

# Brain MRI structural connectome and cognitive impairment in Parkinson's disease

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## OBJECTIVE

✓ To investigate structural brain network abnormalities and explore their relationships with cognitive impairment in a large population of Parkinson's disease (PD) patients with and without mild cognitive impairment (MCI).

## MATERIALS AND METHODS

✓ 170 PD patients (116 without cognitive impairment [PD-ncog]; and 54 PD-MCI), and 41 healthy controls. Fifty-four PD-ncog, matched with PD-MCI for demographical features.

✓ All patients and controls underwent structural magnetic resonance imaging (MRI) at 1.5 T and 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 multidomain 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.

✓ A structural brain network analysis was performed. Individual structural brain connectome was reconstructed using deterministic diffusion tensor tractography and its integrity was measured in terms of fractional anisotropy (FA) and mean diffusivity (MD). Network based statistic was used to assess structural connectivity differences among groups. Correlations of brain connectivity alterations with neuropsychological deficits and motor disability were tested using false discovery rate (FDR) corrected Pearson's correlations.

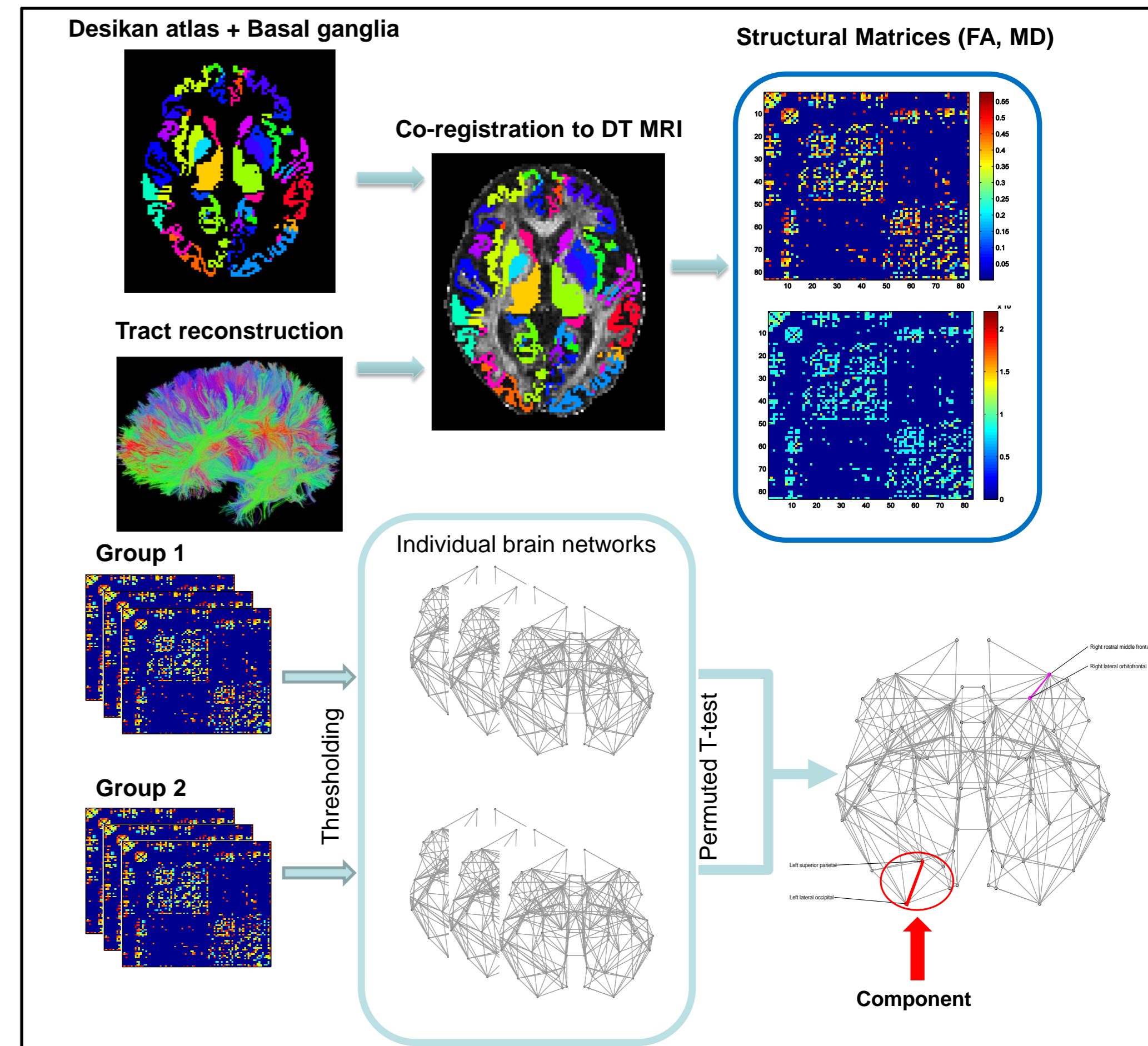
✓ A voxel-wise analysis of DT MRI abnormalities using tract-based spatial statistics (TBSS) was also performed.

