# Functional connectome organization is altered in PD patients with mild cognitive impairment

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## INTRODUCTION AND OBJECTIVE

Investigation of the brain wiring architecture is a powerful approach in the examination of the pathogenic mechanisms of neurodegenerative disease. This study investigated the functional brain connectome organization in patients with Parkinson's disease (PD) with mild cognitive impairment (MCI).

## MATERIALS AND METHODS

- 54 PD-MCI patients, 54 demographically matched PD patients with no cognitive impairment (PD-ncog), and 41 healthy controls (HC) underwent a resting state functional MRI (fMRI) using a 1.5 T MR scanner.
- All patients and controls underwent a comprehensive clinical and neuropsychological evaluation including tests that assess different cognitive domains: attention and working memory, executive functions, memory, language, and visuospatial functions. According to the MDS Task-force criteria (Litvan, et al., 2012), PD-MCI patients had multi-domain MCI with 24% having impairment of attention and working memory, 74% of executive functions, 64% of memory, 74% of language and 80% of visual spatial abilities.
- Graph theory analysis was used to measure the global topological properties of functional brain networks in patients and controls.
- Differences in regional functional networks among groups were investigated using Network-based statistic (NBS).

**Table 1**. Demographic and clinical findings of PD patients and healthy controls.

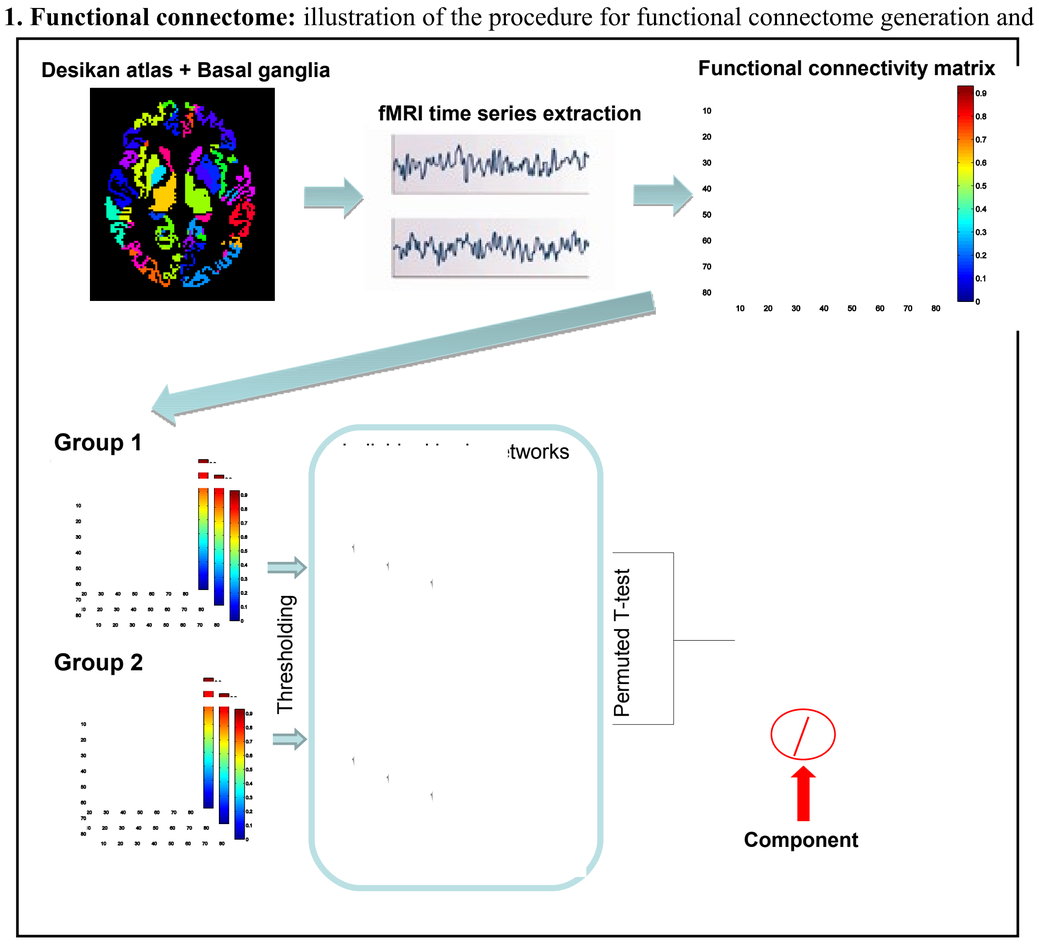
| | Healthy controls | PD-MCI | PD-ncog | PD-MCI *vs* controls | PD-ncog *vs* controls | PD-MCI *vs* PD-ncog |
|---|---|---|---|---|---|---|
| **Number** | 41 | 54 | 54 | - | - | - |
| **Right-handed** | 41 | 52 | 51 | 0.46 | 0.13 | 0.37 |
| **Men/women** | 15/26 | 29/25 | 29/25 | 0.1 | 0.1 | 1 |
| **Age at MRI, ys** | 63 ± 8 (49-77) | 64 ± 9 (39-81) | 63 ± 7 (47-83) | 0.48 | 0.94 | 0.39 |
| **Education, ys** | 13.5 ± 2.9 (8-18) | 10.9 ± 2.4 (8-16) | 11.8 ± 2.2 (8-17) | <0.001 | 0.001 | 0.15 |
| **Age at onset, ys** | - | 58.2 ± 9.3 (38-76) | 58.7 ± 8.0 (44-74) | - | - | 0.89 |
| **Disease duration, ys** | - | 6.2 ± 4.9 (1-22) | 4.6 ± 4.4 (1-19) | - | - | 0.06 |
| **UPDRS III** | - | 37.2 ± 16.3 (12-76) | 26.3 ± 14 (7-61) | - | - | <0.001 |
| **UPDRS total** | - | 55.8 ± 21.9 (16-102) | 39.1 ± 18.4 (11-86) | - | - | <0.001 |
| **H&Y** | - | 2.1 ± 0.9 (1-4) | 1.6 ± 0.8 (1-3) | - | - | 0.01 |
| **Motor phenotype, tremor dominant/rigid akinetic** | - | 23/29 | 22/30 | - | - | 0.98 |
| **Asymmetry, asymmetric/ symmetric** | - | 52/2 | 51/3 | - | - | 0.65 |
| **Side of onset, right/left/ symmetric** | - | 31/21/1 | 35/17/2 | - | - | 0.61 |
| **LEDD** | - | 690.5 ± 433.8 (0-1560) | 447.4 ± 356.4 (0-1200) | - | - | 0.004 |

