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Altered intrinsic functional coupling between core neurocognitive networks in Parkinson's disease

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ABSTRACT

Parkinson's disease (PD) is largely attributed to disruptions in the nigrostriatal dopamine system. These neurodegenerative changes may also have a more global effect on intrinsic brain organization at the cortical level. Functional brain connectivity between neurocognitive systems related to cognitive processing is critical for effective neural communication, and is disrupted across neurological disorders. Three core neurocognitive networks have been established as playing a critical role in the pathophysiology of many neurological disorders: the default-mode network (DMN), the salience network (SN), and the central executive network (CEN). In healthy adults, DMN–CEN interactions are anti-correlated while SN–CEN interactions are strongly positively correlated even at rest, when individuals are not engaging in any task. These intrinsic between-network interactions at rest are necessary for efficient suppression of the DMN and activation of the CEN during a range of cognitive tasks. To identify whether these network interactions are disrupted in individuals with PD, we used resting state functional magnetic resonance imaging (rsfMRI) to compare between-network connectivity between 24 PD participants and 20 age-matched controls (MC). In comparison to the MC, individuals with PD showed significantly less SN–CEN coupling and greater DMN–CEN coupling during rest. Disease severity, an index of striatal dysfunction, was related to reduced functional coupling between the striatum and SN. These results demonstrate that individuals with PD have a dysfunctional pattern of interaction between core neurocognitive networks compared to what is found in healthy individuals, and that interaction between the SN and the striatum is even more profoundly disrupted in those with greater disease severity.

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1. Introduction

Many neurological and psychiatric disorders are associated with disrupted functional connectivity between important neurocognitive networks, providing insights into the aberrant brain organization inherent to these disorders. Large-scale network analysis exploring brain function across healthy adults and brain-disordered individuals has lead to a conceptual framework referred to as the triple network model of pathology. This model highlights three distributed neurocognitive networks which are critical to maintaining effective neural communication and are found to be disrupted across many neuropsychiatric disorders (Menon, 2011): the default-mode network (DMN), the salience network (SN), and the central executive network (CEN) (Greicius et al., 2003; Menon and Uddin, 2010; Seeley et al., 2007). Typically, the SN and CEN increase activation in response to external stimuli (Dosenbach et al., 2006), whereas DMN activity is suppressed, resulting in anti-correlated coupling between the CEN and DMN (Fox et al., 2005a; Greicius et al., 2003; Raichle et al., 2001). Interestingly, these same patterns of interaction among the three core neurocognitive networks are also observable in resting state fMRI data (Menon, 2011; Sridharan et al., 2008). Previous fMRI work demonstrates that resting brain organization is highly related to how the brain functions during external tasks (Fox et al., 2005a; van den Heuvel et al., 2009), suggesting that studying resting brain connectivity patterns will provide useful insight into neurobiology of disordered populations (Fox and Greicius, 2010; Raichle and Mintun, 2006; Shulman et al., 2004) including those with Parkinson's disease (PD).

In addition to the fact that interactions between these three core cognitive networks are disrupted across neuropsychiatric disorders, striatal dysfunction associated with PD (Ravina et al., 2012) may influence these network interactions. Through reciprocal connections,

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striatal neurons are thought to coordinate activity in many cortical regions (Macdonald and Monchi, 2011), emphasizing the idea that PD pathology impacts widespread cortical regions as well as the basal ganglia. A recent resting state study in young adults found that the striatum interacts with regions comprising the DMN and SN (Di and Biswal, 2014). The striatum also is functionally and structurally connected with cortical areas that comprise the CEN through reciprocal circuitry with the dorsolateral prefrontal cortex and posterior parietal cortex (Alexander and Crutcher, 1990; Kish et al., 1988; Leh et al., 2008), which display abnormal activations in PD during cognitively demanding tasks (Carbon et al., 2010; Eidelberg, 2009; Lewis et al., 2003; Schendan et al., 2013; Tinaz et al., 2008). Decreased functional connectivity within the DMN has been observed in PD during the resting state (Tessitore et al., 2012) and during cognitively demanding tasks (van Eimeren et al., 2009), suggesting that disease-related network disruptions may influence the functional coupling between DMN–CEN interactions leading to heightened activation and dysfunctional connectivity of the DMN in PD. However, it remains to be elucidated if PD is associated with specific disruptions in functional coupling between the SN, CEN, and DMN.

Structurally, striatal neurons are highly interconnected with neurons in the insular cortex (Chikama et al., 1997; Fudge et al., 2005), an important node of the SN. Further, dopamine depletion is thought to occur in parallel in the striatum and the insula (Christopher et al., 2014b; Monchi et al., 2007; Shine et al., 2013). It has been hypothesized that the loss of D2 signaling in the insula disrupts the modulation of SN activity, impairing its function in coordinating interactions between other brain networks (Menon and Uddin, 2010). Altered cortico-striatal–thalamocortical neurocircuitry resulting from dysfunctional striatal dopaminergic function, as is observed in PD, is thought to lead to aberrant assignment of salience (Kish et al., 1988; Monchi et al., 2007; Shine et al., 2013), further emphasizing the association between the striatum and salience network in PD. As striatal dysfunction is characteristic of PD and worsens with disease severity, functional coupling between the striatum and the SN is also likely to be disrupted as a function of disease progression.

