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Neural substrates of excessive daytime sleepiness in early drug naïve Parkinson's disease: A resting state functional MRI study

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ABSTRACT

Introduction: Excessive daytime sleepiness (EDS) is a common non-motor symptom in Parkinson's disease (PD), but its neuropathology remains elusive due to the limited studies and the inclusion of medicated patients. This current study examined the neural substrates of EDS in drug naïve PD patients.
Methods: A total of 76 PD patients in the early disease stages were recruited; 16 of them had EDS, while the remaining 60 did not. Resting state functional magnetic resonance imaging (rs-fMRI) was used to determine group differences (patients with EDS vs. patients without EDS) in spontaneous neural activity indicated by regional homogeneity (ReHo). Additionally, functional connectivity (FC) of the regions showing group differences in ReHo with the entire brain was performed.
Results: ReHo analysis controlling for gray matter volume, age, gender, general cognition, depression, postural instability gait difficulty, and rapid eye movement sleep behavior disorder showed decreased ReHo in the left cerebellum and inferior frontal gyrus, but increased ReHo in the left paracentral lobule in PD-EDS patients, compared with patients without EDS. FC analysis controlling for the same variables as in the analysis of ReHo revealed that the three regions showing ReHo differences had decreased FC with regions in the frontal, temporal, insular and limbic lobes and cerebellum in PDs with EDS.
Conclusion: While decreases in ReHo and FC were found, increases in ReHo were also noted, implying both neural downregulation and compensatory mechanisms in early PD patients with EDS. Longitudinal studies are warranted to clarify the long-term impact of EDS in PD.

1. Introduction

In Parkinson's disease (PD), more attention has recently been given to non-motor symptoms due to their impact on quality of life. Excessive daytime sleepiness (EDS) is one of the significant non-motor concomitants of Parkinson disease (PD), characterized by inappropriate and undesirable sleepiness during waking hours [1]. Up to 50% of patients are affected by this symptom [1], suggesting higher prevalence in PD patients than in healthy controls [2]. Previous studies have identified the associated factors of EDS, including rapid eye movement (REM) sleep behavior disorder (RBD) [3], cognitive impairment [4,5], the postural instability/gait difficulty (PIGD) motor subtype, and depression [6].

With the advancement of neuroimaging techniques, there have been several studies [7–12] on the neuropathological mechanisms of EDS in PD with conflicting results. Using T1-weighted MRI, two studies revealed that PD patients with EDS (PD-EDS) showed decreased gray matter volume (GMV) in the cortical and subcortical areas, including the cerebellum and insula, as opposed to patients without EDS [7,8]. However, another study reported that PD-EDS patients had more volume of bilateral hippocampus and parahippocampal gyri, compared to patients without EDS [9]. A study using diffusion tensor imaging (DTI) techniques indicated compromised white matter connectivity mainly in tracts connecting with the frontal and parietal cortices in patients with EDS [9], but another DTI study found reduced connectivity in only the fornix in patients with EDS, compared to patients without EDS [10].

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Likewise, prior work with single-photon emission computed tomography (SPECT) showed both increased and decreased cerebral metabolic activities in the temporal, parietal, and nigrostriatal regions in patients with EDS, compared to patients without EDS [11]; however, contradictory findings were noted [12]. The discrepancies may be due to different imaging modalities and analytical approaches (i.e., whole brain vs. region of interest). Additionally, all previous studies recruited medicated patients, which may have confounded the results [2].

Previous studies using pre-selected seed-based resting state functional MRI (rs-fMRI) to study EDS in healthy individuals have shown a negative association between EDS and functional connectivity (FC) in the thalamocortical and default mode networks (DMN) [13,14]. Rs-fMRI is a non-invasive imaging technique that can provide information about large-scale neural networks by identifying correlated neural activity during a resting state [15]. Although various imaging techniques have been employed in previous studies, there are no known published works using rs-fMRI to characterize the spontaneous neural functional features of EDS with unmedicated PD patients. It therefore remains unknown whether PD patients with EDS might have similar alterations of neural activity, as observed in previous studies with healthy individuals [13,14].

Building on previous observations on EDS of healthy individuals and PD patients, we used rs-fMRI to examine whether EDS in PD is associated with functional alterations in the frontal, temporal, parietal and subcortical regions (e.g., hippocampus, putamen, and cerebellum). We first unbiasedly analyzed the whole-brain neural activity indicated by regional homogeneity (ReHo, see Methods) [16], and then focused on functional connectivity of the regions showing ReHo differences between groups with the entire brain.

