	10	10	0.495
MDS-UPDRS	-	14.6 (7.2)	16.8 (11.0)	0.358
LEDD	-	5.9 (4.0)	10.1 (7.2)	0.013
MMSE	29.7 (0.5)	29.4 (0.7)	28.6 (1.5)	0.001
Episode memory	-0.01 (0.56)	-0.06 (1.04)	-0.91 (0.86)	<0.001
Executive function	0.04 (0.64)	-0.02 (0.65)	-1.69 (1.80)	<0.001
Attention	0.06 (0.75)	0.13 (0.68)	0.31 (0.75)	0.366
Visuospatial score	-0.02 (0.8)	-0.23 (0.62)	-1.53 (1.05)	<0.001

Table 1: Demographic and cognitive outcomes.

Results of analysis of structural connectome

For the analysis of the structural connectome, three properties of the brain network according to graph theory were used: clustering coefficient, network efficiency, and node strength. Comparative analyses between the groups were conducted using the Mann-Whitney U rank test. The analysis of the structural connectome was based on Fractional Anisotropy (FA) and Mean Diffusivity (MD). (p-values significant for $p < 0,05$).

Analysis of significant regions of interest in structural network graph measures:

Clustering coefficient

These results focus on the clustering coefficient, a graph theory metric that indicates the degree to which nodes in a network tend to cluster together. This metric provides insight into the local connectivity and the resilience of networks.

HC vs PD- MCI

- Left precuneus (p = 0.00700901953)
- Left-Thalamus (p = 9.55953723e-06)
- Left-Caudate (p = 1.2395223e-10)
- Left-Amygdala (p = 0.000655636001)
- Right supramarginal (p = 2.66033264e-20)
- Right superiorfrontal (p = 7.08748328e-12)
- Right superiorparietal (p = 1.02764398e-06)
- Right superiortemporal (p = 2.97689042e-05)
- Right frontal pole (p = 0. 000000..)
- Right temporal pole (p = 0.000001028)
- Right transverse temporal (p = 0.000029769)

The results show statistically significant differences in clustering coefficient between Healthy Controls (HC) and Parkinson's Disease patients with Mild Cognitive Impairment (PD-MCI), particularly highlighting:

- Strongly significant decreases in clustering coefficient in several critical brain regions in PD-MCI patients compared to HC, notably in the Left-Caudate, Right superiorfrontal, and Right supramarginal, with extremely low p-values indicating robust differences.

- Regions like the Left-Thalamus and Left-Amygdala also showed significant alterations. These areas are involved in various cognitive and emotional processes, suggesting that the local connectivity in these regions is notably impaired in PD-MCI.

HC vs PD non-MCI

- Left parahippocampal (p = 0.01098218)
- Left frontalpole (p = 0.03857801)
- Right bankssts (p = 0.04935815)
- Right entorhinal (p = 0.04817717)
- Right lateralorbitofrontal (p = 0.00173997)

This comparison shows fewer regions with significant differences, suggesting that the clustering coefficient may be less altered in PD patients without cognitive impairments when compared to HC:

- Mild significance in alterations was found in areas like the Right lateralorbitofrontal and Left parahippocampal. These changes suggest subtle yet measurable differences in how these regions' networks are organized in PD-non-MCI compared to healthy individuals.

PD- MCI vs PD- non-MCI

- Left parahippocampal (p = 0.00109275)
- Right entorhinal (p = 0.02417259)
- Right lateralorbitofrontal (p = 0.00741976)

This set of comparisons directly addresses how mild cognitive impairment in PD affects local network connectivity, as measured by the clustering coefficient:

- Significant differences were noted particularly in the Right lateralorbitofrontal and Left parahippocampal regions. These areas are key in cognitive functions such as decision-making and memory, respectively. The results suggest more pronounced disruption in local connectivity in PD-MCI compared to PD-non-MCI.

General observations

- Highly significant results (e.g., Right supramarginal and Right superiorfrontal in the HC vs PD-MCI comparison) indicate strong evidence of network disruption in PD-MCI, particularly in areas critical for cognitive and sensory integration.

- The clustering coefficient's significance in these analyses underscores the potential impact of PD and MCI on the brain's local network structure, indicating a decline in the efficiency of localized brain functions.

- **Statistical Significance:** Regions with very low p-values suggest highly significant differences and robust findings in terms of the effect of PD and cognitive impairment on local network structures.

Network efficiency

The results presented focus on network efficiency, a key graph-theoretical metric that measures the efficiency of information transfer in the network.

