To rise and to fall: functional connectivity in cognitively normal and cognitively impaired patients with Parkinson's disease

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ABSTRACT

Cognitive decline is a burdensome extra-motor symptom associated with Parkinson's disease (PD). This study aimed at investigating intrinsic functional connectivity (iFC) of the brain in cognitively unimpaired (PD-CU) and impaired PD patients (PD-CI) compared with age-matched healthy controls. "Resting-state" functional magnetic resonance imaging was acquired in 53 subjects, that is, 14 PD-CU patients, 17 PD-CI patients, and 22 control subjects. Cognition and cognitive status for patient classification were assessed using detailed neuropsychological testing. In PD-CU patients versus controls, we demonstrated significantly increased iFC (hyperconnectivity) presenting as network expansions in cortical, limbic, and basal ganglia-thalamic areas. Significantly, decreased iFC in PD-CI patients compared with control subjects was observed, predominantly between major nodes of the default mode network. In conclusion, the increased iFC might be the initial manifestation of altered brain function preceding cognitive deficits. Hyperconnectivity could be an adaptive (compensatory) mechanism by recruiting additional resources to maintain normal cognitive performance. As PD-related pathology progresses, functional disruptions within the default mode networks seem to be considerably associated with cognitive decline.

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1. Introduction

Parkinson's disease (PD) is the second most age-related neurodegenerative disease and was traditionally characterized as a pure movement disorder (Hughes et al., 1992). However, PD patients also experience a broad spectrum of nonmotor symptoms, including burdensome cognitive deficits with attentional problems, memory deficits as well as executive and visual dysfunctions (Litvan et al., 2012). In about 30% of all PD patients, impaired cognition gradually leads to PD-associated dementia, the incidence rate is increased up to 6 times over the general age-matched population (Emre et al., 2007).

The pathologic processes underlying PD can be traced as a topographically ascending spreading scheme from the lower brainstem toward mesencephalic structures and the basal ganglia, finally reaching the neocortex as evident from neuropathologic studies (Braak and Del Tredici, 2009; Braak et al., 2003; Jucker and Walker, 2013). Intrinsic functional connectivity (iFC) has emerged as an important in vivo substrate of dysfunctions in PD patients (Prodoehl et al., 2014). The correlations of low-frequency blood oxygenation level-dependent (BOLD) fluctuations in distinct areas as measured in the "resting" brain by iFC magnetic resonance imaging (iFCMRI) allow to investigate the functional coupling between these areas (Biswal et al., 1995). By *a-priori* defining a "seed" region that is known to share many functional connections with spatially distributed brain regions, the corresponding intrinsic functional connectivity networks (ICNs) can be computed (Van Dijk et al., 2010). Several ICNs have been identified and successively refined on the basis of a comprehensive functional explication and behavioral taxonomy (Beckmann et al., 2005; Laird et al., 2011; Smith et al., 2009), whereas the default mode network (DMN) (Raichle et al., 2001) plays a major role in cognition (Buckner et al., 2008). In a pilot study, we have identified 10 ICNs by using a seed-based approach with consistently reported seed locations (Gorges et al., 2014), in accordance with other studies (Laird et al., 2011; Smith et al., 2009).

Previous iFC studies in PD reported abnormal functional interaction in the sensory motor network (Wu et al., 2009), the DMN (Tessitore et al., 2012), and several other areas (Filippi et al., 2013; Luo et al., 2014; Prodoehl et al., 2014) including dysfunctional connectivity of the striatum (Hacker et al., 2012). Most of these

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studies were conducted in nondemented patients and PD patients confirmed to be free of cognitive problems were not contrasted against cognitively impaired PD patients, so far. A recent study by Agosta et al. (2014) has suggested that structural damage initially manifested in PD patients with mild cognitive impairment, whereas neuropsychologically confirmed cognitively unimpaired cases presented no significant white matter lesions. It remains an open issue whether cognitively unimpaired PD patients already present with functional alterations. We hypothesized that functional connectivity in the PD patients' brains depends on their cognitive status and functional connectivity networks might be altered in association with cognition.

Hence, the present cross-sectional study aimed at comparing iFC within 10 brain networks in neuropsychologically classified cognitively normal and impaired PD patients as well as healthy controls. These 10 ICN, that is, DMN, bilateral frontoparietal control, dorsal- and ventral attention, visuospatial, motor, basal ganglia-thalamic, brainstem, and cerebellar networks, capture most of the cognitively important domains (Laird et al., 2011). We evaluated iFC within these overall networks to unravel their potential role as a substrate of the PD-related pathologic process, without hypothesis-driven restriction of the search area.

