Fatigue in Parkinson's Disease: The Contribution of Cerebral Metabolic Changes

Sang Soo Cho,^{1,2} Kelly Aminian,^{1,2} Crystal Li,² Anthony E. Lang,³
Sylvain Houle,² and Antonio P. Strafella^{1,2,3*}

¹*Division of Brain, Imaging and Behaviour – Systems Neuroscience, Krembil Research Institute, University Health Network, University of Toronto, Ontario, Canada*

²*Research Imaging Centre, Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health, University of Toronto, Ontario, Canada*

³*Movement Disorder Unit & E.J. Safra Parkinson Disease Program, Toronto Western Hospital, Neurology Div., University Health Network, University of Toronto, Ontario, Canada*

Abstract: Fatigue is a common and disabling non-motor symptom in Parkinson's disease associated with a feeling of overwhelming lack of energy. The aim of this study was to identify the neural substrates that may contribute to the development of fatigue in Parkinson's disease. Twenty-three Parkinson's disease patients meeting UK Brain Bank criteria for the diagnosis of idiopathic Parkinson's disease were recruited and completed the 2-[¹⁸F]fluoro-2-deoxy-D-glucose (FDG)-PET scan. The metabolic activities of Parkinson's disease patients with fatigue were compared to those without fatigue using statistical parametric mapping analysis. The Parkinson's disease group exhibiting higher level of fatigue showed anti-correlated metabolic changes in cortical regions associated with the salience (i.e., right insular region) and default (i.e., bilateral posterior cingulate cortex) networks. The metabolic abnormalities detected in these brain regions displayed a significant correlation with level of fatigue and were associated with a disruption of the functional correlations with different cortical areas. These observations suggest that fatigue in Parkinson's disease may be the expression of metabolic abnormalities and impaired functional interactions between brain regions linked to the salience network and other neural networks. *Hum Brain Mapp* 38:283–292, 2017. © 2016 Wiley Periodicals, Inc.

Key words: Parkinson's disease; fatigue; regional glucose metabolism; FDG PET; brain network

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*Correspondence to: Antonio P. Strafella, MD, PhD, FRCPC, Toronto Western Hospital and Institute, CAMH-Research Imaging Centre, University of Toronto, Toronto, Ontario M5T 2S8, Canada. E-mail: antonio.strafella@uhn.ca

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INTRODUCTION

Fatigue is a state of profound physical and/or mental weakness, associated with a feeling of abnormal and overwhelming lack of energy, distinct both qualitatively and quantitatively from general tiredness [Brown et al., 2005]. In Parkinson's disease, this is a common and disabling non-motor symptom affecting up to 70% of patients, and often related to disease progression [Alves et al., 2004; Friedman et al., 2007], however, fatigue has generally been found to be independent of disease severity [Friedman et al., 2011; Friedman et al., 2016].

In healthy subjects, fatigue has often been shown to be associated with various cognitive changes. Individuals with fatigue may display perseveration on the card sorting task and prolonged planning time on the tower of London task [van der Linden et al., 2003a], while others can make more systematic errors on a complex computer task [van der Linden et al., 2003b]. A relationship between fatigue and cognitive function has also been found in Parkinson's disease [Goldman et al., 2014].

To date, only a handful of neuroimaging studies have examined the neural substrates that underpin fatigue. According to some of these studies, prefrontal areas play an important role in the pathophysiological mechanism of fatigue. In particular, activity in the medial orbitofrontal cortex (Brodmann's area 10/11) seems often to be associated with the subjective sensation of fatigue [Tajima et al., 2010]. The fatigue sensation may involve as well a system composed of the insula and posterior cingulate cortex (PCC), where activation of the insula was related with the evaluation of mental effort [Otto et al., 2014] and during high-demand, mental-fatigue-inducing tasks, the increase activation in the PCC was positively associated with the level of fatigue sensation [Cook et al., 2007]. Others studies in Parkinson's disease patients with fatigue have shown also a reduction in serotonin transporter binding in the

cingulate and amygdala and in dopamine storage capacity in the caudate and insular region [Pavese et al., 2010]. The activation abnormalities along with dysregulation of both serotonin and dopamine in cognitive and limbic regions are not surprising, given that fatigue is a complex symptom [Honig et al., 2009] strongly associated with the cognitive and limbic systems.

