Functional connectivity in early Parkinson's disease: a resting-state fMRI study

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BACKGROUND
Hemiparkinsonism

- **At clinical presentation, the motor manifestations of PD are typically restricted to one side of the body, a condition known as hemiparkinsonism.**
- **Even in such initial phase, however, a bilateral putaminal dopamine uptake reduction occurs (Seibyl et al., 1995).**
- **Therefore, in hemiparkinsonian patients, the cerebral hemisphere ipsilateral to the initially affected limbs can be considered “presymptomatic”.**

BACKGROUND

PD and basal ganglia circuit

- In PD, there is a change in spontaneous neural oscillations across the cortico-striatal-thalamic network (Gatev 2006) that is most often invoked to explain clinical deficits of PD (Stoffers 2007; Silberstein 2005).
- Resting state (RS) fMRI studies in patients with mild to moderate PD revealed an altered connectivity of the cortico-striatal-thalamic network (Helmich 2010; Hacker 2012; Wu 2009; Kwak 2012; Yu 2013; Yang 2013).
- A levo(L)-dopa induced spatial remapping of the cortico-striatal connectivity has also been suggested in chronically treated PD patients (t-PD), (Wu 2009; Kwak 2012) and, more recently, in drug-naïve patients (n-PD) (Esposito 2013; Choe 2013).

AIMS

- **To investigate the functional connectivity of the cortico-striatal-thalamic networks in patients with hemiparkinsonism and its association with motor disability.**
- **To assess L-dopa effects on the brain networks at the earliest stage of PD.**

SUBJECTS

Main inclusion / exclusion criteria

INCLUSION CRITERIA

- Clinical diagnosis of PD
- Hemiparkinsonism (Hoehn and Yahr score = 1.0)
- Drug-naïve status (n-PD) or stable/optimized L-dopa treatment (t-PD) in the last three months
- Normal cognitive status defined as MMSE score ?Õ26

EXCLUSION CRITERIA

- Moderate-severe head tremor
- Presence of known genetic mutation
- Ongoing treatments with anticholinergic or other psychotropic drugs
- Cerebrovascular disorders, traumatic brain injury history, or intracranial mass
- Dementia, major depression and other major neurological and medical diseases

MRI ACQUISITION

1.5 T system (Philips Medical Systems, Achieva):

- **T2*-weighted single-shot echo planar imaging (EPI)** (TR=3000 ms, TE=35 ms, echo train length=51, flip angle=90°, thickness= 4 mm, matrix size=128×128, FOV=240×240 mm).
- **Dual-echo turbo (DE) spin-echo (SE)** (TR=3125 ms, TE=20/100 ms, echo train length=6, 44 axial slices, thickness=3.0 mm, matrix size =256×256, FOV=240×240 mm
- **3D-T1-w fast field echo:** TR=7.34 ms, TE=3.40 ms, inversion time= 1000 ms, flip angle=8°, matrix size=256×256×180, FOV=256×256×180 mm, SENSE Parallel Reduction Factor out-of-Plane=1.5, sagittal orientation
- **Pulsed-gradient SE echo:** TR=6713 ms, TE=86 ms, flip angle=90°, matrix size=112×112, FOV=224×224 mm; 50 contiguous, 2.6-mm thick, axial slices), with diffusion-encoding gradients applied in 65 non-collinear directions (b factor= 1000 s/mm^2; seven averages)