Numbers are mean ± standard deviation (range) or number. P values refer to ANOVA models, followed by post-hoc pairwise comparisons. Abbreviations: H&Y: Hoehn & Yahr scale; LEDD: Levodopa Equivalent Daily Dose; PD-MCI: PD patients with mild cognitive impairment; PD-ncog: PD patients with no cognitive impairment; UPDRS: Unified Parkinson's Disease Rating Scale; ys: years.

### Resting-state fMRI processing

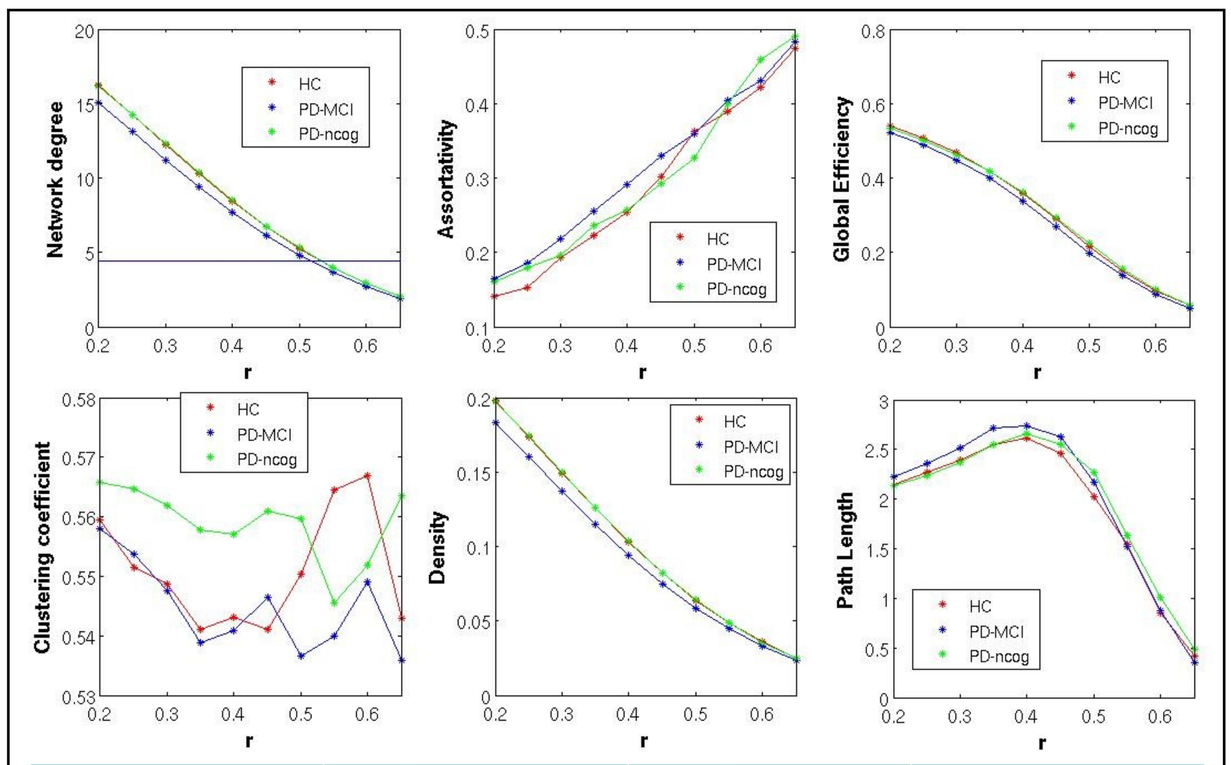
- Pre-processing (realignment, normalization, linear detrend, band-pass filtering 0.01-0.08 Hz).
- Extraction of average fMRI time series from the 68 cortical regions of the Desikan atlas plus the basal ganglia.
- Assessment of bivariate Pearsons' correlation coefficients between each pair of time series, which results in a connectivity matrix for each study subject.
- Calculation of graph theoretical measures using brain connectivity toolbox.
- Computation of between group comparisons and different component extraction using NBS.