Within the limbic network, the insular cortex in particular, part of the salience network (SN), is a key region involved in the processing of relevant information related to the state of the body [Williamson et al., 2003]. This cortical area bridges the default mode network (DMN) into the central executive network (CEN) guiding cognitive/emotional behavior [Goulden et al., 2014; Sridharan et al., 2008]. Dysfunction in the insular cortex plays an important role in the complex symptomatology of Parkinson's disease [Criaud et al., 2016; Gomez-Esteban et al., 2011].

With this background in mind, we hypothesized that parkinsonian individuals with fatigue would likely show metabolic changes in brain regions associated with the three cognitive networks highlighted above (i.e., SN, DMN, and CEN) which may as well correlated with fatigue level and possibly influenced connectivity. Thus, our primary objective was to study the metabolism and potential role of the regions linked to these cortical neural networks (i.e., SN, DMN, and CEN) in Parkinson's disease patients with fatigue, while controlling for potential confounding effects like sleep, disease severity and depression which commonly occur in Parkinson's disease.

SUBJECTS AND METHODS

Patients

Twenty-three Parkinson's disease patients (mean age 64.7 ± 7.2 ; six females) meeting UK Brain Bank criteria for the diagnosis of idiopathic Parkinson's disease patients were recruited and completed the 2- ^{18}F fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET) scan after having given written, informed consent. The study was approved by the University Health Network Research Ethics Board. Parkinsonian disability was assessed using the Hoehn and Yahr Rating Scale and the Unified Parkinson Disease Rating Scale motor score (UPDRS III), while being off medication for a minimum of 12 hours (overnight withdrawal). Levodopa equivalent dose (LED) for each patient was calculated based on Tomlinson et al. [2010]. To reduce possible confounding effects, Montreal Cognitive Assessment (MoCA) and Beck depression inventory (BDI) were obtained in all Parkinson's disease patients. Patients with a history of other neurological diseases, unstable psychiatric illness, sleep disorders or any medical condition that precluded them from PET imaging were excluded from the study. Fatigue Severity Scale (FSS), a self-report instrument was used to assess levels of fatigue and its effect on daily functioning [Krupp et al.,

Abbreviations

ACC	Anterior cingulate cortex
BDI	Beck depression inventory
CEN	Central executive network
DLPFC	Dorsolateral prefrontal cortex
DMN	Default mode network
ESS	Epworth Sleepiness scale
FDG	2- ^{18}F fluoro-2-deoxy-D-glucose
FSS	Fatigue Severity Scale
FWHM	Full width at half-maximum
LED	Levodopa equivalent dose
MNI	Montreal Neurologic Institute
MoCA	Montreal Cognitive Assessment
PCC	Posterior cingulate cortex
PDSS	Parkinson's Disease Sleep Scale
PET	Positron emission tomography
SN	Salience network
TOF	Time-of-flight
UPDRS	Unified Parkinson Disease Rating Scale motor score

1989]. This provides nine statements addressing fatigue's effects on daily functioning, querying its relationship to motivation, physical activity, work, family, and social life. Each item has seven response options from 1 (disagree) to 7 (strongly agree). The final FSS scoring is done by calculating the average response to the questions (FSS total score dividing by nine). A total score higher than 36 can be classified as fatigued. Patients were classified without fatigue ($n = 12$) or with fatigue ($n = 11$) on the basis of their total score. The Epworth Sleepiness scale (ESS) and Parkinson's Disease Sleep Scale (PDSS) were used to assess daytime sleepiness [Kumar et al., 2003] and nighttime sleep disturbances [Chaudhuri et al., 2002], respectively.

