

Default Mode Network and Extrastriate Visual Resting State Network in Patients with Parkinson's Disease Dementia

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Key Words

Default mode network · Extrastriate visual resting state network · Parkinson's disease dementia · Functional connectivity

Abstract

Aims: Using fMRI, we evaluated the default mode network (DMN) and the extrastriate visual resting state network (ESV-RSN) in 14 patients with Parkinson's disease dementia (PDD) as compared with 18 patients with Parkinson's disease (PD) without dementia and 18 healthy controls (HC). **Methods:** We analyzed the seed-based functional connectivity of both resting state data and deactivations during a visual complex scene-encoding task. **Results:** Using the posterior cingulate cortex/precuneus as a seed for the DMN analysis, we observed significant decreases of connectivity in the right inferior frontal gyrus in PDD as compared to PD and HC. Using the caudate nucleus as a seed for the ESV-RSN analysis, we found significant decreases of connectivity in the left and right inferior occipital gyrus in PDD as compared to HC. **Conclusion:** Differences in functional connectivity patterns between PDD and PD/HC were observed in areas known to be engaged in stimulus-driven reorienting of attention and in visual processing.

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Introduction

Dementia among patients with Parkinson's disease (PDD) has an average prevalence of 31% and a cumulative prevalence approaching 80% [1]. Using functional imaging, both posterior cortical and frontal hypometabolism and severe cholinergic dysfunction in the same cortical regions have been demonstrated in Parkinson's disease (PD) patients with cognitive impairment/dementia as compared with cognitively normal PD subjects [2, 3]. Occipital hypoperfusion in PD was associated with impaired cortical visual processing [4], i.e. with the function that is typically compromised in both PDD and dementia with Lewy bodies (DLB) [5]. The corticostriatal projections from the occipitotemporal area terminate in the tail and genu of the caudate nucleus (CN) and form the extrastriate visual pathway [6].

Recently, many studies have examined so-called 'resting state' networks (RSNs). Their function is not primarily to respond to external stimuli but rather to prepare reactions to these stimuli. They are characterized by organized basal activity during rest or passive visual fixation and by low-frequency signal fluctuations. To date, several RSNs have been consistently reported, e.g. including the primary motor, visual and auditory network, the

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Table 1. Demographic and cognitive data

	Age	ACE	MMSE	CVSET	DI	LED
HC						
Average values	60.89	94.17	29.50	75.65		
SD	6.67	3.49	0.71	7.48		
Min	46	89	28	55.83		
Max	77	100	30	88.33		
PD						
Average values	63.50	93.94	29.56	74.12	4.44	696
SD	9.07	3.67	0.78	9.70	2.83	430.35
Min	44	89	27	60.00	1	0
Max	84	100	30	90.00	9	1,500
PDD						
Average values	72.36	69.46	23.23	41.85	9.64	925.54
SD	5.88	8.67	2.59	12.05	6.58	412.00
Min	59	45	18	15.83	1	0
Max	82	77	26	60.00	17	1,748

ACE = Addenbrooke's Cognitive Examination; MMSE = Mini-Mental State Examination; CVSET = complex visual scene-encoding task; DI = duration of illness (years); LED = daily levodopa-equivalent dose (mg/day).

extrastriate visual RSN (ESV-RSN), and the default mode network (DMN) [7, 8]. Functional connections of these RSNs tend to be strongly related to structural white matter connections, suggesting the existence of an underlying structural core of functional connectivity networks in the human brain [7].

The DMN is characterized by an ability to attenuate its activity during goal-directed behavior. When a cognitive task is performed, the DMN shows itself in 'deactivation'. It is assumed that the extent of deactivation or resting state activity reflects the ability of the brain to redirect its activity from internal to external, goal-directed processes, review past knowledge, and plan future behaviors [8]. Previous studies have documented that the DMN is disrupted in patients with specific neurodegenerative and psychiatric diseases, including Alzheimer's disease, PD and DLB [8–10]. In nonmedicated PD [9] and in DLB [10], disturbances in deactivations or functional connectivity pattern were observed specifically for the posterior cingulate cortex/precuneus (PCC/PCu) core region.

Our aim was to evaluate the DMN and the ESV-RSN using the seed-based functional connectivity analysis of resting state data or deactivations in patients with PDD as compared with PD without dementia and healthy controls (HC).