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

	Healthy controls	All PD	p*	PD-MCI	Matched PD-ncog	All PD-ncog	PD-MCI vs controls	Matched PD-ncog vs controls	All PD-ncog vs controls	PD-MCI vs matched PD-ncog
Number	41	170		54	54	116	-	-	-	-
Right-handed	41	162	0.37	52	51	110	0.46	0.13	0.14	0.37
Men/women	15/26	100/70	0.01	29/25	29/25	71/45	0.1	0.1	0.01	1
Age at MRI, ys	63 ± 8 (49-77)	62 ± 8 (39-83)	0.68	64 ± 9 (39-81)	63 ± 7 (47-83)	61 ± 8 (43-83)	0.48	0.94	0.33	0.39
Education, ys	13.5 ± 2.9 (8-18)	12.4 ± 2.6 (8-20)	0.01	10.9 ± 2.4 (8-16)	11.8 ± 2.2 (8-17)	13.1 ± 2.4 (8-20)	<0.001	0.001	0.19	0.15
Age at onset, ys	-	57.2 ± 9.1 (31-76)	-	58.2 ± 9.3 (38-76)	58.7 ± 8.0 (44-74)	56.8 ± 9.2 (31-74)	-	-	-	0.89
Disease duration, ys	-	5.1 ± 5.2 (1-26)	-	6.2 ± 4.9 (1-22)	4.6 ± 4.4 (1-19)	5.4 ± 5.4 (1-26)	-	-	-	0.06
UPDRS III	-	28.8 ± 16.1 (5-76)	-	37.2 ± 16.3 (12-76)	26.3 ± 14 (7-61)	24.9 ± 14.4 (5-61)	-	-	-	<0.001
UPDRS total	-	43.5 ± 21.5 (7-102)	-	55.8 ± 21.9 (16-102)	39.1 ± 18.4 (7-86)	37.9 ± 18.9 (7-86)	-	-	-	<0.001
H&Y	-	1.7 ± 0.8 (1-4)	-	2.1 ± 0.9 (1-4)	1.6 ± 0.8 (1-3)	1.7 ± 1 (1-3)	-	-	-	0.01
Motor phenotype, tremor dominant/rigid akinetik	-	69/95	-	23/29	22/30	46/66	-	-	-	0.98
Asymmetry, asymmetric/symmetric	-	163/7	-	52/2	51/3	111/5	-	-	-	0.65
Side of onset, right/left/symmetric	-	103/61/5	-	31/21/1	35/17/2	72/40/4	-	-	-	0.61
LEDD	-	522 ± 425.4 (0-1930)	-	690.5 ± 433.8 (0-1560)	447.4 ± 356.4 (0-1200)	443.6 ± 399.6 (0-1930)	-	-	-	0.004