**Figure 1. Functional connectome:** illustration of the procedure for functional connectome generation and analysis.



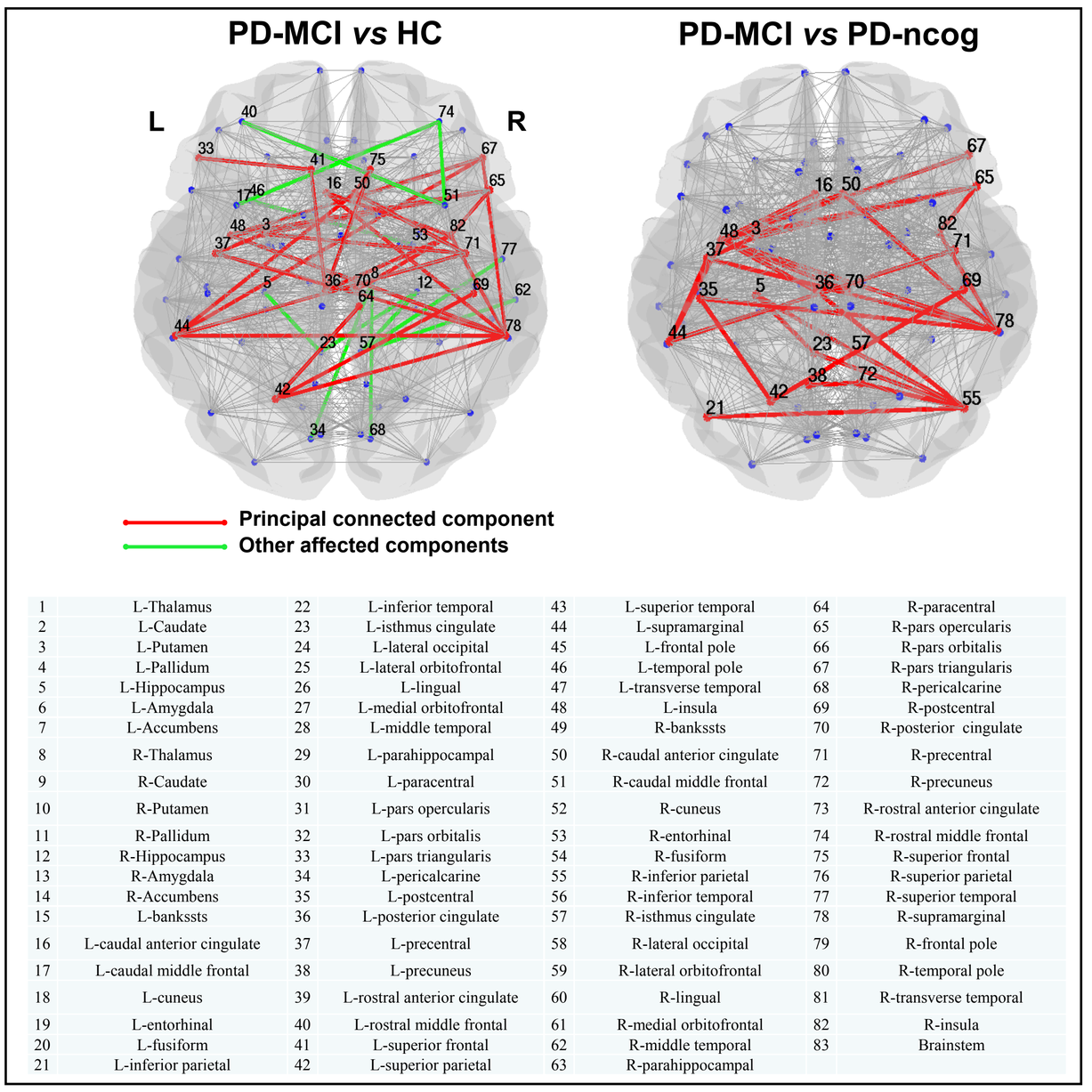

## RESULTS

**Figure 2. Graph analysis:** the analysis of the global graph theoretical measures showed that PD-MCI had significantly lower mean network degree, connections density, and global efficiency as well as higher path length when compared to HC and PD-ncog. No significant differences in clustering coefficient and assortativity were found. Exact p-values are reported in the table at the bottom.




| | PD-MCI *vs* Healthy controls | PD-MCI *vs* PD-ncog | PD-ncog *vs* Healthy controls |
|---|---|---|---|
| **Network degree** | P=0.04 at r=0.2 | p=0.03 at r=0.2 | NS |
| **Assortativity** | NS | NS | NS |
| **Global efficiency** | p=0.02 at r=0.2 | p=0.05 at r=0.2 | NS |
| **Clustering coefficient** | NS | NS | NS |
| **Density** | p=0.04 at r=0.2 | p=0.03 at r=0.2 | NS |
| **Path length** | p=0.01 at r=0.2<br>p=0.05 at r =0.4 | p=0.004 at r=0.2<br>p=0.05 at r =0.4 | NS |

**Figure 3. NBS:** networks showing reduced functional connectivity in PD-MCI *vs* HC (p=0.015) and in PD-MCI *vs* PD-ncog (p=0.007). There were no significant functional connectivity changes when comparing PD-ncog to HC. Connections belonging to the principal connected component are shown in red, while the connections belonging to minor components are shown in green. The table at the bottom of the figure reports the nodes of the network with the corresponding number.