Methods

Participants

We enrolled 14 patients with PDD [1] (7 females, 7 males), 18 cognitively normal PD patients (8 females, 10 males) and 18 HC (10 females, 8 males) in the First Department of Neurology, Masaryk University and St. Anne's Hospital in Brno, Czech Republic (table 1). All participants were right-handed with at least 8 years of education and had normal vision. All PD/PDD patients were scanned on dopaminergic medication in the 'ON' state without dyskinesias. None of them had visual hallucinations during the experiment. Informed consent was obtained from each participant and the study was approved by the local ethics committee.

Task

The experiment comprised 2 parts: (1) a complex visual scene-encoding task (CVSET), and (2) resting state functional measurement. During the epoch-related task, the subjects were instructed to view the pictures showing complex scenes and try to remember them. Active epochs were intermixed with passive ones showing degraded images. The task has been described in detail elsewhere [11]. It was followed by a 15-min resting state measurement. Memory encoding was then tested outside the scanner by a recognition phase of the task. The relative achievement score (in %) was calculated as correctly marked images/all presented images.

Image Acquisition

Imaging was performed on a 1.5-tesla Siemens Symphony scanner. Two hundred and sixty functional images for the visual task were acquired using a gradient-echo echo-planar imag-

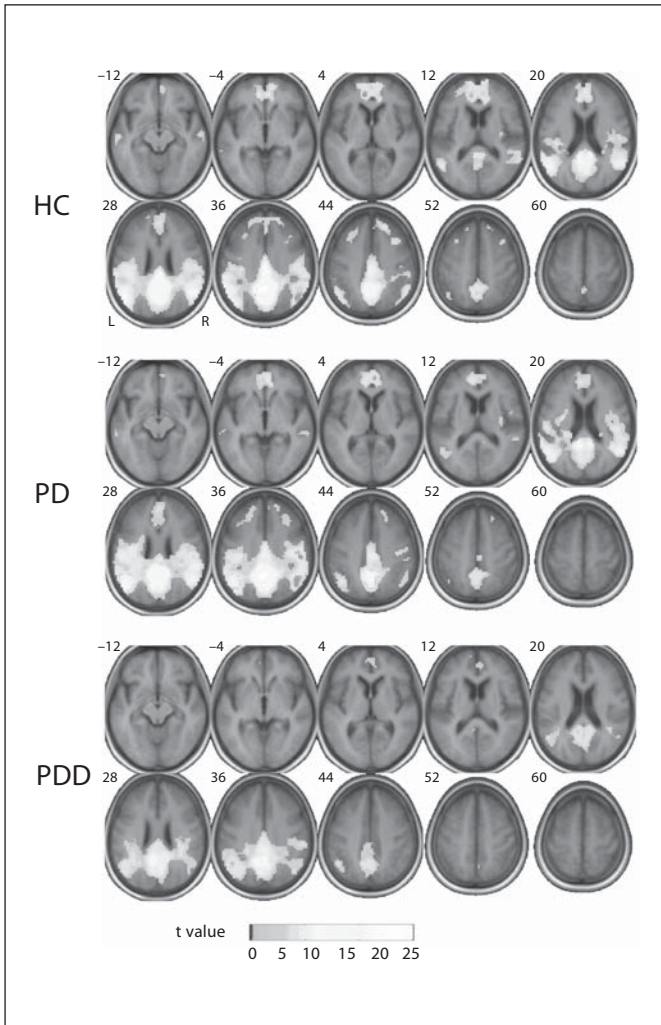


Fig. 1. The mean connectivity maps for each group by seeding the PCC/PCu (data from deactivation during CVSET performance).

