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

Martin Gorges, Hans-Peter Müller, Dorothée Lulé, LANDSCAPE Consortium, Elmar H. Pinkhardt, Albert C. Ludolph, Jan Kassubek

Department of Neurology, University of Ulm, Ulm, Germany

A R T I C L E   I N F O

Article history:
Received 9 October 2014
Received in revised form 22 December 2014
Accepted 23 December 2014
Available online 31 December 2014

Keywords:
Cognitive decline
Functional connectivity
Hyper-connectivity
Magnetic resonance imaging
Movement disorder
Networks
Resting-state

A B S T R A C T

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.

© 2015 Elsevier Inc. All rights reserved.

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
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 participant characteristics are summarized in Table 1. All subjects had no clinical history of psychiatric illness (except from cognitive deficits). According to neuropsychological assessment of all 53 participants, 3 subject groups for the iFC MRI 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” iFC MRI and a T1-weighted 3-D scan were acquired on a 3 Tesla MRI scanner (Magnemot Allegra (syngo MRA30), Siemens, Erlangen, Germany). Whole-brain iFC MRI 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 acquisition of the fMRI.

Table 1

<table>
<thead>
<tr>
<th>Parameter</th>
<th>PD, all</th>
<th>Controls</th>
<th>p-valueb</th>
<th>PD-CI</th>
<th>PD-CU</th>
<th>p-valueb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number, n</td>
<td>31</td>
<td>22</td>
<td>NA</td>
<td>17</td>
<td>14</td>
<td>NA</td>
</tr>
<tr>
<td>Gender, M/F</td>
<td>19/12</td>
<td>15/7</td>
<td>0.773</td>
<td>8/9</td>
<td>11/3</td>
<td>0.197</td>
</tr>
<tr>
<td>Age, y</td>
<td>71 (64–74)</td>
<td>68 (65–73)</td>
<td>0.598</td>
<td>72 (64–74)</td>
<td>70 (65–77)</td>
<td>0.650</td>
</tr>
<tr>
<td>Duration of disease, y</td>
<td>6 (4–13)</td>
<td>NA</td>
<td>NA</td>
<td>5 (4–13)</td>
<td>6 (4–9)</td>
<td>0.905</td>
</tr>
<tr>
<td>Hoehn and Yahr, score</td>
<td>3 (2–3)</td>
<td>NA</td>
<td>NA</td>
<td>3 (2–3)</td>
<td>2 (2–3)</td>
<td>0.657</td>
</tr>
<tr>
<td>UPDRS III, score</td>
<td>12 (8–14)</td>
<td>NA</td>
<td>NA</td>
<td>12 (9–18)</td>
<td>10 (5–13)</td>
<td>0.091</td>
</tr>
<tr>
<td>MMSE, score</td>
<td>28 (26–29)</td>
<td>30 (30–30)</td>
<td>&lt;0.001</td>
<td>27 (26–28)</td>
<td>29 (28–30)</td>
<td>&lt;0.0016,1</td>
</tr>
<tr>
<td>PANDA, score</td>
<td>20 (18–25)</td>
<td>NA</td>
<td>NA</td>
<td>18 (13–20)</td>
<td>26 (23–27)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PANDA (depression), score</td>
<td>3 (0–6)</td>
<td>NA</td>
<td>NA</td>
<td>4 (0–6)</td>
<td>2 (0–6)</td>
<td>0.034</td>
</tr>
<tr>
<td>Duration of education, y</td>
<td>11 (10–13)</td>
<td>15 (13–16)</td>
<td>&lt;0.001</td>
<td>11 (8–11)</td>
<td>11 (11–15)</td>
<td>&lt;0.0011</td>
</tr>
<tr>
<td>CERAD, total score</td>
<td>98 (78–97)</td>
<td>NA</td>
<td>NA</td>
<td>79 (74–88)</td>
<td>96 (92–100)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LEDD, mg</td>
<td>380 (214–659)</td>
<td>NA</td>
<td>NA</td>
<td>360 (231–620)</td>
<td>475 (205–880)</td>
<td>0.565</td>
</tr>
</tbody>
</table>

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.