MRI ANALYSIS

RS fMRI

- **Pre-processing (FSL):** 1. T1-images skull-stripping (BET) 2. Brain segmentation (FAST) 3. Registration of resulting images to RS-fMRI native space of each subject through a 7 degree-of-freedom (FLIRT). 4. Removal of the first 4 volumes of the RS-fMRI data 5. Individual RS-fMRI images processing with MELODIC: (i) motion correction; (ii) high-pass temporal filtering (cut-off: 100 s); (iii) spatial smoothing (Gaussian Kernel of FWHM 6 mm); (iv) single-session ICA; (v) visual inspection of IC and removal of non-brain signals.
- **Flipping:** Connectivity maps of patients whose symptoms were on the left (L) side were left-right (R) flipped along the x-axis using 'fslswapdim', so that the hemisphere contralateral to the affected limbs was the L for all patients.
- **Seed-based FC:** caudate and putamen nuclei, globus pallidus and thalamus as seed regions of interest.
- **Between group comparisons:** Between-group differences were tested using a mixed-effects model (FLAME), adjusting for age. Corrections for multiple comparisons were carried out at a cluster-level using Gaussian random field theory ($Z>2.3$; cluster significance: $p<0.05$, corrected).
- **Correlation analysis:** regression analysis to correlate FC with UPDRS III.

MRI ANALYSIS
Structural MRI

GM atrophy:

- **VBM and DARTEL in SPM8**
- **each PD group (n-PD and t-PD) *vs* matched healthy controls adjusting for age and TICV**

WM damage:

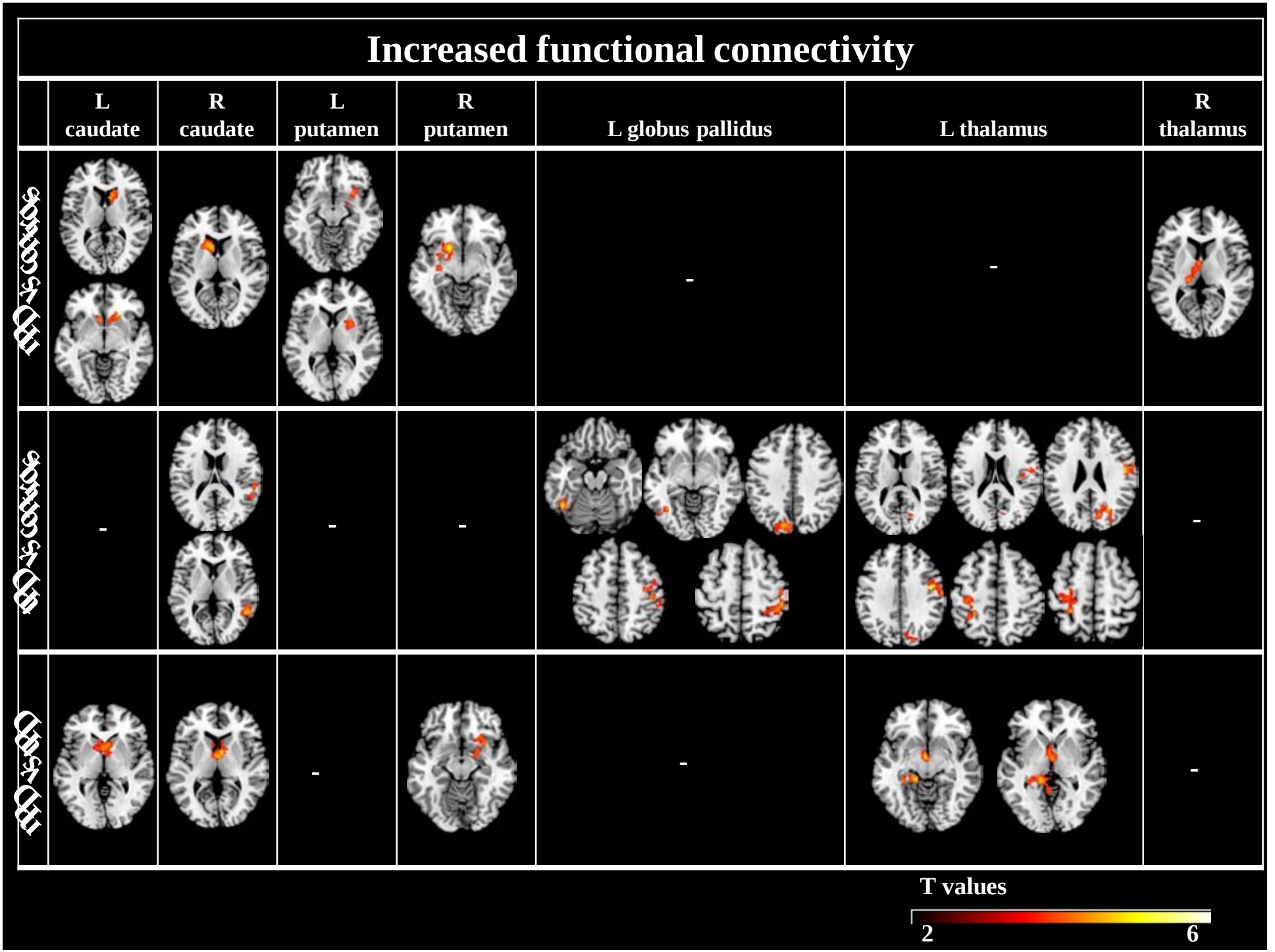
- **TBSS analysis in FSL**
- **FA and MD differences: each PD group (n-PD and t-PD) *vs* matched healthy controls, adjusting for age**
- **permutation-based inference tool for nonparametric statistical thresholding (“randomize”; 5000 permutations)**