2. Methods

2.1. Participants

Fifty-three subjects, that is, 31 PD patients and 22 healthy control subjects, were included. The subjects participated in the multicenter LANDSCAPE study according to given guidelines (Balzer-Geldsetzer et al., 2011). Informed written consent was obtained in accordance with the protocol approved by the Ethics Committee of the University of Ulm, Germany (No. 36/12). All participant characteristics are summarized in Table 1. All subjects were native German speakers and right-handed according to the Edinburgh Handedness Inventory (Oldfield, 1971). None had any clinically significant medical condition (except from PD) or psychiatric illness (except from cognitive deficits). According to neuropsychological assessment of all 53 participants, 3 subject groups

for the iFCMRI data analysis were classified as: (1) 14 cognitively unimpaired PD patients (PD-CU); (2) 17 cognitively impaired PD patients (PD-CI) comprising 6 cases with PD-associated dementia; and (3) 22 healthy control subjects free of cognitive deficits. All PD patients were diagnosed by a board-certified neurologist specialized in movement disorders, according to UK Brain Bank Criteria and received antiparkinsonian medication. All measurements were performed in the ON state. Patients with symptoms or signs of other neurodegenerative or symptomatic parkinsonian syndromes or dementia with Lewy bodies were not included. A certified clinical psychologist performed comprehensive neuropsychological testing in all patients on average within 3 days around the MRI. Mini-Mental State Examination (MMSE) (Folstein et al., 1975), Parkinson Neuropsychometric Dementia Assessment (PANDA) (Kalbe et al., 2008) for overall cognition (part A) and depression (part B) as well as Consortium to Establish a Registry for Alzheimer's Disease (CERAD) (Fillenbaum et al., 2008) test battery, including verbal fluency, modified Boston Naming Test, Word List Learning, Word List Recall, and Word List Recognition were obtained from all patients (for outcomes see Table 1). Patients were classified as PD-CI according to level I of the new criteria of the Movement Disorder Society Task Force for mild cognitive impairment in PD (Litvan et al., 2012). This criterion was met when patients performed at least 1 standard deviation below the normative mean score in at least 2 cognitive domains within relevant cognitive tests including executive functions, attention, visuospatial abilities, memory, and language.

2.2. MRI data acquisition

"Resting-state" iFCMRI and a T1-weighted 3-D scan were acquired on a 3 Tesla MRI scanner (Magnetom Allegra (syngo MRA30), Siemens, Erlangen, Germany). Whole-brain iFCMRI at rest was performed using a BOLD sensitive T2*-weighted echo planar imaging sequence (repetition time/echo time [TR/TE] 2200 ms/30 ms, echo distance 0.49 ms, flip angle 80°, 36 transversal slices, isotropic resolution 3.5 mm, acquisition time 7:24 minutes). Participants were advised to stay motionless and relaxed with their eyes closed but to remain awake throughout the

Table 1
Characteristics for 53 subjects

Parameter	PD, all	Controls	p-value[a]	PD-CI	PD-CU	p-value[b]
Number, n	31	22	NA	17	14	NA
Gender, M/F	19/12	15/7	0.773	8/9	11/3	0.197
Age, y	71 (64–74)	68 (65–73)	0.598	72 (64–74)	70 (65–77)	0.650
Duration of disease[c], y	6 (4–13)	NA	NA	5 (4–13)	6 (4–9)	0.905
Hoehn and Yahr, score	3 (2–3)	NA	NA	3 (2–3)	2 (2–3)	0.657
UPDRS III[d], score	12 (8–14)	NA	NA	12 (9–18)	10 (5–13)	0.091
MMSE[e], score	28 (26–29)	30 (30–30)	<0.001	27 (26–28)	29 (28–30)	<0.001[#,†,‡]
PANDA[f], score	20 (18–25)	NA	NA	18 (13–20)	26 (23–27)	<0.001
PANDA (depression)[f], score	3 (0–6)	NA	NA	4 (0–6)	2 (0–6)	0.034
Duration of education, y	11 (10–13)	15 (13–16)	<0.001	11 (8–11)	11 (11–15)	<0.001[†,‡]
CERAD[g], total score	98 (78–97)	NA	NA	79 (74–88)	96 (92–100)	<0.001
LEDD[h], mg	380 (214–659)	NA	NA	360 (231–620)	475 (205–880)	0.565

Data are given as median (interquartile range).
Demographic and clinical variables between groups were compared using Fisher exact test for categorical variables (gender) and the Mann-Whitney U test or Kruskal-Wallis analysis of variances (ANOVA) on ranks for continuous variables.
Key: F, Female; M, Male; NA, not applicable; PD, Parkinson's disease; PD-CI, cognitively impaired PD patients; PD-CU, cognitively unimpaired PD patients.
[a] Comparison between all PD patients (PD-CI and PD-CU) and control subjects.
[b] Comparison between PD-CI, PD-CU patients, and control subjects or between PD-CU and PD-CI patients, as appropriate. Post hoc comparison: p < 0.05 for PD-CI versus PD-CU patients[#], PD-CI patients versus controls[†], and PD-CU patients versus controls[‡].
[c] Time since motor symptom onset.
[d] Unified Parkinson's disease rating scale (UPDRS III, motor assessment) (Fahn and Elton, 1987) assessed under antiparkinsonian medication (ON state).
[e] Mini-Mental State Examination (MMSE).
[f] Parkinson Neuropsychometric Dementia Assessment (PANDA).
[g] Consortium to Establish a Registry for Alzheimer's Disease (CERAD) total score corrected for age and education was calculated according to Chandler et al. (2005).
[h] Levodopa equivalent daily dose (LEDD) computed according to Tomlinson et al. (2010).