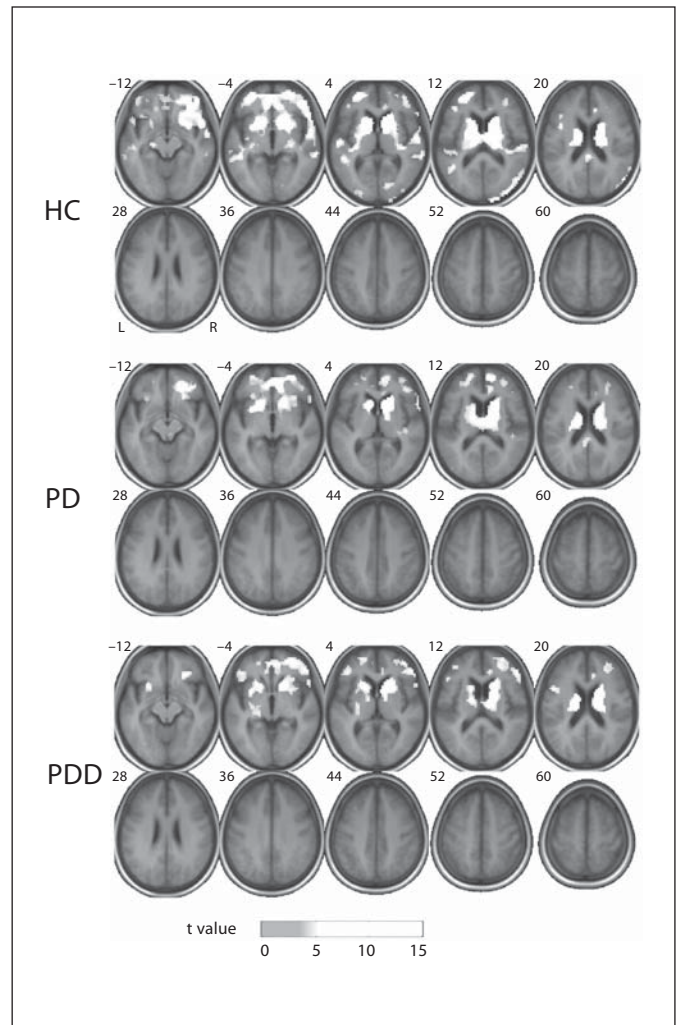


Fig. 2. The mean connectivity maps for each group by seeding the right CN (resting state data).

ing sequence: TR = 2,050 ms, TE = 50 ms, FOV = 240 mm, flip angle = 90°, matrix size 64 × 64, slice thickness = 5 mm, 20 transversal slices. Then 300 scans of the resting state were acquired using gradient-echo echo-planar imaging: TR = 3,000 ms, TE = 40 ms, FOV = 220 mm, flip angle = 90°, matrix size 64 × 64, slice thickness = 3.5 mm, 32 transversal slices per scan. The last high-resolution anatomical T₁-weighted images were acquired using a 3-dimensional sequence (160 sagittal slices, resolution 256 × 256 resampled to 512 × 512, slice thickness = 1.17 mm, TR = 1,700 ms, TE = 3.96 ms, FOV = 246 mm, flip angle = 15°).

Conventional Analysis of fMRI Data from the Cognitive Task (CVSET)

The SPM5 running under Matlab 7.6 (Mathworks Inc., USA) was used to analyze the fMRI data. The preprocessing consisted of realignment and unwarping of functional scans; norma-

lization with oversampling to 3 × 3 × 3 mm resolution to fit a standard anatomical space (MNI) and spatial smoothing using a Gaussian filter with a full width at half maximum of 8 mm. The effect of stimulation was computed using a general linear model as implemented in SPM5. The experimental stimulation time course was convolved with a canonical hemodynamic response function; t statistics maps were computed to assess the effects of activation or deactivation with respect to the active condition. Corresponding contrast files were then used in the second-level random effect analyses to assess the differences between the groups (two-sample t test). Age and gender were used as covariates. Group results were assessed using cluster level inference at p(FWE) < 0.05 at a height threshold of p(uncor) < 0.001.