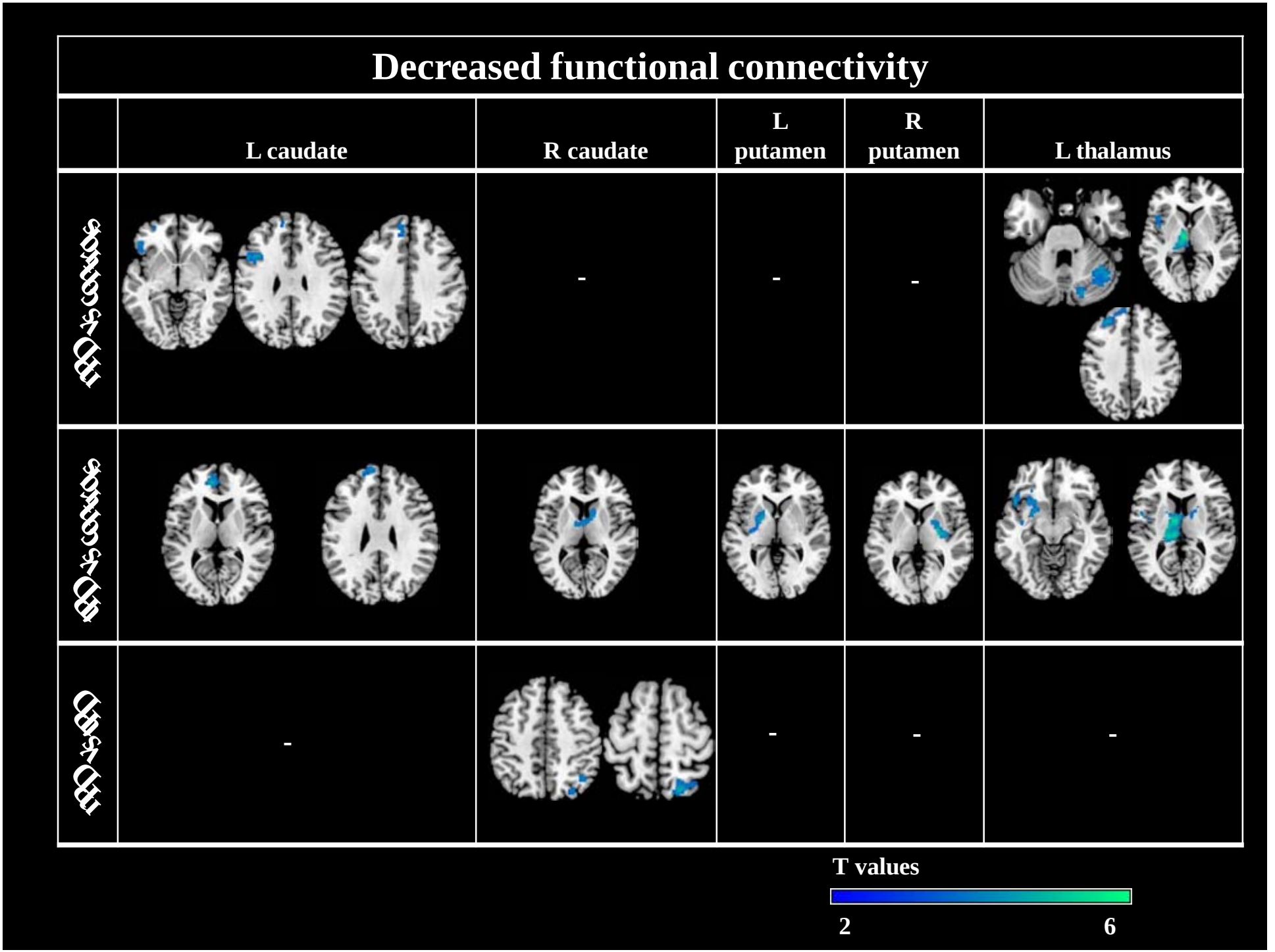
RESULTS

Demographic and clinical features

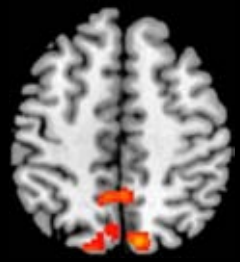
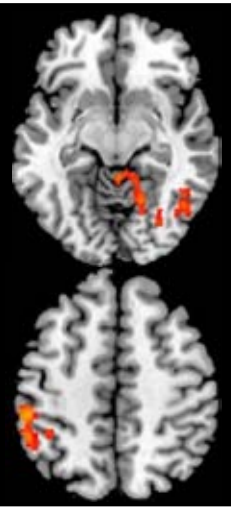
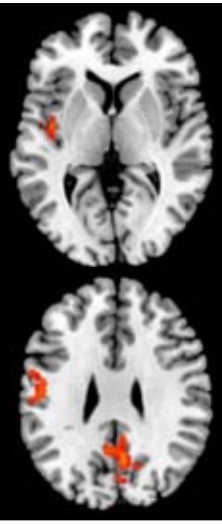
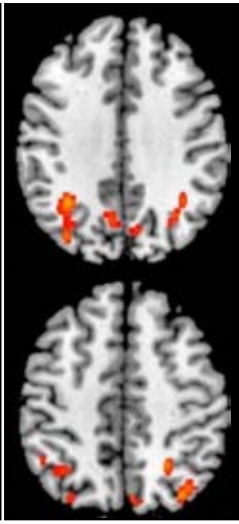
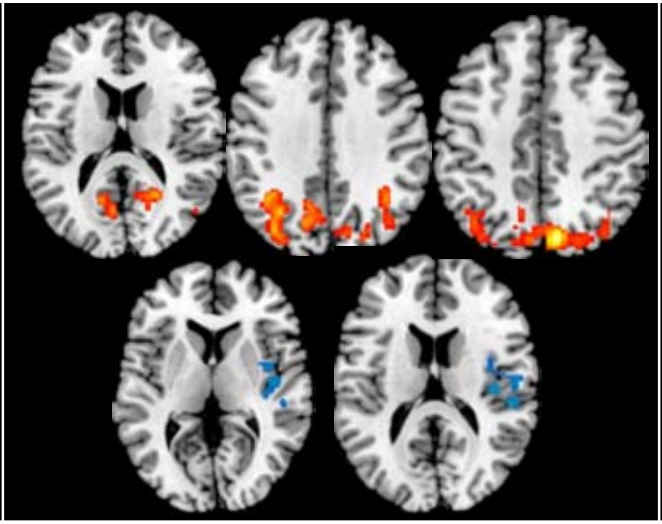
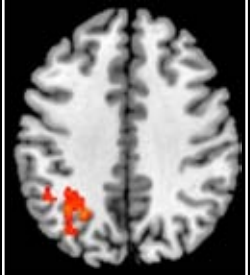
	Healthy controls	All PD	n-PD	t-PD
Number	27	69	25	44
Right-handed	27	69	25	44
Women/men	12/15	32/37	10/15	22/22
Age at MRI, ys	58 ± 11	61 ± 9	57 ± 9#	62 ± 7
Education, ys	14 ± 2	13 ± 3	13 ± 2	13 ± 3
Age at onset, ys	-	58 ± 12	56 ± 8	60 ± 9
Disease duration, ys	-	1.7 ± 1.6	1.4 ± 1.1	2.0 ± 1.4
Tremor dominant/Akinetic-rigid	-	44/25	17/8	27/17
Hoehn and Yahr scale	-	1.2 ± 0.2	1.2 ± 0.2	1.2 ± 0.2
UDPSR III-motor	-	16.0 ± 4.5	16.9 ± 4.9	15.4 ± 4.1
Tremor subscore	-	1.04 ± 1.05	1.28 ± 0.96	0.90 ± 1.08
MMSE	29.7 ± 0.7	28.2 ± 3.7*	28.8 ± 1.2*	27.8 ± 4.4*
WMH load [ml]	0.2 ± 0.4	0.2 ± 0.6	0.3 ± 0.8	0.2 ± 0.5