* 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*.

* Time since motor symptom onset.

Unified Parkinson’s disease rating scale (UPDRS III, motor assessment) (Fahn and Elton, 1987) assessed under antiparkinsonian medication (ON state).

* Mini-Mental State Examination (MMSE).

* Parkinson Neuropsychometric Dementia Assessment (PANDA).

* 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).

* Levodopa equivalent daily dose (LEDD) computed according to Tomlinson et al. (2010).
Fig. 1. Statistically significant group effects in intrinsic functional connectivity networks (ICN), illustrated as representative orthogonal slices for each comparison: (A) PD-CU versus controls, (B) PD-CI versus controls, and (C) PD-CI versus PD-CU. Results are displayed in Montreal Neurological Institute (MNI) stereotaxic space (cubic 1 mm grid) overlaid on the averaged MPRAGE image (from all 53 subjects); slice positions are indicated by MNI coordinates in each first panel and are identical for all panels. Each subpanel depicts 5 pairs of sagittal (upper rows) and axial (lower rows) slices, illustrating Student t statistics of pairwise group comparison for each ICN. Student t statistic maps show the corresponding
“resting-state” sequence. High-resolution 3-D whole-brain T1-weighted scans were acquired using magnetization-prepared gradient echo image sequence (TR/TE 2500 ms/432 ms, echo distance 10.8 ms, flip angle 7°, 192 sagittal slices, isotropic resolution 1 mm, acquisition time 9:22 minutes).

2.3. MRI data processing

The iFCMRI data processing procedure was performed by use of the Tensor Imaging and Fiber Tracking software package (Müller and Kassubek, 2013; Müller et al., 2007; Unrath et al., 2010), the
utilized fICMRI algorithms have been described previously (Gorges et al., 2014). In brief, preprocessing of the fICMRI data included (1) head motion-correction; (2) resampling to a cubic 1 mm grid; (3) deformation to MNI stereotaxic space (Brett et al., 2002); (4) spatial smoothing (7 mm full-width at half maximum Gaussian blur filter); (5) linear detrending (Friston et al., 2004); and bandpass filtering (0.01 Hz $< f < 0.08$ Hz); and (6) removing the first 15 of the 200 volumes (Song et al., 2011). Deformation to MNI stereotaxic space was applied by using a study-specific template together with landmarks defined on the individual imaging data computed from all patients and control subjects ($N = 53$) (Gorges et al., 2014; Müller et al., 2007b). This preprocessing step thus additionally addresses possible gray matter atrophy as a confounding factor on functional connectivity analysis.

Then, 10 large scale correlation maps were computed (Beckmann et al., 2005; Di Martino et al., 2008; Greicius et al., 2003; Laird et al., 2011; Smith et al., 2009; Van Dijk et al., 2010) in a seed-based approach (Gorges et al., 2014), that is, (1) DMN (voxel-seed: posterior cingulate cortex; MNI coordinates: $0, 0, 55$); (2) left lateralized frontoparietal control (inferior parietal lobule; $-50, -52, 49$); (3) right lateralized frontoparietal control (inferior parietal lobule; $50, 54, 49$); (4) motor (motor cortex; $-27, -27, 68$); (5) visuospatial (extrastriate cortex; $47, -72, 15$); (6) dorsal attention (frontal eye field; $30, 0, 9$); (7) ventral attention (ventral striatum; $11, 13, 0$); (8) basal ganglia-thalamic (caudate; $18, 2, 20$); (9) brainstem (midbrain; $2, -31, 20$); and (10) cerebellar (cerebellum; $32, -79, -34$). The extracted time-courses of the seed-voxels were correlated with the time series of all other voxels across the whole brain. The resulting brain maps ($r$-values) were transformed voxelwise to Z-statistics using Fisher rtoz transformation.