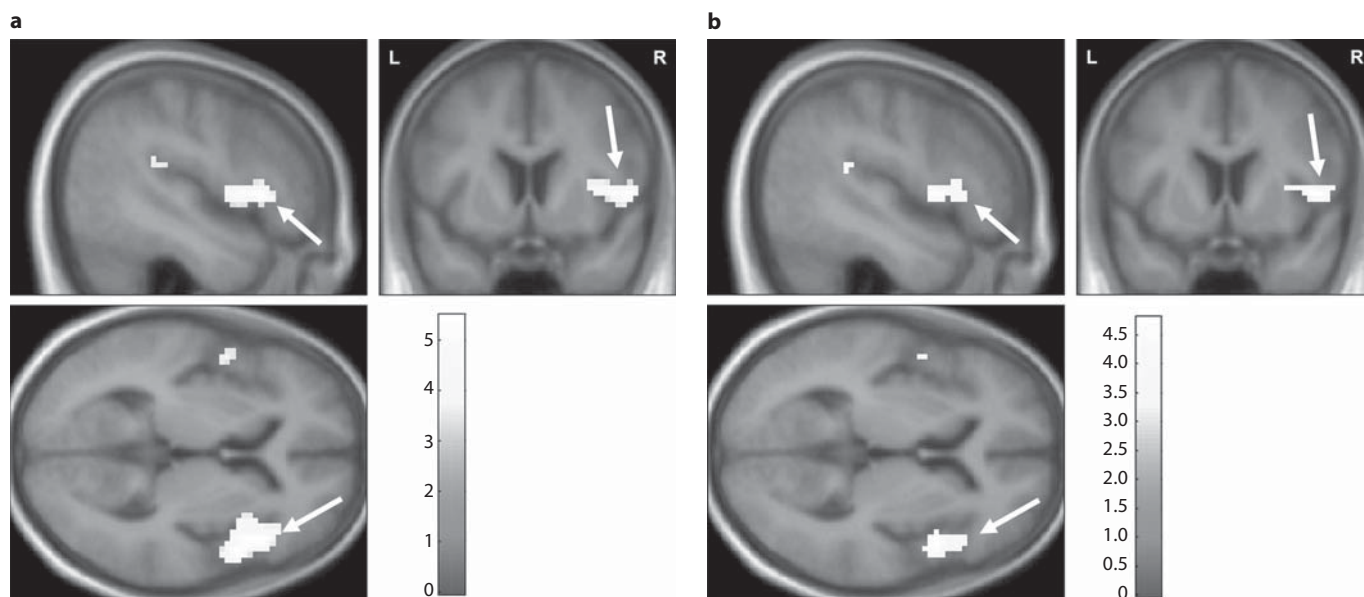


Fig. 3. Between-group differences in functional connectivity by seeding the PCC/PCu (data from deactivations). Arrow shows significantly decreased connectivity between PCC/PCu and the right IFG in PDD as compared with PD (a) and with HC (b).

Seed Correlation Analysis of fMRI Data from the CVSET and Resting State: DMN Evaluation

A coordinate of local maxima from a mean deactivation map across all participants was selected from the PCC/PCu (−6, −54, 33). Seed correlation analysis of data from the CVSET was performed as follows: subject-specific seed time series (eigenvalue from a sphere with a radius of 6 mm centered at the peak voxel), global signal time series, signal from white matter and cerebrospinal fluid, and 6 movement parameters time series were included in the general linear model design matrix. The second-level statistics were computed on contrast images related to correlation with the seed region. Age and gender were used as covariates. For resting state data, the preprocessing and the seed correlation analysis with the seed placed in the PCC/PCu were done in the same manner as for a cognitive task.

Seed Correlation Analysis of fMRI Data from the Resting State: ESV-RSN Evaluation

A coordinate for the right CN was defined using an anatomical mask created by the WFU Pickatlas, since we were interested in the whole CN including the tail [6]. We were interested in the right CN because of its lateralized involvement in spatial working memory [12] or retrieval of declarative memories [13]. These cognitive processes are thought to be engaged or triggered by the CVSET in addition to visual processing, and visuospatial and verbal memory [11]. Time series were extracted as eigenvalues from all voxels within the mask (seed region with an approx. size of 7.95 cm³), and we checked fMRI data separately in each participant to make sure that our seed had always been placed within the CN. We used the same preprocessing and seed correlation analysis approach as described for the DMN evaluation.

Results

Although we made efforts to match groups for age and gender, PDD patients were significantly older compared to PD patients/HC and had a longer disease duration compared to PD patients (table 1).

The mean connectivity maps for each group (PDD, PD and HC) by seeding the PCC/PCu and CN are shown in figures 1 and 2. We identified involvement of the PCC/PCu, anterior cingulate/medial prefrontal cortex, insulae, inferior parietal lobules, angular gyri, supramarginal gyri, the superior and middle temporal gyri, precentral gyri, and middle frontal gyri (all bilaterally) within the DMN in all groups. As for the CN-based functional connectivity analysis, we found engagement of the basal ganglia, thalamus, anterior cingulate/medial prefrontal cortex, posterior cingulate, insulae, frontal and temporal gyri (all bilaterally), and hippocampus mostly on the right side.

