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Functional connectome correlates of chronic dopaminergic therapy in Parkinson's disease.

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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 investigates the relationship between functional brain networks and the chronic dopaminergic therapy dose quantified as levodopa equivalent daily dose (LEDD) in a large population of Parkinson's disease (PD) patients without dementia.

MATERIALS AND METHODS

- 170 PD patients (116 without cognitive impairment) performed resting state functional MRI (fMRI) using a 1.5 T MR scanner.
- All patients 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.
- Cortical and subcortical brain areas (i.e., the nodes of the connectome) were identified on volumetric T1-weighted images using Freesurfer.
- Functional connectome was reconstructed for each subject using two thresholds, i.e., r=0.2 (p=0.0045) and r=0.3 (p<0.0001).
- Measures of functional connectivity (FC) obtained at both thresholds were correlated with the LEDD of each subject using Spearman's partial correlation.
- UPDRS III score, disease duration and age were considered as nuisance variables.

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

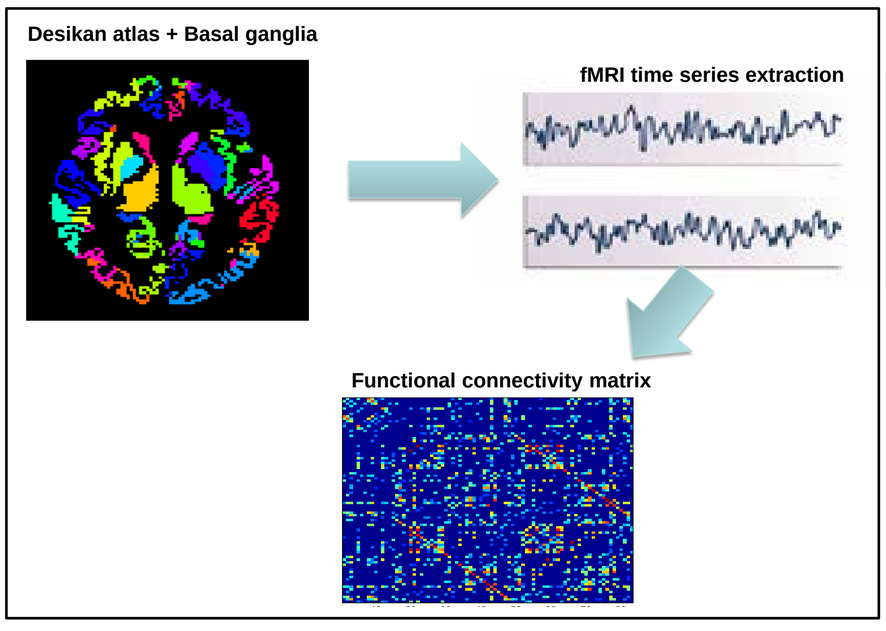
	Healthy controls	All PD	p*	PD-MCI	All PD-ncog	PD-MCI *vs* controls	All PD-ncog *vs* controls
Number	41	170		54	116	-	
Right-handed	41	162	0.37	52	110	0.46	0.14
Men/women	15/26	100/70	0.01	29/25	71/45	0.1	0.01
Age at MRI, ys	63 ± 8 (49-77)	62 ± 8 (39-83)	0.68	64 ± 9 (39-81)	61 ± 8 (43-83)	0.48	0.33
Education,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