2.4. Statistical analysis

Demographic and clinical data were described as nonparametric statistics using the median (and the interquartile range). Statistical contrasts between groups (PD-CI, PD-CU, control subjects) were performed by use of the Kruskal-Wallis nonparametric 1-way analysis of variances, in the event of significance followed by a Mann-Whitney $U$ test to detect differences between 2 groups. These analyses were performed using the “Statistics Toolbox” provided by MATLAB (The Mathworks Inc, Natick, MA, USA). All tests were 2-sided, and a $p < 0.05$ was considered as significant.

The 2-sided parametric Student $t$ test for unequal variances was used to test voxelwise differences between 2 groups in each of the 10 ICN; $p < 0.05$ indicated statistical significance. The resulting $p$-values were corrected for multiple comparisons using the false discovery rate approach (Genovese et al., 2002) at 5% level. Further correction for multiple comparisons for reduction of the alpha error was performed by a parametric correlation-based clustering procedure that discarded isolated clusters not exceeding the minimum size of 343 voxels at cubic 1 mm resolution according to Unrath et al. (2010). These thresholds, that is, significance level for false discovery rate correction and minimum voxel size for clusterwise correction, resulted from 10 independent Monte Carlo simulations before the statistical contrast for each of the 10 ICN between groups. Finally, the results were masked using a binary network mask to prevent statistical effects outside the ICN. Three masks for pairwise group contrasts were created as follows: set all voxels to “one” satisfying $|z(r)| > 0.4$ in any of the averaged ICN of either 2 groups to be compared and “zero” otherwise. The threshold of 0.4 (Hyde and Li, 2014) represents a good balance threshold between ICN voxels and nonconnected voxels and resulted in brain maps that closely resembled those reported by other studies, that is, Smith et al. (2009).

Data were additionally tested for a possible confounding influence of the control subjects’ higher education level by regressing out the years of education. Regression analysis was performed on the z$(r)$ brain maps for each ICN using the general linear model. The resulting z$(r)$ brain maps from the regression were used for further statistical group interference as described previously.

Spearman rank order correlation was used to detect possible relationships in PD-CU and PD-CI patients between cognitive scores (i.e., MMSE, PANDA part A, CERAD total scores) and clusters indicating significantly altered iFC within ICN. Correlations were tested at $p < 0.05$ (familywise error corrected for multiple comparisons).

3. Results

3.1. Identification of 10 ICNs

As shown in Supplementary Fig. 1, all 10 coherent spatial brain maps were identified for control subjects (left panels), PD-CU patients (center panels), and PD-CI patients (right panels). The 10 ICNs, as computed by use of the seed-based approach, were similar to previous ICA-based studies (Laird et al., 2011; Smith et al., 2009).

3.2. Increased functional connectivity in cognitively unimpaired PD

In the PD-CU sample, significantly stronger activity patterns in the sense of hyperconnectivity, as compared with control subjects, were observed in the DMN, left and right frontoparietal control, ventral attention, motor, basal ganglia-thalamic, and brainstem ICN (Fig. 1). Notably, the significant clusters were predominantly localized “outside” the controls’ ICN areas indicating network expansions rather than showing up as stronger iFC between core nodes of the respective ICN—see the DMN in Fig. 2 as an example. No effect was observed in the visual, dorsal attention, and cerebellar ICN when comparing PD-CU patients and control subjects.

3.3. Decreased functional connectivity in cognitively impaired PD

The connectivity pattern of the ICN in PD-CI patients indicated decreased iFC (hypoconnectivity) in comparison with controls, that is, contrasting PD-CI patients and controls resulted in significantly decreased iFC within the DMN, the motor network, and the dorsal attention systems (Fig. 1). Decreased iFC was preferentially observed in brain structures associated with the DMN including the long-distance midline cores and the hippocampus. These clusters were localized in areas known to serve as core nodes of the DMN (Fig. 2), thus suggesting a reduced functional coupling of those regions in PD-CI patients compared with control subjects. There were no regions within the frontoparietal control, visual, ventral attention, basal ganglia-thalamic, brainstem, and cerebellar ICN that displayed altered iFC in PD-CI patients compared with control subjects.