Image Acquisition

PET scans were obtained using a high resolution PET/CT, Siemens mCT (Siemens Medical Solutions USA, Inc.) operating in 3D mode with an in-plane resolution of approximately 4.6 mm full width at half-maximum (FWHM). The patients fasted at least 6 hours before the scan. After the intravenous bolus injection of 5 mCi of FDG, patients were allowed to rest in a dimly lit room for 45 min during the uptake phase. Five minutes of emission scan were acquired followed by a low dose (0.2 mSv) CT scan for attenuation correction. To minimize subjects' head movements in the PET scanner, we used a custom-made thermoplastic facemask together with a head-fixation system (ORFIT mask system). PET images were reconstructed with time-of-flight (TOF) and displayed in 256×256 matrix (pixel size = 1.59×1.59 mm). Patients were imaged after overnight withdrawal of their antiparkinsonian medications. This withdrawal time is standard practice in parkinsonian research [Defer et al., 1999] and ensures to standardize and minimize the effect of medication while patients are still functional.

PET Analysis

All PET images were preprocessed and analyzed using Statistical Parametric Mapping 8 (SPM 8; Wellcome Department of Imaging Neuroscience, London, UK, <http://www.fil.ion.ucl.ac.uk/spm>). Images were transformed into Montreal Neurologic Institute (MNI) template using a standardized PET template image to remove the individual anatomical variability. We used the normalization algorithm provided by SPM 8 that employs a 12-parameter affine transformation followed by nonlinear deformations. Then, the spatially normalized images were smoothed with a FWHM 8-mm Gaussian kernel to increase the signal-to-noise ratio and to remove subtle variations in anatomic structures. Individual voxel counts were normalized versus total brain counts (proportional scaling in SPM) to remove individual global brain metabolism differences.

After spatial and count normalization, significant differences in glucose metabolism between Parkinson's disease with and without fatigue were estimated at every voxel using t -statistics. Differences of regional brain glucose metabolism between the two PD groups were investigated at the whole-brain level using SPM 8, and significant clusters were tested if it was located within our a priori region of interests (ROIs) (i.e., SN: insula, anterior cingulate cortex, DMN: posterior cingulate/precuneus, medial prefrontal cortex, inferior parietal lobule, medial temporal lobe, lateral temporal cortex, CEN: dorsolateral prefrontal cortex (DLPFC) and posterior parietal cortex). Each ROI was defined using WFU-PickAtlas toolbox (<http://www.fmri.wfubmc.edu/cms/software>) [Maldjian et al., 2003]. A height threshold of uncorrected $P < 0.005$ and an extent threshold of 100 voxels were used for generating the initial t -map to determine the predicted peaks and visualization. Brain regions that showed $P < 0.001$ at voxel level were considered significant. A subsequent correlation analysis between FSS and brain glucose metabolism of the statistically significant regional cluster was conducted using SPSS 16.0 (SPSS Inc., Chicago, Illinois). Considering the possible comorbidity of depression shown in other studies [Defer et al., 1999; McDonald et al., 2003], BDI was used as a nuisance variable for the analysis.

In order to examine the whole-brain metabolic connectivity in the SN and CEN, we selected seed regions (right insula for SN and PCC for DMN) from the significant clusters from the group analysis. Count from normalized FDG mean value of seed areas were extracted using SPM-VOI tool, and a seed-based connectivity analyses was performed to test function relationship between cognitive networks using SPM 8 (uncorrected $P < 0.005$, $k = 100$ voxels).

The local maxima of each cluster in the Montreal Neurological Institute (MNI) coordinates were transformed using Talairach Daemon (<http://www.talairach.org>), expressed in Talairach coordinates.

For the demographic comparisons, student t -test was used, and for psychometric analysis, Pearson's partial correlation analysis (two-tailed) was performed using SPSS 16.0. $P < 0.05$ was considered significant for all analysis. All data were expressed as mean $\pm$ SD.

