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Salience and default mode network coupling predicts cognition in aging and Parkinson's disease

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Abstract

Objective—Cognitive impairment is common in Parkinson's disease (PD). Three neurocognitive networks support efficient cognition: the salience network, the default mode network, and the central executive network. The salience network is thought to switch between activating and deactivating the default mode and central executive networks. Anti-correlated interactions between the salience and default mode networks in particular are necessary for efficient cognition. Our previous work demonstrated altered functional coupling between the neurocognitive networks in non-demented individuals with PD compared to age-matched control participants. Here, we aim to identify associations between cognition and functional coupling between these neurocognitive networks in the same group of participants.

Methods—We investigated the extent to which intrinsic functional coupling among these neurocognitive networks is related to cognitive performance across three neuropsychological domains: executive functioning, psychomotor speed, and verbal memory. Twenty-four non-demented individuals with mild to moderate PD and twenty control participants were scanned at rest and evaluated on three neuropsychological domains.

Results—PD participants were impaired on tests from all three domains compared to control participants. Our imaging results demonstrated that successful cognition across healthy aging and Parkinson's disease participants was related to anti-correlated coupling between the salience and default mode networks. Individuals with poorer performance scores across groups demonstrated more positive SN-DMN coupling.

Conclusion—Successful cognition relies on healthy coupling between the salience and default mode networks, which may become dysfunctional in PD. These results can help inform non-

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pharmacological interventions (rTMS) targeting these specific networks before they become vulnerable in early stages of Parkinson's disease.

Keywords

Cognitive impairment; Functional Magnetic Resonance Imaging; Intrinsic Connectivity Networks; Neurodegeneration; Default Mode Network; Salience Network

INTRODUCTION

Cognitive dysfunction is common in early stages of Parkinson's disease (PD), affecting up to half of newly diagnosed individuals at disease onset (Janvin, Aarsland, Larsen, & Hugdahl, 2003), many of whom are at risk of developing dementia as the disease progresses (Aarsland, Andersen, Larsen, Lolk, & Kragh-Sorensen, 2003; Williams-Gray et al., 2009). Cognitive impairment in PD is related to functional impairment in activities of daily living and lower quality of life (Klepac, Trkulja, Relja, & Babic, 2008), with earlier occurrence of cognitive impairment associated with more rapid decline (Janvin, Larsen, Aarsland, & Hugdahl, 2006; Uc et al., 2009). Cognitive deficits in PD are heterogeneous, manifesting most reliably as executive dysfunction (Dirnberger & Jahanshahi, 2013; Foltynie, Brayne, Robbins, & Barker, 2004; Miller, Neargarder, Risi, & Cronin-Golomb, 2013), impaired learning and memory (Bronnick, Alves, Aarsland, Tysnes, & Larsen, 2011; Lewis, Cools, et al., 2003), and decreased psychomotor processing speed (Uc et al., 2005). The pathophysiology of cognitive impairment in PD is complex, and is thought to involve cortical networks distinct from the circuitry subserving classic motor symptoms of PD (Bosboom, Stoffers, & Wolters, 2004; Huang et al., 2007). The pathogenesis and progression of cognitive impairment in PD is still not clearly understood (Barone et al., 2011). Elucidating the networks involved at the earliest stages of cognitive impairment could inform non-pharmacological treatment.

Cognition arises from dynamic interactions of distributed brain regions operating as large-scale networks (Bressler & Menon, 2010). Recent large-scale network analyses exploring cognitive function reveal three core neurocognitive networks that are disrupted across many neuropsychiatric disorders (Menon, 2011): the salience network (SN), the default-mode network (DMN), and the central executive network (CEN) (Greicius, Krasnow, Reiss, & Menon, 2003; Menon & Uddin, 2010; Seeley et al., 2007). Typically, in healthy individuals, the SN and CEN increase in activation during cognitive tasks requiring attention to external stimuli (Dosenbach et al., 2006), whereas DMN activity is suppressed (Greicius et al., 2003; Raichle et al., 2001). The SN is thought to be responsible for detecting and filtering information necessary to maintain goal-directed behavior by shifting attention between external and internal processes (Menon, 2011; Seeley et al., 2007), mechanistically observed as SN-mediated switching in activation between the CEN and DMN (Menon, 2011; Seeley et al., 2007). These patterns are observable during cognitive tasks as well as the resting state (Sridharan, Levitin, & Menon, 2008).

In PD, the hallmark features of striatal dysfunction and concomitantly altered corticostriatal-thalamo-cortical neurocircuitry (Kish, Shannak, & Hornykiewicz, 1988; Ravina et al., 2012)

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suggest that distributed cortical networks are affected by disease progression (Monchi, Petrides, Mejia-Constain, & Strafella, 2006; Moustafa, Krishna, Eissa, & Hewedi, 2013). Specifically, the SN is affected by striatal disruption as striatal neurons are highly interconnected with neurons in the insular cortex (Chikama, McFarland, Amaral, & Haber, 1997; Fudge, Breitbart, Danish, & Pannoni, 2005), a key node of the SN. Striatal dysfunction and the parallel loss of D2 signaling in the insula (Christopher, Marras, et al., 2014) are thought to disrupt SN activity, impairing its function in switching between other brain networks, including the CEN and DMN (Menon & Uddin, 2010). Our previous work has shown that functional coupling between the striatum and SN decreases as disease severity increases (Putcha, Ross, Cronin-Golomb, Janes, & Stern, 2015), emphasizing that the communication between the striatum and SN becomes dysfunctional as PD progresses.