3.4. Cerebellar and visuospatial ICN

The connectivity pattern in the visuospatial and cerebellar ICNs was similar in all the investigated groups (Supplementary Fig. 1). No effect was observed in a pairwise comparison of the groups (PD-CI, PD-CU, and control subjects).

3.5. Cognitive decline in PD paralleled a reduction in functional connectivity

The comparison between both patient groups, that is, PD-CI versus PD-CU, demonstrated significantly decreased iFC preferentially in the DMN, but also in the motor, dorsal and ventral attention...
as well as the basal ganglia-thalamic ICN (Fig. 1). There were no regions within the bilateral frontoparietal control, visual, brainstem, and cerebellar ICN that displayed altered iFC when contrasting PD-CI versus PD-CU.

3.6. Regression of cognitive reserve

The results showed only marginal differences when using years of age as a regressor to minimize the possible influence of cognitive reserve. This indicates that the higher educated control subjects most probably did not bias our results.

3.7. Correlations between neuropsychological scores and functional connectivity

In PD-CI and PD-CU patients, respectively, cognitive scores (i.e., MMSE, PANDA part A, CERAD total) did not correlate with any of the iFC measures.

4. Discussion

In this controlled “resting-state” fMRI study, we assessed brain functional connectivity in cognitively impaired and unimpaired PD patients as neuropsychologically classified according to the recently proposed guidelines (Litvan et al., 2012). Increased correlations of BOLD fluctuations (hyperconnectivity) were demonstrated in PD patients without cognitive deficits, whereas decreased connectivity (hypoconnectivity) was observed after cognitive decline. In particular, decreased iFC was observed preferentially between core nodes of the DMN, in association with declined cognitive capabilities in PD. These findings suggest that recruiting additional resources may be the initial response to the pathologic process in PD before the (additional) resources are exhausted and iFC between core nodes diminishes as a consequence of critical cell loss.

4.1. Increased functional connectivity in cognitively unimpaired PD patients: response to maintain cognitive performance

Increased iFC was consistently found in several ICNs beyond the sensorimotor networks in cognitively unimpaired PD patients. This hyperconnected state in PD-CU patients might be interpreted as stronger synchronous BOLD fluctuations of the observed clusters (Mevel et al., 2011). A straightforward explanation of increased iFC is a compensatory or adaptive response to disease-related pathology (Douaud et al., 2011; Mevel et al., 2011). Abnormal, tightly correlated BOLD fluctuations could also be associated, however, with some disease-specific pathologic processes as suggested by Douaud et al. (2011); these authors proposed a loss of the inhibitory influence as a possible cause for increased iFC attributable to the underlying pathologic process in patients with amyotrophic lateral sclerosis. Following this hypothesis, a “system failure” might result from a pathologic firing pattern in a “denial-of-service” fashion, that is, brain areas excessively communicating with each other are no longer capable of functional interaction with other structures. This statement is consistent with the notion that dynamic up and downregulation of ICNs activity may be crucial for normal brain functioning (Leech and Sharp, 2014). However, this assumption may not be sufficient to explain hyper-iFC in PD: first, hyper-iFC appeared to diminish toward decreased iFC in PD-CI patients; hence, the relationship of iFC within disease progression in PD appears to be negative. Second, GABA-ergic cell degeneration is not prominent compared with dopaminergic cell loss in PD (Braak and Del Tredici, 2008). Third, clusters showing increased iFC in PD-CU patients were predominantly localized “outside” the controls’ brain maps, indicating a network expansion. This may considerably support the notion of allocating additional resources as observed in other neurodegenerative disorders (Heimrath et al., 2014). The ability to recruit capacities of networks that are not engaged in the respective function is related to the concept of cognitive reserve (Stern, 2002). Fourth, evidence has emerged that antiparkinsonian medication (e.g., L-DOPA) significantly enhances iFC in PD and contributes to the reorganization of functional networks (Prodohl et al., 2014). Finally, structural damage does not seem to manifest in PD-CU patients as indicated by Agosta et al. (2014) who compared structural connectivity by DTI in cognitively unimpaired PD patients with control subjects and showed that atonic connections remain intact in PD-CU patients.