In the present study, we used resting state functional magnetic resonance imaging (rs-fMRI) to identify SN–DMN, SN–CEN and CEN–DMN interactions in a group of non-demented individuals with PD and age-matched healthy participants (MC). As disease severity in PD is correlated with increased striatal disruption (Lozza et al., 2002; Ravina et al., 2012), we also sought to determine whether disease severity was related to functional coupling between the striatum and the SN. We hypothesized that MC participants would demonstrate negative DMN coupling with SN and CEN, and positive SN coupling with CEN, consistent with the observed patterns in young neurologically normal adults (Fox et al., 2005a; Sridharan et al., 2008). In contrast, we expected dysfunctional SN coupling with the DMN and CEN in PD participants compared to MC. We also predicted that within the group of PD individuals, increased disease severity would be related to reduced SN–striatum functional coupling.

2. Methods

2.1. Participants

Twenty-six individuals diagnosed with PD and 24 healthy MC adults were enrolled. Two individuals with PD and 4 MC participants were excluded on the basis of excess motion (greater than 2 mm displacement) in the magnetic resonance imaging (MRI) scanner, resulting in a total of 24 PD (12 female, mean age 62.5 years, 2 left-handed) and 20 MC (11 female, mean age 65.9 years, 2 left-handed) participants (Table 1). All participants provided informed consent in a manner approved by the institutional review boards of Boston University and Partners Human Research Committee. All participants were screened for other neurological and psychiatric illness via self-report questionnaires and physician record confirmation.

Table 1
Participant characteristics.

	PD (N = 24)	MC (N = 20)
Age (years)	62.5 ± 6.4	65.9 ± 9.4
Male/female	12/12	9/11
Education (years)	17.6 ± 2.2	16.6 ± 2.2
MMSE (out of 30)	28.6 ± 0.9	28.8 ± 0.8
BDI-II	5.8 ± 4.4*	2.3 ± 2.9
BAI	5.3 ± 3.7**	1.5 ± 2.1
UPDRS total	27.1 ± 10.8	–
UPDRS motor	16.1 ± 7.2	–
Levodopa equivalent dosage (mg/day)	368.9 ± 261.9	–
Hoehn and Yahr	2 (median); 1 (min) to 3 (max)	–
RPD/LPD	13/11	–
T-PD/AR-PD/G-PD	12/7/5	–

MMSE: Mini-Mental State Examination. UPDRS: Unified Parkinson's Disease Rating Scale. BDI-II: Beck Depression Inventory, 2nd Edition. BAI: Beck Anxiety Inventory. RPD: Right-side of body symptom at onset. LPD: Left-side of body symptom at onset. T-PD: Tremor at onset. AR-PD: Akinetic–Rigid at onset. G-PD: Gait-instability at onset.
Values presented in the table are means ± standard deviations, unless otherwise noted.
* Indicates group differences at a significance level of $p < 0.05$.
** Indicates group differences at a significance level of $p < 0.005$.

Participants diagnosed with idiopathic PD were recruited from the Parkinson's Disease Center at Boston Medical Center. All participants taking anti-parkinsonian medications were scanned at peak "ON" levels of medication, approximately 60–90 min after the optimized daily dose was taken. All of the participants with PD were on a combination of levodopa–carbidopa, dopamine receptor agonists, or monoamine oxidase B inhibitors. Three were also on antidepressant medication, and two of those three were also taking anti-anxiety medication as needed. All participants completed self-report mood inventories including the Beck Depression Inventory (BDI-II) and the Beck Anxiety Inventory (BAI); control participants reported minimal symptoms of anxiety and depression while PD participants reported very mild levels of anxiety and depression (Table 1). While there are statistical differences between PD and MC groups on anxiety and depression scores, all participants were well below clinically significant levels of anxiety and depression disorder. No participant reported major mood or behavioral disturbance. Levodopa equivalent dosage (LED) was calculated as per recent convention (Tomlinson et al., 2010) to be 368.9 mg/day on average in the PD group. All PD participants met the clinical criteria for mild to moderate disease staging (Hoehn and Yahr stages I-III) as assessed by the Unified Parkinson's Disease Rating Scale (UPDRS) (MDS, 2003). The median Hoehn and Yahr staging was 2, ranging from 1 (unilateral) to 3 (moderate bilateral). Out of 24 participants with Parkinson's disease, 3 patients were classified as Hoehn and Yahr stage 1, 4 participants as stage 1.5, 12 participants as stage 2, 3 participants as stage 2.5, and 2 participants as stage 3. Twelve participants identified tremor as being their initial symptom, 7 participants identified rigidity, and 5 participants identified difficulty with gait or balance. Average total score on the UPDRS was 27.1 and average motor subscore was 16.1 (Table 1). Average disease duration of the PD group overall was 5.6 years. The average disease duration of PD individuals whose initial symptom was tremor was 5.9 years and for those whose initial symptom was akinetic/rigid was 5.3 years, which was not significantly different ($p > 0.5$). Of the 24 PD participants, 13 were classified as right-onset (RPD) and 11 were classified as left-onset (LPD). Average disease duration of LPD participants was 4.5 years, and average disease duration of RPD participants was 6.5 years, which was not statistically different ($p > 0.2$).

All participants were screened for contraindications to MRI. At study entry, the modified Mini-Mental State Examination (MMSE) was administered to screen for mental status. These scores were converted to standard MMSE scores on a scale of 30; all participants were classified as non-demented, averaging 28 points out of 30 (Table 1). Although

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