2. Methods

2.1. Participants

All PD patients in the current study were participants of the Parkinson's Progression Markers Initiative (PPMI; an observational, international multicenter study) [17]. The study was approved by the institutional review board of all participating sites. Written informed consent was obtained from all patients before study enrollment. To be enrolled into the PPMI study, all patients were required to fulfill the following criteria: 1) met the standard diagnostic criteria for PD, 2) diagnosed within 2 years before the initial visit, 3) Hoehn & Yahr (H&Y) stage ≤ 2 at baseline, 4) demonstrated deficits on DaTscan imaging, and 5) not on any PD medication. All patients also received comprehensive clinical assessments of motor, cognitive and behavioral functions at study entry. Only patients with rs-fMRI data were included in the study. Initially, a total of 91 patients were included; however, 5 patients were removed due to excessive head motion (see below), 6 were removed due to poor imaging quality, and 4 due to lack of information on EDS. Of the 76 remaining patients suitable for analysis, 16 were considered to have EDS, as indicated by the Epworth Sleepiness Scale scores $>=10$ (see below). The majority of participants in the study did not have cardiac, respiratory, and psychiatric co-morbidities. There were no significant differences between patients with and with EDS in these co-morbidities and in the use of psychoactive or other medications that may contribute to EDS. Table 1 presents the demographic and clinical characteristics of these patients.

2.2. Clinical assessment

After initial screening, all patients were comprehensively assessed at the baseline visit for clinical performance on motor, non-motor, cognitive, and neuropsychiatric functions by the site investigators. Specifically, motor severity was assessed using part III of the Movement Disorders Society (MDS) Unified Parkinson's Disease Rating Scale (UPDRS-III) [18]. PIGD scores were calculated following the method provided by the PPMI. In addition, information about laterality of motor symptoms was also collected at the recruiting sites. Global cognitive function was assessed using the Montreal Cognitive Assessment (MOCA) [19]. Neuropsychiatric assessment was performed using the 15-item Geriatric Depression Scale (GDS) [20]. For sleep disturbance, RBD and EDS were measured with the REM Sleep Behavior Disorder Screening Questionnaire (RBDSQ) [21], and Epworth Sleepiness Scale (ESS) [22], respectively. All patients' EDS scores and MRI scan (described below) were collected within the same month.

Table 1
Demographic and clinical characteristics of 76 PD patients.

	PD-no EDS	PD-EDS	t/χ^2	p
	Mean (SD)	Mean (SD)		
Age	60.33 (10.78)	62.29 (8.98)	−0.67	0.51
Gender (male, %)	63.3	75.0	0.76	0.38
Education	15.45 (3.11)	14.50 (3.03)	1.09	0.28
Handedness (R/L/Mixed, %)	86.7/10.0/3.3	93.8/6.3/0		0.89[a]
Hoehn and Yahr	1.17 (0.46)	1.06 (0.25)	0.31	0.76
UPDRS-III	18.40 (8.97)	24.06 (14.41)	−1.50	0.15
Laterality (%)			1.22	0.65
Left-side	36.7	25.0		
Right-side	61.7	75.0		
Symmetric	1.7	0.0		
Disease duration (months)	5.45 (6.92)	5.06 (5.01)	0.21	0.84
PIGD	0.19 (0.22)	0.46 (0.47)	−3.39	0.035
ESS	4.77 (2.40)	12.94 (3.09)	−11.36	0.000
RBDSQ	3.63 (2.41)	5.56 (2.45)	−2.83	0.006
GDS	2.08 (1.99)	2.81 (2.86)	−1.18	0.24
MOCA	27.28 (2.19)	25.81 (4.17)	1.36	0.19

ESS = Epworth Sleepiness Scale; GDS = Geriatric Depression Scale; MOCA = Montreal Cognitive Assessment; PIGD = posterior instability and gait disturbance; RBDSQ = REM Sleep Behavior Disorder Screening Questionnaire (RBDSQ); UPDRS-III = Part III of the Movement Disorders Society (MDS) Unified Parkinson's Disease Rating Scale.

[a] Fisher's Exact test was used for this variable due to less than 5 counts in the 'mixed' cells.

2.3. MRI acquisition and preprocessing

Both whole-brain T1 structural and functional MRI scans were acquired on 3T Siemens Trio Tim scanners. More details can be found in the MRI technical operations manual at http://www.ppmi-info.org/. For each patient, a 3D T1 image was acquired using a MPRAGE protocol with the following parameters: repetition time (TR) = 2300 ms, echo time (TE) = 2.98 ms, field of view (FOV) = 256 mm, flip angle (FA) = 9° and voxel size = 1 mm^3. For rs-fMRI, 210 images (40 axial slices in an ascending order) per patient were also acquired using the echo-planar sequence and the following parameters: TR = 2400 ms, TE = 25 ms, FOV = 222 mm, FA = 80° and voxel size = 3.3 mm^3. Patients were instructed to rest quietly, keeping their eyes open, and not to fall asleep. The total scanning time for rs-fMRI was around 8 min and 4 s.

Both T1 structural and rs-fMRI images were preprocessed using the toolboxes of Data Processing Assistant for Resting-State fMRI Advanced Edition (DPARSFA version 3.1), Statistical Parametric Mapping (SPM8, http://www.fil.ion.ucl.ac.uk/spm/) and Data Processing & Analysis of Brain Imaging toolbox (version 1.2) running on MATLAB R2012a (Mathworks). T1 images were bias-corrected, tissue classified, and registered using linear (12-parameter affine) and nonlinear transformations, within a unified model. The gray matter (GM) partitions were then modulated to preserve actual GM