Values are means ± standard deviations or number of subjects. §Tremor subscore was calculated as the sum of the item 20 of the UPDRS III. *p<0.05 *vs.* healthy controls; #p<0.05 *vs.* t-PD patients.


Increased functional connectivity
L caudate
R caudate
L putamen
R putamen
L globus pallidus
L thalamus
R thalamus
HD vs. Controls
Symptomatic HD vs. Controls
Pre-symptomatic HD vs. Controls
-
T values
2
6


Decreased functional connectivity
L caudate
R caudate
L putamen
R putamen
L thalamus
-
-
-
-
-
-
-
-
T values
2
6

UPDRS III *vs* functional connectivity

	R caudate	L putamen	R putamen	R pallidus	R thalamus
OFF	-	-			-
ON				-	

T values 2 6

T values 2 6

Discussion (1)
Increased reciprocal FC of BG and decreased thalamic outflow in n-PD

- **The increased reciprocal FC of BG might be related to a dysfunction of the cortico-striatal-thalamic network due to the dopamine deficit.**

- **According to the cortico-striatal-thalamic network dysfunction model in PD, cortical regions show a decreased activity due to a reduction in the excitatory thalamic outflow (i.e., deafferentation).**

- **The reduced FC of frontal and insular regions in n-PD patients may underlie the characteristic early impairment of executive and attentional functions in this condition.**

Discussion (2)

Decreased reciprocal FC of BG and increased thalamic outflow in t-PD

- **The decreased reciprocal FC of BG might be related to L-dopa modulation.**
- **The increased thalamo-cortical connectivity of our t-PD patients could be interpreted as a compensatory mechanism associated with chronic dopaminergic treatment**
- **The decreased input from the subcortical motor network can be reversed with L-dopa administration.**

Discussion (3)

Correlations between motor disability and cortico-striatal-thalamic network FC

- **The spatial distribution of the correlations with the UPDRS III score resembles the posterior nodes of the default mode (DMN) and visual networks.**

- **Previous RS fMRI studies in PD showed associations of altered DMN and visual network connectivity with cognitive impairment (Tessitore, 2012) and freezing of gait (Tessitore, 2012).**

- **The enhanced connectivity between Bg and posterior brain regions may be related to the increased dependence on visuospatial abilities and visual information processing during the generation of motor plans in PD patients (Hemich 2007).**

Conclusions

- **Cortico-striatal-thalamic functional abnormalities occur in patients with hemiparkinsonism, antecede the onset of motor symptoms on the opposite body side, and are modulated by L-dopa.**

- **In patients at the earliest phases of PD, L-dopa is likely to facilitate a compensation of brain functional abnormalities possibly through an increased thalamic outflow.**