HC vs PD- MCI

- Left isthmuscingulate (p = 0.0111918063)
- Left-Thalamus (p = 0.000453629604)
- Left-Caudate (p = 0.00112222406)
- Right caudalmiddlefrontal (p = 0.000736419769)
- Right supramarginal (p = 9.04144232e-11)
- Right superiorfrontal (p = 1.47339763e-05)

This comparison highlights significant reductions in network efficiency between Healthy Controls (HC) and Parkinson's Disease patients with Mild Cognitive Impairment (PD-MCI), particularly:

- Significant decreases in network efficiency were found in key brain regions such as the Left-Thalamus, Left-Caudate, and multiple right hemisphere areas including the Right superiorfrontal and Right supramarginal, with extremely low p-values suggesting robust differences.

- These areas are critical for cognitive processing and motor functions, indicating that PD-MCI significantly impacts the efficient communication within these regions.

HC vs PD non-MCI

- Left isthmuscingulate (p = 0.00882365491)
- Left-Thalamus (p = 8.77053264e-06)
- Left-Caudate (p = 1.53981149e-06)
- Right-Thalamus (p = 0.0209903399)
- Right-Accumbens-area (p = 0.0379682393)
- Right caudalmiddlefrontal (p = 0.00175829969)
- Right lateralorbitofrontal (p = 0.0388428177)
- Right supramarginal (p = 1.48230833e-20)

- Right superiorfrontal (p = 2.06622947e-09)
- Right superiorparietal (p = 7.86717948e-05)
- Right superiortemporal (p = 0.00230709056)

This comparison also shows significant differences, but includes both hemispheres more uniformly, suggesting that PD without overt cognitive impairment still affects network efficiency:

- Notably, significant findings were more widespread, including the Left and Right Thalamus, Left-Caudate, and various frontal and parietal regions. This widespread distribution suggests a broad impact of PD on brain network efficiency, even in the absence of cognitive impairment.
- The consistency of findings in areas like the Thalamus and Caudate across comparisons highlights their vulnerability and importance in the pathology of PD.

PD-MCI vs PD non-MCI

- Right entorhinal (p = 0.03842198)

This comparison specifically addresses differences within the PD spectrum regarding cognitive impairment:

- Less widespread changes, with a notable finding in the Right entorhinal region, which is linked with memory and spatial navigation. The statistical significance (p = 0.03842198) suggests a difference in network efficiency that could be associated with the additional cognitive load or decline in PD-MCI compared to PD-non-MCI.

General observations

- Areas like the Thalamus and Caudate, repeatedly identified across different comparisons, underscore their central role in the neural networks affected by Parkinson's. Their involvement in both motor and cognitive circuits could explain their sensitivity to changes in network efficiency.
- **Statistical significance:** The extremely low p-values in some regions (e.g., Right supramarginal in HC vs PD-MCI and HC vs PD-non-MCI comparisons) provide strong evidence of significant network efficiency reduction. These areas might be critical targets for therapeutic interventions aimed at improving or stabilizing network function.
- Right Hemisphere Prominence in many findings could reflect the lateralization of brain functions and how PD might asymmetrically affect brain networks.

Node strength

HC vs PD- MCI

- Left isthmuscingulate (p = 0.0032500538)
- Left parahippocampal (p = 0.019283092)
- Left precuneus (p = 0.00962300758)
- Left superiorfrontal (p = 0.0389497894)
- Left supramarginal (p = 0.048501059)
- Left-Caudate (p = 8.32667369e-09)
- Left-Pallidum (p = 0.000431789603)
- Left-Amygdala (p = 1.0916502e-05)
- Left-Accumbens-area (p = 0.0139714584)
- Right-Thalamus (p = 1.23138222e-05)
- Right entorhinal (p = 0.0214094648)
- Right inferiorparietal (p = 0.018613159)
- Right paracentral (p = 0.00734343909)
- Right supramarginal (p = 9.04144232e-11)
- Right superiorfrontal (p = 0.00117634209)
- Right superiorparietal (p = 0.0389497894)

This comparison shows significant differences in node strength predominantly in the left hemisphere, but also some in the right. Notably:

- Highly significant decreases in node strength in PD-MCI as compared to HC were observed in the Left-Caudate, Left-Pallidum, Left-Amygdala, and Right-Thalamus (all with $p < 0.001$). These areas are crucial in cognitive and motor functions, suggesting marked network disruptions in PD-MCI patients.
- Other regions such as the Left isthmus cingulate, left precuneus, and Right superior frontal also showed significant differences, indicating potential alterations in connectivity affecting both cognitive and emotional processing.