RESULTS

The clinical features of each group are summarized in Table I. There were no significant differences between groups in age ($t = 0.94$, $P = 0.36$), year education ($t = 0.92$, $P = 0.37$), MoCA ($t = 1.22$, $P = 0.24$), BDI ($t = 1.23$, $P = 0.23$), UPDRS III ($t = 0.70$, $P = 0.49$), LED ($t = 0.90$, $P = 0.38$) and H-Y score ($t = 0.54$, $P = 0.60$). None of PD patients in this study was taking antidepressant medication. Controlling for the effect of sleep, there were no significant differences in sleep quality between Parkinson's disease with and without fatigue when measured with PDSS ($t = 0.59$, $P = 0.57$) and ESS ($t = 0.19$, $P = 0.85$). We did not observe

TABLE I. Demographics of Parkinson's disease patient without (PD-Fatigue-) and with fatigue (PD-Fatigue+)

	PD-fatigue-	PD-fatigue+	P value
N (F:M)	12 (2:10)	11 (4:7)	0.28a
Mean age year (SD, range)	63.3 (8.4, 52–76)	66.2 (5.6, 54–72)	0.36
UPDRS III (SD)	37.1 (12.2)	33.5 (12.8)	0.49
Hoehn and Yahr Scale (SD)	2.1 (0.5)	2.0 (0.2)	0.60
LED mg (SD)	776.6 (326.0)	665.9 (259.1)	0.38
Levodopa	518.8 (362.6)	506.8 (215.1)	0.93
DA agonist	145.8 (137.7)	86.4 (119.0)	0.23
BDI (SD)	8.0 (4.0)	9.9 (3.4)	0.23
MoCA (SD)	27.5 (1.9)	26.2 (3.2)	0.24
ESS (SD)	9.2 (4.3)	9.5 (5.4)	0.85
PDSS (SD)	107.0 (16.4)	102.7 (18.6)	0.57
FSS (SD)	3.2 (0.8)	5.0 (0.9)	$P < 0.0001$

^aChi-square analysis; SD: Standard Deviation; N.S: not significant; UPDRS: unified Parkinson's disease rating scale LED: levodopa equivalent dose; BDI: Beck depression Inventory; MoCA: Montreal Cognitive Assessment; ESS: Epworth sleepiness scale; PDSS: Parkinson's Disease Sleep Scale; FSS: Fatigue Severity Scale (total score dividing by nine).

any relationship between fatigue level and disease severity index (UPDRS III: $r = -0.02$, $P = 0.45$; H-Y: $r = 0.15$, $P = 0.23$) nor daily pharmacological therapy (LED: $r = -0.24$, $P = 0.27$; levodopa: $r = -0.11$, $P = 0.63$; dopamine-agonist: $r = -0.16$, $P = 0.46$) indicating that neither disease severity nor pharmacological therapy was directly related with fatigue in Parkinson's disease patients. We also tested the relationship between the level of fatigue in each patient and overall cognitive function and mood status. There was no relationship with MoCA score ($r = -0.21$, $P = 0.33$), indicating that the level of fatigue in our cohort of patients was not directly related with the overall cognitive function. BDI as well did not show significant level of correlation with fatigue but showed trend level of relationship ($r = 0.39$, $P = 0.06$), and for this reason BDI was used as nuisance variance for analysis.

To test the first hypothesis, we conducted a voxel-wise group comparison analysis to test changes in regional glucose metabolism. The results are shown in Figure 1 and Table II. The imaging analysis showed that the Parkinson's

disease group exhibiting higher level of fatigue presented lower in regional glucose metabolism in the right insular cortex (BA 13) region of the SN, in the left superior (BA 41) and right middle (BA 21) temporal gyri. Greater regional glucose metabolism was found in the bilateral posterior cingulate cortex (PCC, BA 29), a region known to be part of the DMN.

To test our second hypothesis, we extracted relative metabolism from the brain region that showed group differences and tested if there was any significant correlation with individual fatigue level. The level of regional glucose metabolism in those brain regions correlated with fatigue score when controlling for BDI score (Fig. 2). The right insular cortex showed a significant negative correlation ($r = -0.49$, $P = 0.02$) along with the left superior temporal gyrus ($r = -0.53$, $P = 0.03$), implying that lower metabolism in these regions was associated with a higher fatigue level. In contrast, the region associated with DMN (i.e., PCC) showed a positive correlation ($r = 0.57$, $P = 0.006$) with fatigue score.