Using the PCC/PCu as a seed for the functional connectivity analysis of deactivations, we observed significant decreases of connectivity in the right inferior frontal gyrus (IFG; BA 45) in PDD as compared with PD (cluster peak at 48, 21, 3; cluster significance $p = 0.001$ FWE corrected, cluster size = 188 voxels; cluster level inference), and with HC (cluster peak at 48, 9, 3; cluster significance

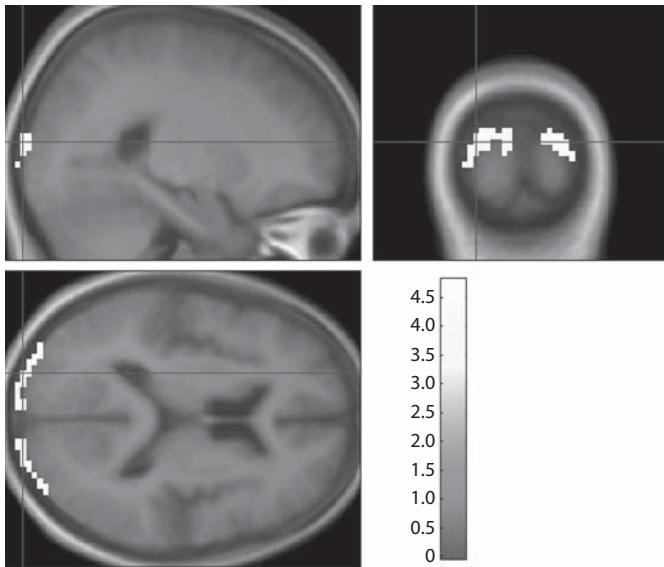


Fig. 4. Between-group differences in functional connectivity by seeding the right CN (resting state data).

$p = 0.015$ FWE corrected, cluster size = 77 voxels; cluster level inference) (fig. 3 a, b). Correlations between PCC/PCu and the right IFG changed the connectivity direction from positive correlations in PD and HC to anticorrelations in PDD. No difference was observed between PDD and PD/HC when the same seed was used for the functional connectivity analysis of resting state data.

The seed-based functional connectivity with a seed in the right CN was significantly decreased in the left and right inferior occipital gyrus (BA 18) in PDD as compared to HC (cluster peak at $-24, -102, 12$; cluster significance $p = 0.010$ FWE corrected, cluster size = 91 voxels; cluster level inference and cluster peak at $21, -102, 12$; cluster significance $p = 0.042$ FWE corrected, cluster size = 64 voxels; cluster level inference) (fig. 4). Correlations between the CN and the inferior occipital gyrus changed the connectivity direction from positive correlations in HC to anticorrelations in PDD.

Discussion

Clinical symptoms of PDD include fluctuation of attention and prominent visuoperceptual impairments [5]. Weissman et al. [14] explored the neural basis of momentary lapses in attention in HC by investigating trial-by-

trial relationships between brain activity and response time. They found that reduced activity in the right IFG predicted momentary lapses in attention. We found decreased connectivity between the same area and the core posterior node of the DMN in our PDD participants as compared with PD and HC. Since the right IFG is thought to participate in stimulus-triggered reorienting of attention [14], it might well be possible that the disturbed pattern of connectivity between the DMN and the right IFG underlies fluctuations of attention and might serve as a marker for PDD. Further longitudinal studies assessing attentional control and its fluctuations in PD will be needed to explore this possibility.

Another interesting observation was the decreased connectivity between the CN and the inferior occipital gyrus bilaterally in PDD as compared to HC. CN and inferior occipital gyrus constitute the core regions of the ESV-RSN and are thought to be involved in visual processing [6]. Visuoperceptual impairments are again characteristic for parkinsonian dementias [5]. In the study by Galvin et al. [10], cases with DLB had decreased positive connectivity between the DMN and secondary visual cortices as compared with HC. Disrupted connectivity of the inferior occipital gyrus may be caused by either hypometabolism/hypoperfusion, atrophy, and/or by cortical cholinergic dysfunction of this area [2–5]. Further studies are needed to confirm our results and reveal pathophysiological mechanisms that may underlie the observed changes.

Conclusion

In PDD as compared with PD/HC, we demonstrated significant differences in patterns of seed-based functional connectivity in areas that have been engaged in reorienting of attention toward behaviorally relevant stimuli and visual processing, i.e. in cognitive functions typically affected in PDD. Measurements of functional connectivity within the RSNs can potentially shed further light on neuroanatomic connections and pathophysiological mechanisms that distinguish PDD from PD.

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