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

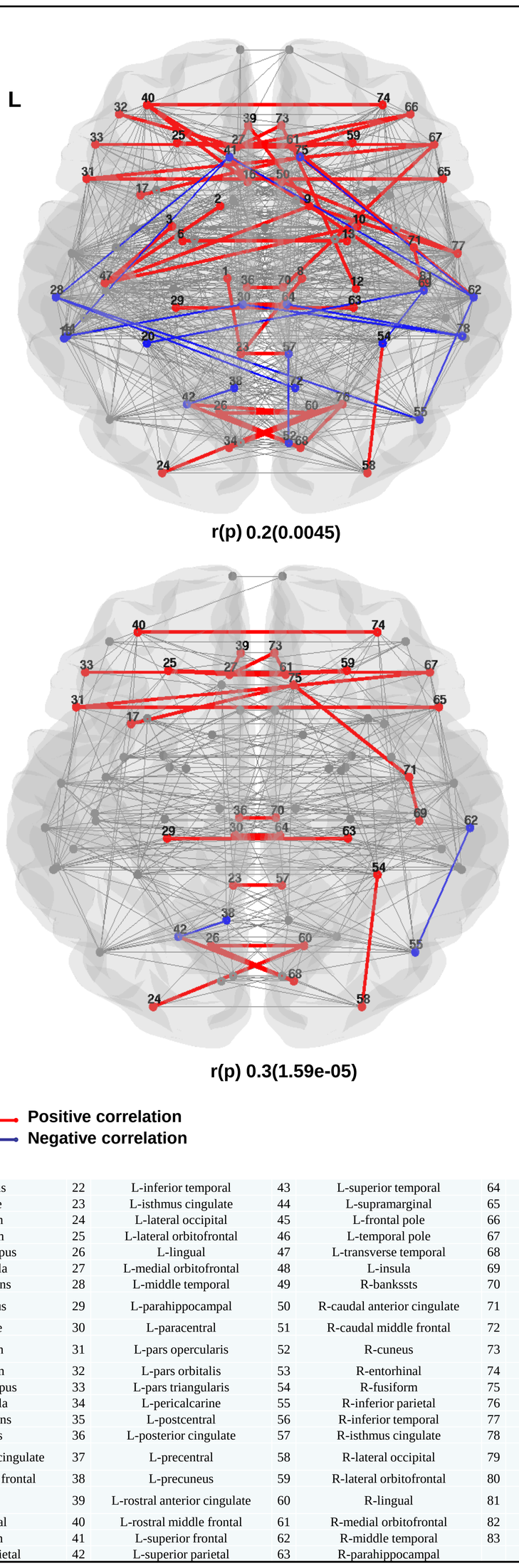
- Pre-processing (realignment, normalization, linear detrend, band-pass filtering 0.01-0.08 Hz).
- Extraction of average fMRI time series from the 68 cortical regions of the Desikan atlas plus the basal ganglia.
- Assessment of bivariate Pearsons' correlation coefficients between each pair of time series, which results in a connectivity matrix for each study subject.

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



RESULTS

Figure 2. Functional connectome correlation analysis: At p=0.0045, we observed a positive correlation of LEDD with a distributed network including regions of prefrontal cortex, such as the bilateral inferior and middle frontal gyri, and the orbitofrontal cortex as well as anterior cingulate gyrus. There was also a positive correlation with FC between the bilateral striatum and temporal structures such as the right superior temporal gyrus and right transverse temporal lobe. LEDD positively correlated with another posterior network involving bilateral visual regions such as the pericalcarine and lateral occipital cortex. On the other hand, a large bilateral FC network negatively correlated with LEDD and included precuneus, inferior parietal and supramarginal gyri, paracentral lobule as well as fusiform gyrus, middle temporal gyrus and superior frontal gyrus. At p<0.0001, we observed a similar pattern of positive correlations with LEDD mainly located in the frontal and visual networks, with a predominant involvement of interhemispheric connections



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

- Chronic dopaminergic therapy enhanced frontal and occipito-parietal FC and inhibited temporo-parietal FC in PD. This finding could explain the influence of the dopaminergic drugs on cognition and mood in PD as well as the appearance of therapy-related side effects.
- On other hand LEDD did not correlate with fronto-striatal FC, which is expected since dopaminergic therapy is mainly augmented to counter the worsening of motor symptoms and thus it probably restores some of the striatal FC lost due to the disease.
- Analysis of functional connectome might add novel insights into the understanding of therapy-related changes and prediction of side effects in PD.

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