Taken together, the observed widely distributed hyperconnectivity pattern pointed toward a largely distributed ICN reorganization as the initial response to ongoing cell loss (Hillary et al., 2015) that may be partly attributable to antiparkinsonian treatment. Dopaminergic drugs, typically used to treat patients with PD, enhance functional coupling of attention-related networks (Dang et al., 2012) and may, therefore, facilitate the functional reorganization as observed here in PD-CU patients to maintain “normal” cognitive performance. This interpretation, however, remains speculative because medication was not controlled for.

Additional cognitive resources may be allocated in reorganizing functional networks by bypassing affected regions in a “more-withless” fashion until the neuronal reserve is exhausted (Mevel et al., 2011). In addition, it can be hypothesized that ongoing functional remapping accompanies the spreading of the pathologic process until the onset of axonal fiber damage: for instance, a hyperconnectivity state in Alzheimer’s disease was consistently reported to reflect adaptive changes as an attempt to maintain cognitive performance and was found before the Alzheimer’s disease-related symptoms of cognitive decline (Mevel et al., 2011; Stern, 2012). Likewise, compensatory processes may also be present in PD (Hacker et al., 2012; Wu and Hallett, 2013), however, the interpretation of increased synchronicity in terms of the potential functional consequences has not been fully understood and its explanation appears to be disease specific.

4.2. Hypoconnectivity state may be linked to cognitive decline in PD

In PD-CI patients, one of the main findings was a decoupling of DMN-related brain regions along the midline cores and the hippocampus from the posterior cingulate cortex (PCC). Disrupted functional integration within the DMN is believed to be linked to cognitive deficits as suggested in many previous studies (Greicius et al., 2003; He et al., 2007; Lehmann et al., 2013; Mevel et al., 2011). In Alzheimer’s disease, hypometabolism in the PCC is related to the mental status (Buckner et al., 2008), and the spreading of pathology (Jucker and Walker, 2013) remarkably resembles the pattern of the DMN (Buckner et al., 2005). Moreover, current theories suggest that the PCC is crucially involved in cognitive functions including memory consolidation, attention, and control of the balance between internal and external thoughts (Leech and Sharp, 2014). We have also observed decreased iFC along the midline cores within the DMN in nondemented PD patients (Gorges et al., 2013). These findings receive further support from DTI studies in mildly cognitively impaired PD patients who showed structural disruption between the midline cores but no global gray matter atrophy as assessed by voxel-based morphometry (Agosta et al., 2014). Moreover, in line with the present findings, Baggio et al. (2015) reported reduced iFC within the DMN and within the dorsal attention network in PD patients with mild cognitive impairment (Baggio et al., 2015) and, more generally, the
topological properties of brain networks to be altered when cognition declines in PD patients (Baggio et al., 2014). Although PD-CU patients were characterized by increased iFC, decreased iFC was demonstrated for PD-CI patients, in support of the hypothesis of a transient process from the hyper-to toward the hypoconnected state closely linked to cognitive decline.

4.3. Cerebellar and visuospatial networks in PD

The cerebellar and visuospatial ICNs revealed similar activity in all groups and served as reference networks. From the methodological point of view, this is of note because iFCMRI is sensitive to confounding factors which could be differentially present within groups (Buckner et al., 2013; Van Dijk et al., 2012). Thus, the pathologic process appears to spare the functional integration of the cerebellar and visuospatial networks. However, intact functional integration within the identified visuospatial ICN is apparent at odds with the reported broad spectrum of visual symptoms such as visuospatial dysfunctions or impaired color discrimination in PD (Kassubek et al., 2013; Sauerbier and Chaudhuri, 2013). Pronounced myelinated nerve cells and short local axonal circuits within the primary sensory fields were found to be resistant to the selective neuropathologic process in PD (Braak and Del Tredici, 2009). A straightforward conclusion from the intact iFC within the visuospatial network is, thus, that the functional integration of primary and associated visual areas may not be responsible for these clinical observations. The iFC correlate of the clinical observations of visuospatial abnormalities in PD may be more likely to result from an impaired functional integration of other brain regions outside the visuospatial ICN, promoting the association areas as a critical relais with other networks. This observation is in agreement with a recently published fMRI study in PD patients that shows an impaired dynamic interplay between DMN connectivity and brain areas involved in bottom-up visual processing (Rektorova et al., 2014).