Figure 1.

Brain regions showing a significant decrease (cold color scale) and increase (hot color scale) in cerebral glucose metabolism on resting state FDG PET scans in Parkinson's disease patient with fatigue, controlled for depression. Significant voxels in statistical T-maps were overlaid on "ch256" brain template using MRICroGL (<http://www.mccauslandcenter.sc.edu/mricrogl/>).

TABLE II. Brain regions showing hypo/hyper metabolism in Parkinson's disease patient with fatigue (PD-Fatigue-) and Parkinson's disease patient without fatigue (PD-Fatigue+)

		BA	Coordinate ^a			T-value	Cluster size
			X	Y	Z		
PD-fatigue− > PD-fatigue+							
Lt	Superior Temporal Gyrus	BA 41	−50	−25	7	4.82	212
Rt	Insular	BA 13	44	12	−4	3.88	137
Rt	Middle Temporal Gyrus	BA 21	53	−24	−7	3.72	103
PD-fatigue− < PD-fatigue+							
Bi	Posterior Cingulate	BA 29	−4	−44	13	4.29	126

Lt: left, Rt: right, Bi: bilateral, BA: Brodmann's area.

^aTalairach coordinate (mm).

Figure 2.

Correlation between regional glucose metabolism and FSS score in the right insular cortex, left STG, and PCC, controlled for depression. Open circle indicate PD with fatigue and closed circle indicate PD without fatigue. The correlation coefficients r and corresponding p (two-tailed) values are shown for each correlation.

A) PD without fatigue

B) PD with fatigue

Figure 3.

Brain regions where significant functional correlations with the right insular seed were overlaid on "ch256" brain template (upper row) and its topographical connectivity map (bottom row), were shown in Parkinson's disease patient without fatigue (A) and Parkinson's disease patient with fatigue (B). Seed area marked on yellow, red node/path indicates positive connectivity and blue node/path indicate negative connectivity (bottom row).

TABLE III. Brain regions that showed significant functional correlate with right insular seed in each Parkinson's disease group ($P < 0.005$ uncorrected for multiple comparisons with 100 voxels of spatial extended threshold)

		BA	Coordinate ^a			T-value	Cluster size
			X	Y	Z		
PD-Fatigue–							
	<Positive>						
Rt	Inferior Frontal Gyrus	BA 47	43	13	–4	9.74	1429
Rt	Inferior Frontal Gyrus	BA 9	51	19	22	5.31	
Rt	Inferior Frontal Gyrus	BA 44	44	9	31	3.97	
Rt	Inferior Frontal Gyrus	BA 45	54	24	17	3.90	
Rt	Middle Frontal Gyrus	BA 10	39	51	5	4.49	
Rt	Middle Frontal Gyrus	BA 10	28	49	2	3.85	317
Rt	Middle Frontal Gyrus	BA 9	30	36	30	3.27	
Rt	Superior Frontal Gyrus	BA 10	17	53	7	4.53	
Rt	Superior Temporal Gyrus	BA 22	53	11	–5	5.59	
Rt	Thalamus		8	–11	4	4.88	
RT	Putamen		15	0	5	4.87	137
Lt	Inferior Frontal Gyrus	BA 9	–50	16	23	4.54	
	<Negative>						
Lt	ParaHippocampal Gyrus		–30	6	–27	4.89	211
Rt	ParaHippocampal Gyrus		32	6	–27	4.45	101
Lt	Superior Parietal Lobule	BA 5	–24	–45	63	4.29	158
Rt	Postcentral Gyrus	BA 4	20	–26	69	3.87	126
Rt	Precuneus	BA 7	12	–46	58	3.86	120
Lt	Precuneus	BA 7	–10	–47	50	3.58	166
Lt	Paracentral Lobule	BA 6	–4	–23	49	3.57	
PD-Fatigue+							
	<Positive>						
Rt	Inferior orbitofrontal Gyrus	BA 47	53	21	–4	5.74	734
Lt	Inferior Frontal Gyrus	BA 44	–55	7	18	5.91	2044
Lt	Inferior Frontal Gyrus	BA 47	–53	24	–3	5.91	
Lt	Superior Temporal Gyrus	BA 22	–50	–10	–3	5.49	
Lt	Insular	BA 13	–40	2	4	5.84	
Lt	Thalamus		–4	–12	–2	5.17	
Rt	Thalamus		8	–12	2	4.88	801
Rt	Caudate		6	17	–5	4.22	
	<Negative>						
Rt	Middle Orbitofrontal Cortex	BA 11	26	44	–14	4.17	232