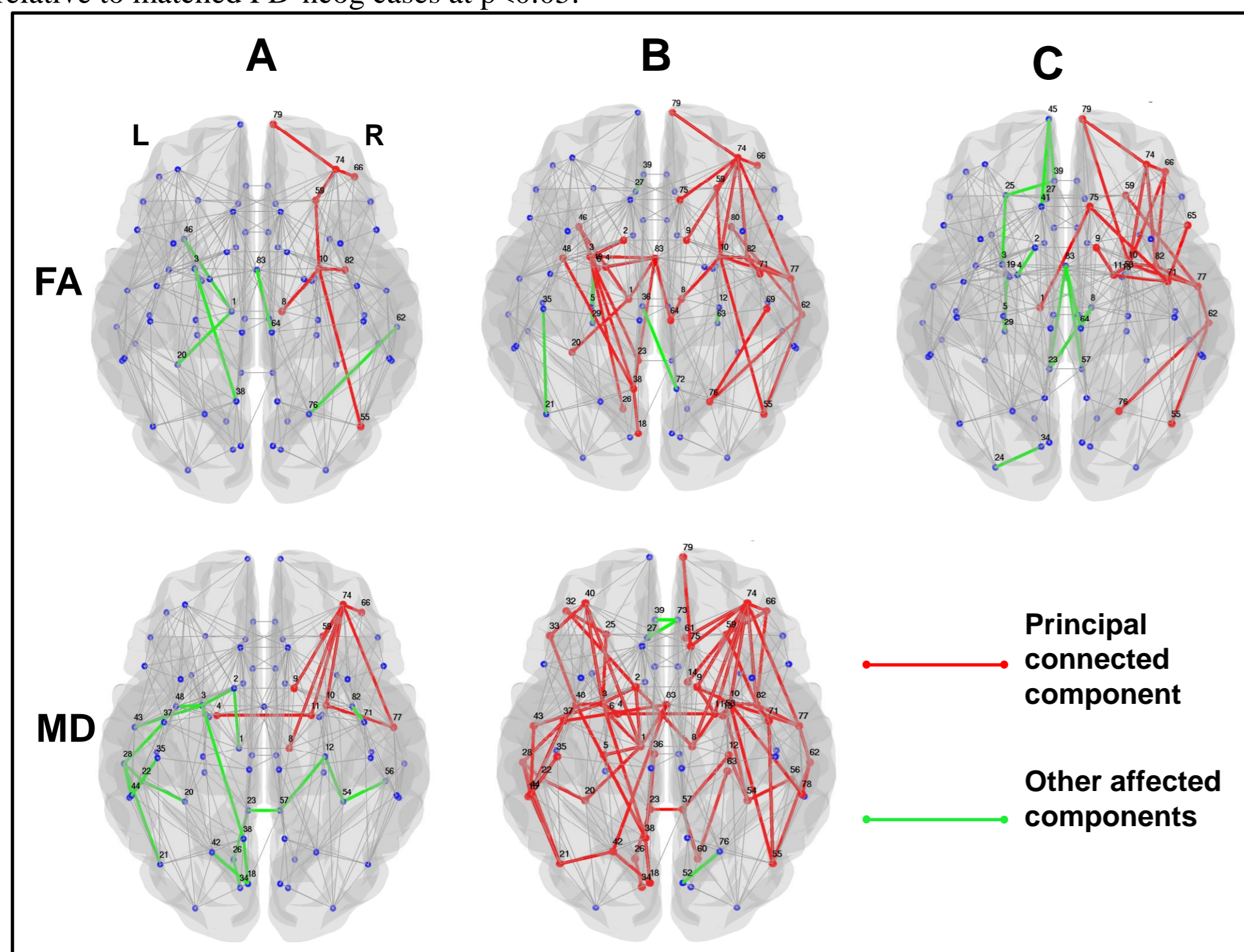
Numbers are mean ± standard deviation (range) or number. P values refer to ANOVA models, followed by post-hoc pairwise comparisons. \*All PD patients vs healthy controls. Abbreviations: H&Y: Hoehn & Yahr scale; LEDD: Levodopa Equivalent Daily Dose; PD-MCI: PD patients with mild cognitive impairment;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