No alteration of cerebellar iFC was demonstrated although there is evidence for the cerebellum to be involved in the pathophysiology in PD both in a compensatory and pathologic manner, as summarized by Wu and Hallett (2013). These authors attributed cerebellar dysfunction primarily to abnormal dopaminergic mediation by the basal ganglia. This conclusion could be in accordance with our observation that the cerebellar network, mainly covering the cerebellum itself, revealed a normal iFC pattern. The functional communication with other brain areas remains to be addressed in future studies. Again, an explanation emerges from the neuro-pathologic findings by Braak and Del Tredici (2009) who reported lesions in the sensory association areas that manifest in the late stages of the disorder. Hubs of the cerebellar circuit are connected by long-axoned nerve cells that are resistant or become involved, in some instances, in the final stages of the disease (Braak et al., 2006). Taken together, the present findings in association with literature may suggest impaired functional integration within ICN rather than a cerebellar dysfunction itself.

4.4. PD-specific functional connectivity and its link to cognitive state

A hypothetical model of iFC alterations during progression in PD proposes that iFC alterations might be considered a possible adaptive mechanism until the peak of available additional resources is reached. This hypothesis is in general agreement with others (Hillary et al., 2015). As the disease progresses, a critical loss of resources because of ongoing cell degeneration may result in gradually functional decoupling of core hubs (Brier et al., 2014) so that higher cognitive functions begin to decline. Moreover, it might be speculated that alterations of iFC in the presymptomatic phase could possibly form the basis for the development of an fCMRI biomarker. Autopsy-controlled studies provide ample evidence for PD-associated pathology before motor symptoms become recognizable (Braak et al., 2003; Del Tredici et al., 2002), and there has been growing awareness that some nonmotor symptoms manifest before the cardinal motor symptoms become evident (Chaudhuri et al., 2011). The intrinsic functional architecture of the DMN appears to be crucially targeted by the PD-related pathologic process in PD-CU and PD-CI patients. Our findings support the proposed concept of the potentially predictive nature of the DMN (Sandrone, 2012). Following this concept, the brain’s default mode cerebral connectivity in the “resting” brain may predict behavioral performance in large scale studies (Sandrone, 2013).

However, the correlation analysis between regions associated with abnormal iFC and cognitive scores yielded no significant relationship in both PD-CI and PD-CU patients. The lack of correlations might be because of the limited sample size on the one hand, and on the other hand, this constellation in PD-CU patients might be interpreted as further evidence for adaptive changes because increased iFC was demonstrated as network expansions that appear to be independent of the performance in overall cognition scores. Notably, Agosta et al. (2014) did also not observe any correlation in cognitively impaired PD patients between overall cognitive scores and white matter damage.

4.5. Limitations of the study

The study is limited by the relatively small sample size of PD patients and control subjects. However, this limitation is partly caused by the quality control of the phenotype definition including the broad spectrum of clinical, neuropsychological, and imaging assessment, which in turn can be considered as a major strength of the study. Moreover, larger sample sizes in PD-associated dementia patients may allow us to distinguish these patients as a third subgroup which also might be of great interest to study iFC alterations underlying the development of PD-associated dementia. Another limitation refers to the subjects’ education level where the control group was higher educated compared with the PD patients. The level of education is generally associated with a higher cognitive reserve and is thought to provide the ability to recruit additional resources to compensate for brain damage (Stern, 2002). A higher brain reserve capacity may accompany intellectual performance that in turn was reported to be associated with an increased functional integration based on more efficient utilization of brain networks (Van den Heuvel et al., 2009). Moreover, the nigrostriatal dopaminergic system contributes to cognitive performance and PD-related executive deficits were shown to be linked to altered cortical-subcortical functional processing (Lebedev et al., 2014). In addition, this was a cross-sectional study in 2 PD patient samples in different disease stages because cognition is known to decline later in the course of PD.