Lt: left, Rt: right, BA: Brodmann's area.

^aTalairach coordinate (mm).

We did not find any significant metabolic differences between two groups in CEN related brain regions, thus the seed-based connectivity analysis was conducted using the right insula and PCC as a seed to test the third hypothesis. The connectivity analysis using the right insular region within the SN as the seed showed a clear pattern of functional relationship with different cortical/subcortical regions (Fig. 3 and Table III). In Parkinson's disease without fatigue, the metabolic activity in bilateral prefrontal regions (part of the CEN), right thalamus and putamen showed a positive correlation with the insular activity, while other brain regions associated with somatosensory regions (i.e., right post-central gyrus, left superior parietal lobule), bilateral precuneus within the DMN, and parahippocampal gyrus were inversely related (Fig. 3A).

In contrast, in Parkinson's disease patients with fatigue, several of these functional correlations with the insular activity did not reach a significant level (i.e., prefrontal, somatosensory) and new positive correlations emerged with metabolic activities in the contralateral insular, bilateral thalamus and inferior frontal gyri. A negative correlation was found only in the ipsilateral middle orbitofrontal cortex (Fig. 3B). Comparing of two patient groups, bilateral DLPFC and right orbitofrontal cortex showed less metabolic correlation with right insula in PD with fatigue than without fatigue ($P < 0.001$, $k > 100$), these results reflect the disrupted functional connectivity between these two brain regions in patients with fatigue.

Connectivity analysis within the DMN was completed using the PCC as the seed (Fig. 4 and Table IV). In

Figure 4.

Brain regions where significant functional correlations with the PCC seed were overlaid on “ch256” brain template (upper row) and its topographical connectivity map (bottom row) were shown in Parkinson's disease patient without fatigue (A) and Parkinson's disease patient with fatigue (B). Seed area marked on yellow, red node/path indicates positive connectivity and blue node/path indicate negative connectivity.

Parkinson's disease without fatigue, the PCC seed showed positive correlations with bilateral occipital regions, angular gyrus and right post-central gyrus, while an inverse, negative correlation was observed only with the right insular region (Fig. 4A). In Parkinson's disease patients with fatigue, several of these functional relationships with PCC again did not reach a significant level (i.e., somatosensory) with new positive correlations with left middle frontal, superior orbitofrontal gyri. Several negative correlations were instead observed between PCC and bilateral insular, anterior cingulate (ACC) (both part of the SN), middle/inferior frontal gyri (part of the executive network) and bilateral temporal areas (Fig. 4B). Comparing of two patient groups, right somatosensory area showed less metabolic correlation with right PCC in PD with fatigue than without fatigue ($P = 0.001$, $k = 85$).

DISCUSSION

The results of this study provide evidence of significant cortical metabolic changes in Parkinson's disease patients with fatigue mainly in cerebral regions associated with the salience and default networks. In particular, within the SN, we observed a lower regional glucose metabolism in the right insular which was associated with higher level of fatigue. Further, the connectivity analysis produced evidence of a significant disruption of the functional relational pattern between this region and different

subcortical/cortical areas, prevalently involving prefrontal and somatosensory regions.