**Figure 1.** Structural brain network analysis procedure.



## RESULTS

**Figure 2.** Affected structural connections in PD-MCI relative to healthy controls and PD patients without cognitive impairment (Network Based Statistic). A) Subnetworks showing altered structural connectivity (decreased fractional anisotropy [FA] or increased mean diffusivity [MD]) in PD-MCI patients relative to healthy controls at  $p < 0.01$ . B) Subnetworks showing altered structural connectivity (decreased FA or increased MD) in PD-MCI patients relative to healthy controls at  $p < 0.05$ . C) Subnetworks showing impaired structural connectivity (decreased FA) in PD-MCI patients relative to matched PD-ncog cases at  $p < 0.05$ .



**Table 2.** Brain nodes included in the Network Based Statistic analysis.

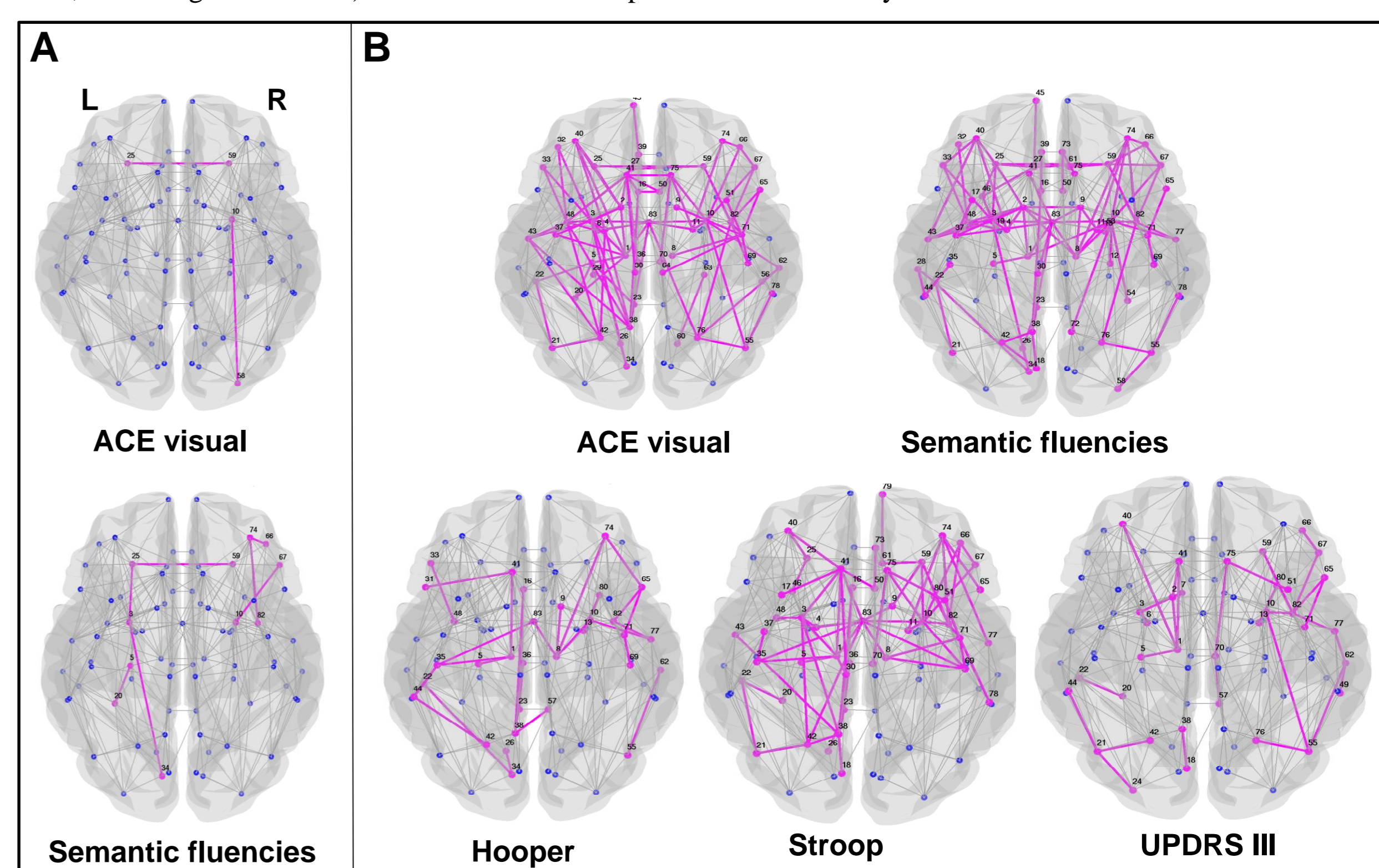
1 L-Thalamus	22 L-inferior temporal	43 L-superior temporal	64 R-paracentral
2 L-Caudate	23 L-isthmus cingulate	44 L-supramarginal	65 R-pars opercularis
3 L-Putamen	24 L-lateral occipital	45 L-frontal pole	66 R-pars orbitalis
4 L-Pallidum	25 L-lateral orbitofrontal	46 L-temporal pole	67 R-pars triangularis
5 L-Hippocampus	26 L-lingual	47 L-transverse temporal	68 R-pericalcarine
6 L-Amygdala	27 L-medial orbitofrontal	48 L-insula	69 R-postcentral
7 L-Accumbens	28 L-middle temporal	49 R-bankssts	70 R-posterior cingulate
8 R-Thalamus	29 L-parahippocampal	50 R-caudal anterior cingulate	71 R-precentral
9 R-Caudate	30 L-paracentral	51 R-caudal middle frontal	72 R-precuneus
10 R-Putamen	31 L-pars opercularis	52 R-cuneus	73 R-rostral anterior cingulate
11 R-Pallidum	32 L-pars orbitalis	53 R-entorhinal	74 R-rostral middle frontal
12 R-Hippocampus	33 L-pars triangularis	54 R-fusiform	75 R-superior frontal