The patients in this study were all medicated because the patients should not be withdrawn from their medication for ethical reasons, and fCMRI studies in untreated or OFF-mediated patients face a challenge because of the possibility of discomfort-induced motion artefacts (Van Dijk et al., 2012). It has to be considered that there is ample evidence that antiparkinsonian medication has an effect on iFC in patients with PD (Prodoehl et al., 2014). Increased connectivity was described in the sensorimotor network in PD patients taking antiparkinsonian medication (Esposito et al., 2013), and such regionally increased connectivity in PD patients tested when taking antiparkinsonian medication appears to be a consistent finding (Prodoehl et al., 2014). Specifically, deep brain stimulation as an invasive treatment and
dopamine as a pharmacologic treatment in PD appears to increase iFC (Mueller et al., 2013). Taken together, antiparkinsonian treatment seems to modulate the architecture of cortico-subcortical network connectivity (Cole et al., 2013), and these findings are in a general line of agreement with our current results. The lack of a comparison of medication ON versus OFF state may, thus, be counted as a limitation. However, our aim was to investigate the functional substrate of “normal” and impaired cognition in PD as they manifest in patients under the influence of their regular medication. Because medication dosage could not be controlled for (because of clinical reasons), our study can be considered a “real life” investigation in patients in different disease stages with their regular medication. Because the loss of functional connectivity in demented patients was demonstrated, it seems safe to conclude that dopaminergic medication could not prevent the patients from this functional decrease. However, it has to be held that the possible role of antiparkinsonian treatment in this process was not disentangled.

5. Conclusion

The cognitively unimpaired status in PD appears to be characterized by widespread increased iFC (hyperconnectivity) that can be considered as an early adaptive response by recruiting additional resources preceding manifest cognitive deficits. These signs of altered functions may occur in the absence of detectable structural white matter damage so that functional may “drive” structural damage in PD. The PD-related pathologic process in cognitively unimpaired patients resulted in global topographical remapping and significant expansion of higher function networks. This reorganization could be interpreted as compensatory mechanisms, that is, an attempt to maintain cognitive performance as long as possible. Decreased iFC in PD-CI patients, preferentially between core nodes of the DMN, that is, along the midline cores and the hippocampus, appears to indicate a hallmark in iFCMRI for cognitive deficits that may gradually lead to PD-associated dementia.

These results provide a framework for future studies in PD utilizing iFCMRI as a possible, noninvasive neuroimaging marker. Such studies might include the identification of different neuropathological PD-stages on the basis of brain connectivity reflecting the cognitive dysfunctions experienced by PD patients. Models of functional and structural integration in the human brain may enhance the pathophysiological understanding of PD in the future. These studies should preferably focus on the brain’s default mode network which appears to be crucially involved in cognition and to become targeted by the PD-related pathologic process.

Disclosure statement

All authors declare no conflicts of interest.

Acknowledgements

Data were generated within the LANDSCAPE study (representatives: Prof. Dr R. Dodel, Prof. Dr D. Berg, Prof. Dr R. Hilker-Roggendorf, Prof. Dr E. Kalbe, Prof. Dr J. Kassubek, Prof. Dr B. Mollenhauer, Prof. Dr J. Schulz, Dr A. Spotte, Prof. Dr A. Storch, Prof. Dr H.U. Wittchen). The LANDSCAPE study is part of the Competence Network Degenerative Dementias (KNDD) which was funded by the German Federal Ministry of Education and Research (project number 01GI1008C). The authors thank S. Fuchs for the MRI data acquisitions as well as D. Hueske and S. Schile for their administration assistance.

Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.neurobiolaging.2014.12.026.

References


e