HC vs PD- non-MCI

- Left isthmuscingulate (p = 0.000246866547)
- Left medialorbitofrontal (p = 0.0430630293)

- Left posteriorcingulate (p = 0.0117281424)
- Left precuneus (p = 0.00714257446)
- Left-Caudate (p = 1.75117799e-14)
- Left-Pallidum (p = 0.00146791876)
- Left-Amygdala (p = 1.93194313e-06)
- Left-Accumbens-area (p = 0.0316382174)
- Right-Thalamus (p = 4.13870308e-07)
- Right caudalmiddlefrontal (p = 0.0101533732)
- Right cuneus (p = 0.0316369657)
- Right entorhinal (p = 0.00637430156)
- Right paracentral (p = 0.00128769427)
- Right supramarginal (p = 2.83521221e-20)
- Right superiorfrontal (p = 5.13616995e-05)
- Right superiorparietal (p = 0.000583970292)
- Right superiortemporal (p = 1.47416651e-05)

This comparison generally follows similar patterns of significant differences but involves a few additional areas:

- Significant findings in the basal ganglia (Left-Caudate, Left-Pallidum, Right-Thalamus) with extremely low p-values suggest profound impacts on these regions even in PD patients without cognitive impairments.
- Differences in areas like the Left medial orbitofrontal and Right cuneus indicate broader disruptions in cortical regions involved in emotional processing and visual information processing, respectively.

PD-MCI vs PD-non-MCI

- Left bankssts (p = 0.01599027)
- Left parahippocampal (p = 0.00140672)
- Left parsorbitalis (p = 0.02111273)
- Left superiorfrontal (p = 0.00765145)
- Left supramarginal (p = 0.03857801)
- Left-Accumbens-area (p = 0.03228352)
- Right bankssts (p = 0.02986811)
- Right entorhinal (p = 0.04817717)
- Right lateralorbitofrontal (p = 0.06704723)
- Right medialorbitofrontal (p = 0.03576295)

This comparison directly assesses the impact of cognitive impairment within Parkinson's disease on network connectivity:

- Significant differences were observed in regions like the Left parahippocampal and Left superior frontal, areas associated with memory and higher cognitive functions.
- The results indicate more localized changes when comparing PD subtypes, suggesting specific network alterations associated with the progression from PD to PD-MCI.

General observations

- Regions with multiple significant findings across comparisons (like the Left-Caudate and Right-Thalamus) highlight their potential role in the neuropathology of Parkinson's disease and its impact on cognitive functions.
- The use of node strength as a measure suggests that not only the number of connections but also the quality and robustness of these connections are affected in Parkinson's disease, especially with cognitive decline.
- **Statistical Significance and Interpretation:** Regions with p-values less than 0.05 are typically considered statistically significant. The results here often show much lower p-values, indicating strong evidence against the null hypothesis of no difference between groups.

Discussion

- **Significance of Reduced Network Efficiency and Clustering Coefficients in PD:** The results show significant reductions in both network efficiency and clustering coefficients, particularly in patients with PD-MCI compared to HC and PD-non-MCI. This highlights the profound impact of cognitive impairment on the neural connectivity in PD. Such findings suggest that the structural and functional deterioration in PD is not just limited to motor symptoms but extends significantly into cognitive domains, disrupting the efficiency of neural networks crucial for cognitive processing and emotional regulation [20].
- **Critical Brain Regions Affected:** The Thalamus and Caudate repeatedly appear as regions with significantly reduced network efficiency and clustering coefficients. The

Thalamus, being a central relay in the brain, and the Caudate, part of the basal ganglia critical for motor and cognitive functions, highlight the neural circuits most vulnerable to the effects of PD. Additionally, right hemisphere regions such as the Right supramarginal and Right superiorfrontal have shown considerable changes, which could be linked to the lateralization of brain functions and the possible asymmetric progression of PD [21].

- **Implications for PD Progression:** Differences in network metrics between PD-MCI and PD-non-MCI patients underline the progressive nature of Parkinson's Disease and how cognitive decline can be mapped with declining network integrity. The progression from PD-non-MCI to PD-MCI involves further declines in connectivity, pointing towards potential biomarkers for early detection and monitoring of cognitive decline in PD [22].
- **Graph Theory as a Tool for Neurological Disorders:** Employing graph theory to examine the connectome provides a robust framework for understanding complex network alterations in neurological disorders. Future research should continue to leverage these methods to unravel the intricate changes in network architecture associated with diseases like PD [23].
- **Therapeutic Intervention:** Understanding which regions and network properties are most affected offers a target for therapeutic interventions aimed at slowing disease progression or mitigating its symptoms. For instance, interventions that enhance network efficiency or stabilize clustering coefficients might prove beneficial in maintaining cognitive function in PD patients [24].
- **Integration with Clinical Practices**: Incorporating findings from graph theoretical analyses into clinical practice could help in developing personalized medicine approaches for PD patients. By identifying individual patterns of network disruption, treatment plans can be more closely tailored to the patient's specific neural connectivity profile [25].