13 R-Amygdala	34 L-pericalcarine	55 R-inferior parietal	76 R-superior parietal
14 R-Accumbens	35 L-postcentral	56 R-inferior temporal	77 R-superior temporal
15 L-bankssts	36 L-posterior cingulate	57 R-isthmus cingulate	78 R-supramarginal
16 L-caudal anterior cingulate	37 L-precentral	58 R-lateral occipital	79 R-frontal pole
17 L-caudal middle frontal	38 L-precuneus	59 R-lateral orbitofrontal	80 R-temporal pole
18 L-cuneus	39 L-rostral anterior cingulate	60 R-lingual	81 R-transverse temporal
19 L-entorhinal	40 L-rostral middle frontal	61 R-medial orbitofrontal	82 R-insula
20 L-fusiform	41 L-superior frontal	62 R-middle temporal	83 Brainstem
21 L-inferior parietal	42 L-superior parietal	63 R-parahippocampal	

## CONCLUSIONS

✓ This study suggests that a disruption of structural connections between brain areas forming a network might be important to determine an altered information integration and organization and thus cognitive deficits in patients with PD.

✓ Our results provide novel information concerning the structural substrates of MCI in PD and may offer markers of cognitive deterioration in these patients.

**Figure 3.** Correlations between altered structural connectivity and cognitive deficits in PD. Structural connections showing correlations between FA (A) and MD (B) values and performance on neuropsychological tests (i.e., lower FA values, lower cognitive scores). Results are shown at  $p < 0.05$  false discovery rate corrected.



**Figure 4.** Microstructural white matter damage (Tract-based spatial statistics). Areas of decreased FA (red) and increased MD (blue) in PD patient groups compared to healthy controls ( $p < 0.05$  corrected for multiple comparisons).