The insular cortex is a limbic region well known for processing relevant information related to the state of the body [Williamson et al., 2003] linking the DMN to the CEN in guiding cognitive/emotional behavior [Goulden et al., 2014; Sridharan et al., 2008]. This brain region plays a prominent role in parkinsonian disorders [Criaud et al., 2016; Gomez-Esteban et al., 2011]. As a multi-faceted brain structure, it is also involved in various other functions [Augustine, 1996], such as receiving important autonomic feedback [Chaudhuri et al., 2001] and being activated during tasks involving interoception (how the body ‘feels’) and subjective awareness of both positive and negative feelings [Craig, 2002]. Recent studies using large-scale brain connectivity analyses have highlighted the role of the insular cortex in detecting salient events and enabling switching between the DMN and CEN, corroborating the hypothesis that this region operates as an “outflow hub” which coordinates other large-scale networks [Menon and Uddin, 2010]. With this in mind, the impaired connectivity between the insular and prefrontal and somatosensory regions detected by our analysis may contribute to the development and maintenance of central fatigue possibly through a disrupted flow of critical interoceptive information, emotional and cognitive processes also described below.

Other imaging studies have suggested an impairment of both dopaminergic and serotonergic function contributing

TABLE IV. Brain regions that showed significant functional correlate with PCC seed in each Parkinson's disease group ($P < 0.005$ uncorrected for multiple comparisons with 100 voxels of spatial extended threshold)

		BA	Coordinate ^a			T-value	Cluster size
			X	Y	Z		
PD-Fatigue–							
	<Positive>						
Rt	Superior Occipital Gyrus	BA 19	30	–87	30	5.74	485
Rt	Precuneus		14	–67	60	4.98	124
Lt	Precuneus		–5	–69	51	3.59	
Rt	Postcentral Gyrus		18	–29	77	4.60	135
Rt	Angular Gyrus	BA 7	40	–72	45	4.58	114
Lt	Angular Gyrus	BA 7	–32	–75	44	4.52	110
Lt	Superior Occipital Gyrus	BA 19	–18	–89	32	3.99	204
	<Negative>						
Rt	Insular	BA 13	41	0	–13	3.61	210
PD-Fatigue+							
	<Positive>						
Lt	Middle Frontal Gyrus	BA 6	–26	8	47	6.17	201
Rt	Superior Orbitofrontal Gyrus	BA 11	22	44	–16	5.61	179
Rt	Middle Occipital Gyrus	BA 18	14	–87	14	3.94	144
Rt	Superior Occipital Gyrus	BA 19	24	–86	34	3.88	171
	<Negative>						
Lt	Middle Temporal Gyrus	BA 21	–50	2	–34	5.80	172
Lt	Insular	BA 13	–32	19	–1	5.08	1387
Lt	Superior Temporal Gyrus	BA 22	–51	4	–2	4.58	
Lt	Inferior Frontal Gyrus	BA 47	–53	27	0	4.28	
Lt	Inferior Frontal Gyrus	BA 44	–58	6	16	3.76	
Lt	Inferior Frontal Gyrus	BA 45	–50	20	6	3.24	
Rt	Insular	BA 13	43	7	–5	4.83	464
Rt	Superior Temporal Gyrus	BA 38	50	4	–20	4.45	
Lt	Thalamus		–4	–18	–3	4.42	193
Bi	Anterior Cingulate	BA 25	0	19	–8	4.05	105

Lt: left, Rt: right, Bi: bilateral, BA: Brodmann's area.

^aTalairach coordinate (mm).

to the symptom of fatigue in Parkinson's disease [Pavese et al., 2010]. Further, according to Braak's staging hypothesis of Parkinson's disease [Braak et al., 2006], the deposition of alpha-synuclein throughout the insular could also play an important role in alteration of synaptic activity and receptor functions in this region. The relevance of the insular to fatigue has also been reported in other diseases, e.g., stroke [Manes et al., 1999], as resulting from damage of this region with disconnection between the insular and the frontal lobe and cingulate cortex.