Conclusion

The discussion of these results provides a comprehensive view of the alterations in brain networks due to Parkinson's Disease and its cognitive impairments. By further exploring these connections, researchers and clinicians can better understand the underpinnings of PD and enhance therapeutic strategies aimed at the neural basis of this disorder. Future studies might expand on these findings by including larger cohorts, longitudinal data to track progression, and exploring the effects of various treatments on these network properties.

Bibliography

1. Olanow CW and Mcnaught K. "Parkinson's disease, proteins, and prions: Milestones". In Movement Disorders 26.6 (2011): 1056-1071.
2. Sporns O., *et al*. "The human connectome: A structural description of the human brain". In PLoS Computational Biology 1.4 (2005a): 0245-0251.
3. Pablo Martinez-Martin MD., *et al*. "Validation study of the Hoehn and Yahr scale included in the MDS-UPDRS". *Movement Disorders* 33.4 (2018): 134-165.
4. Tomlinson C L., *et al*. "Systematic review of levodopa dose equivalency reporting in Parkinson's disease". *Movement Disorder* 25 (2010): 2649-2653.
5. Rey A. "L'examen psychologique dans les cas d'encéphalopathie traumatique. [The psychological examination in cases of traumatic encephalopathy]". *Archives de Psychologie* 28 (1964): 286-340.
6. Dubois B., *et al*. "The FAB A frontal assessment battery at bedside". (2000).
7. Stroop J R. "Studies of interference in serial verbal reactions". *Journal of Experimental Psychology* 18.6 (1935):643-662.
8. Mirsky A F., *et al*. "Analysis of the elements of attention: A neuropsychological approach". *Neuropsychology Review* 2.2 (1991): 109-145.
9. Osterrieth P A. "Le test de copie d'une figure complexe: Contribution à l'étude de la perception et de la mémoire. [Test of copying a complex figure: Contribution to the study of perception and memory]". *Archives de Psychologie* 30 (1944): 286-356.
10. Harbi Z., *et al*. "Clock Drawing Test Interpretation System". *Procedia Computer Science* 112 (2017): 1641-1650.
11. Folstein M F., *et al*. ""Mini-mental state": A practical method for grading the cognitive state of patients for the clinician". *Journal of Psychiatric Research* 12.3 (1975): 189-198.

12. Desikan R S., *et al*. "An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest". *NeuroImage* 31.3 (2006): 968-980.

13. Friston K J., *et al*. "A critique of functional localizers". *Neuroimage* 30 (2006): 1077-1087.

14. Zalesky A., *et al*. "Network-based statistics: identifying differences in brain networks". *Neuroimage* 53 (2010): 1197-1207.

15. Caviness VS Jr., *et al*. "The human brain age 7-11 years: a volumetric analysis based on magnetic resonance images". *Cereb Cortex* 5 (1996): 726-736.727.

16. Fischl B. "FreeSurfer". In NeuroImage 62.2 (2012): 774-781).

17. Seidman SB. "Network structure and minimum degree". Soc. Netw. 5 (1983): 269-287.

18. de Reus M A and van den Heuvel MP. "Estimating false positives and negatives in brain networks". *NeuroImage* 70 (2013):402-409.

19. Wold H. "Partial Least Squares". In S. Kotz & N.L. Johnson (Eds.), *Encyclopedia of Statistical Sciences* 6 (1985): 581-591. New York: Wiley.

20. Crossley N A., *et al*. "The hubs of the human connectome are generally implicated in the anatomy of brain disorders". *Brain* 137.8 (2014): 2382-2395.

21. Helmich RC., *et al*. "Spatial remapping of cortico-striatal connectivity in Parkinson's disease". *Cerebral Cortex* 20.5 (2010): 1175-1186.

22. Aarsland D., *et al*. "A systematic review of prevalence studies of dementia in Parkinson's disease". *Movement Disorders* 20.10 (2005): 1255-1263.

23. Bullmore E and Sporns O. "Complex brain networks: graph theoretical analysis of structural and functional systems". *Nature Reviews Neuroscience* 10.3 (2009): 186-198.

24. Zeighami Y., *et al*. "Network structure of brain atrophy in de novo Parkinson's disease". *eLife* 4 (2015): e08440.

25. Stam CJ. "Modern network science of neurological disorders". *Nature Reviews Neuroscience* 15.10 (2014): 683-695.