| | | | | | |
|---|---|---|---|---|---|
| 1 | L-Thalamus | 22 | L-inferior temporal | 43 | L-superior temporal |
| 2 | L-Caudate | 23 | L-isthmus cingulate | 44 | L-supramarginal |
| 3 | L-Putamen | 24 | L-lateral occipital | 45 | L-frontal pole |
| 4 | L-Pallidum | 25 | L-lateral orbitofrontal | 46 | L-temporal pole |
| 5 | L-Hippocampus | 26 | L-lingual | 47 | L-transverse temporal |
| 6 | L-Amygdala | 27 | L-medial orbitofrontal | 48 | L-insula |
| 7 | L-Accumbens | 28 | L-middle temporal | 49 | R-bankssts |
| 8 | R-Thalamus | 29 | L-parahippocampal | 50 | R-caudal anterior cingulate |
| 9 | R-Caudate | 30 | L-paracentral | 51 | R-caudal middle frontal |
| 10 | R-Putamen | 31 | L-pars opercularis | 52 | R-cuneus |
| 11 | R-Pallidum | 32 | L-pars orbitalis | 53 | R-entorhinal |
| 12 | R-Hippocampus | 33 | L-pars triangularis | 54 | R-fusiform |
| 13 | R-Amygdala | 34 | L-pericalcarine | 55 | R-inferior parietal |
| 14 | R-Accumbens | 35 | L-postcentral | 56 | R-inferior temporal |
| 15 | L-bankssts | 36 | L-posterior cingulate | 57 | R-isthmus cingulate |
| 16 | L-caudal anterior cingulate | 37 | L-precentral | 58 | R-lateral occipital |
| 17 | L-caudal middle frontal | 38 | L-precuneus | 59 | R-lateral orbitofrontal |
| 18 | L-cuneus | 39 | L-rostral anterior cingulate | 60 | R-lingual |
| 19 | L-entorhinal | 40 | L-rostral middle frontal | 61 | R-medial orbitofrontal |
| 20 | L-fusiform | 41 | L-superior frontal | 62 | R-middle temporal |
| 21 | L-inferior parietal | 42 | L-superior parietal | 63 | R-parahippocampal |

| | | | |
|---|---|---|---|
| 64 | R-paracentral | 68 | R-pericalcarine |
| 65 | R-pars opercularis | 69 | R-postcentral |
| 66 | R-pars orbitalis | 70 | R-posterior cingulate |
| 67 | R-pars triangularis | 71 | R-precentral |
| 68 | R-pericalcarine | 72 | R-precuneus |
| 69 | R-postcentral | 73 | R-rostral anterior cingulate |
| 70 | R-posterior cingulate | 74 | R-rostral middle frontal |
| 71 | R-precentral | 75 | R-superior frontal |
| 72 | R-precuneus | 76 | R-superior parietal |
| 73 | R-rostral anterior cingulate | 77 | R-superior temporal |
| 74 | R-rostral middle frontal | 78 | R-supramarginal |
| 75 | R-superior frontal | 79 | R-frontal pole |
| 76 | R-superior parietal | 80 | R-temporal pole |
| 77 | R-superior temporal | 81 | R-transverse temporal |
| 78 | R-supramarginal | 82 | R-insula |
| 79 | R-frontal pole | 83 | Brainstem |
| 80 | R-temporal pole | | |
| 81 | R-transverse temporal | | |
| 82 | R-insula | | |
| 83 | Brainstem | | |

## CONCLUSIONS

- The topological properties of brain networks are altered in PD patients with cognitive deficits, suggesting a loss of efficiency of long-distance functional connections.
- The pattern of the alterations of the functional connectome and their anatomical distribution suggest that they might reflect the neuropathological substrate underlying PD-related cognitive impairment.
- Assessing functional brain network abnormalities in PD patients with cognitive impairment could improve our understanding of the relationship between PD pathology and cognitive deficits.

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