Within the DMN, fatigue level was associated instead with greater cerebral glucose metabolism at the level of PCC with a disruption of normal connectivity and increased number of inverse, negative correlations with several cortical regions included within the salience and executive networks. The PCC within DMN is a highly connected and metabolically active brain region. Studies suggest that this complicated area through its anatomical connections plays an important role in cognitive and mental processing [Goldman and Holden, 2014; Leech and Sharp, 2014; Lou et al., 2004; Schilbach et al., 2012]. In

particular, Leech and Sharp [2014] proposed that activity within the PCC is relatively high in the broad attentional, unfocused mental state allowing rapid transitions between different neural/cognitive states and becoming deactivated during specific attentional tasks. They suggested that the activation of the SN (particularly the right anterior insular cortex) is critically important in the control of task-dependent deactivation of the PCC in response to unexpected events, and together form an anti-correlated system regulating the attentional/mental focus. Thus, the impaired activation observed in our study of the insular region (either due to mesolimbic dopaminergic degeneration and/or alpha-synuclein deposition), may lead to uncontrolled, high metabolic activity of the PCC that can be responsible for a persistent broad, unfocused mental state resulting in distracting, internally-focused information contributing to mental fatigue. Both of these brain regions that showed functional differences correlated significantly with fatigue level.

In the present study, we found no prefrontal metabolic change in Parkinson's disease with fatigue. The DLPFC

and orbitofrontal cortex may be involved in the self-evaluation of mental fatigue, in fact both these brain regions may show fatigue related activation during performance of cognitively demanding task [Klaassen et al., 2016]. Patients with chronic fatigue syndrome have reduced gray-matter volume in the bilateral prefrontal cortex [Okada et al., 2004], and a decrease in delta band power of MEG signal in the DLPFC is positively related to the daily level of fatigue sensation [Ishii et al., 2014]. Subjective sensation of fatigue has also been found to be associated with the medial orbitofrontal cortex activity [Tajima et al., 2010]. The lack of changes in regional glucose metabolism in our study does not necessarily indicate a lack of role of these prefrontal regions in Parkinson's disease patients with fatigue. The reduced connectivity from the insula to the prefrontal brain region in fatigued patients may indeed contribute to the disconnection from the SN core to CEN causing higher top-down mental effort in the prefrontal cortex.

As already noted above, we cannot neglect the importance of the dopamine and serotonergic system. While serotonergic changes may be one of the pathophysiological contributors to chronic fatigue syndrome [Yamamoto et al., 2004], more recent study have shown no association between raphe serotonin transporter availability and fatigue in early PD patient [Qamhawi et al., 2015]. The potential role of dopaminergic-related medications for the treatment of fatigue symptom have also been reported [Lou et al., 2009; Mendonça et al., 2007] nevertheless the evidence of their effect remain controversial [Franssen et al., 2014].

To avoid potential confounding factors influencing fatigue, we controlled for demographic and clinical profile, including age, gender, disease severity, mood, parkinsonian disability, medication as well as individual sleep quality. However, the small sample size still remains as a limitation of this study, and further investigations are needed to validate current findings. Less conservative statistical inferences can also be another factor limiting the generalization of our results. However, these can be used, when there are specific predictions to be tested. Another potential limitation of our study is the use of self-reporting questionnaires for measuring individual fatigue, however, reliability and validity of FSS has been reported consistently in other diseases [Krupp et al., 1989] as well as in PD patients [Hagell et al., 2006]. In addition, mental fatigue in particular, may rely on a more personal perception of self-status, difficult to measure with more objective scales.

In summary, fatigue in Parkinson's disease is a state of profound physical and/or mental weakness, associated with a feeling of abnormal and overwhelming lack of energy which can be associated with metabolic changes and impaired functional connectivity between brain regions linked to neural systems within the SN and other important cognitive networks such as DMN and CEN. This

underappreciated clinical problem represents one of the major complaints of patients in the daily clinical practice [Friedman et al., 2016]. The current study provides important insights into the complicated neural mechanisms underlying this non-motor symptom and opens the door for new research studies exploring the interactions between receptor abnormalities and cognitive networks and their causal role in the development of fatigue in Parkinson's disease.

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