Although interactions among all three core neurocognitive networks are relevant for efficient cognition, functional coupling between the SN and the DMN in particular is critically important for performing tasks requiring cognitive control, or switching attention between externally and internally salient stimuli (Fransson & Marrelec, 2008; Menon & Uddin, 2010; Sridharan et al., 2008). In response to externally salient events requiring a high level of cognitive effort, the SN is activated (Seeley et al., 2007) and the DMN is suppressed (Buckner, Andrews-Hanna, & Schacter, 2008), whereas during internally focused attention, such as self-monitoring or memory retrieval, the DMN is activated (Spreng, Mar, & Kim, 2009). This pattern results in anti-correlated activity between the SN and DMN during episodes of successful cognitive effort. Several studies have demonstrated that the SN has a causal influence on activity within the DMN across a range of cognitive tasks (Chiong et al., 2013; Jilka et al., 2014; Sridharan et al., 2008), suggesting that SN dysfunction impacts the modulation of DMN activity. We postulate that SN dysfunction due to PD-related striatal disruptions could also impact the interaction between the SN and DMN, leading to cognitive impairment.

In addition to striatal connections to the SN and DMN, the striatum is also connected with cortical areas that comprise the CEN through reciprocal circuitry with the dorsolateral prefrontal cortex and posterior parietal cortex (Middleton & Strick, 2000; Postuma & Dagher, 2006), which display abnormal activations in PD during cognitively demanding tasks (Lewis, Dove, Robbins, Barker, & Owen, 2003; Schendan, Tinaz, Maher, & Stern, 2013; Tinaz, Lauro, Hallett, & Horovitz, 2015; Tinaz, Schendan, & Stern, 2008). Our previous work has demonstrated diminished functional coupling between the SN and CEN as well as aberrant positive functional coupling between the CEN and DMN in individuals with PD compared to age-matched control participants (Putcha et al., 2015), suggesting that neurocognitive network interactions become dysfunctional in early stages of PD.

A unifying framework presenting large-scale network connectivity of neurocognitive networks allows a systematic examination of cognitive dysfunction (Bressler & Menon, 2010). Here, we investigate the association between cognitive performance and functional coupling across three neurocognitive networks in non-demented individuals with PD compared to age- and education-matched healthy control participants (MC). We hypothesized that we would observe cognitive deficits in PD compared to MC participants. We also hypothesized that better cognitive performance would be associated with anti-

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correlated functional coupling between the SN and DMN and positive functional coupling between the SN and CEN, consistent with the patterns observed in young neurologically normal adults (Fox et al., 2005; Sridharan et al., 2008). Identifying associations between cognitive changes in PD and functional communication between the core neurocognitive networks has important implications for extending our understanding of the neural mechanisms of cognitive impairment prior to the onset of dementia.

METHODS

Participants

The cohort studied here are the same individuals reported in Putcha et al., 2015. Twenty-four individuals diagnosed with PD (12 female, mean age 62.5 years, 2 left-handed) and 20 age- and education-matched control participants (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 Board of Boston University and the Partners Human Research Committee. All participants were screened for other neurological and psychiatric illness. Please refer to Putcha et al., 2015 and the supplemental materials for further detail.

Neuropsychological Assessment

An abbreviated three-domain neuropsychological assessment consisting of one test per domain (executive function, psychomotor speed/fine motor dexterity, and verbal memory) was used to assess cognitive abilities. Each of these cognitive tasks required the individual to focus on external demands and suppress internal self-referential thoughts, thereby exhibiting cognitive control of attentional resources. In order to compare performance across domains, performance scores from each test were converted to z-scores, normalized on the basis of the mean and standard deviation of the age- and education-matched control participants (MC). Independent samples t-tests were conducted on these z-scores to determine group differences on cognitive test performance. Effect sizes were also calculated and reported based on established methods (Lakens, 2013). Standard multiple linear regression was conducted in order to investigate whether functional connectivity between the core neurocognitive networks (SN, DMN, CEN) related to cognitive performance. Functional coupling measures and group membership, as well as the interaction of functional coupling and group membership were entered as predictors of cognitive performance across neuropsychological tests. We also conducted hierarchical linear regression entering age and education as demographic variables in Step 1, and our variables of interest in Step 2, to determine if the demographic variables were significantly affecting our findings. Subsequent mediational analyses using Sobel's test of mediational significance was conducted to further assess significant interaction effects. Within-group analysis was conducted using Pearson's correlations, between cognitive performance and the functional coupling of neurocognitive networks. Bonferroni correction was applied to address the multiple correlations across three cognitive tests, so p-values less than 0.016 are considered significant (0.05 divided by 3).

Executive functioning (set-shifting) was assessed with the Trail Making Test, consisting of two subtests, Parts A and B) (Tombaugh, 2004). Trails A is a test of simple attention and psychomotor speed, in which participants connect numbered circles in ascending order

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(1-2-3, etc.). Trails B is a measure of combined visual search, psychomotor speed, cognitive flexibility, and the ability to shift and maintain response set. Participants sequentially alternate between alphanumeric sequences (1-A-2-B, etc.). Test-retest reliability varies with age range and population studied (Dikmen, Heaton, Grant, & Temkin, 1999; Strauss, Sherman, & Spreen, 2006), but is considered adequate for Part A (0.79) and Part B (0.89). Time to completion on Trails B was used as our primary measure of executive function as it represents a holistic measure of both lower-order executive function (sustained attention) and higher-order set-switching abilities (Kortte, Horner, & Windham, 2002). As a secondary step to isolate only the set-switching ability, the time to complete Trials A was subtracted from the time to complete Trails B ("Trails B minus A") in order to isolate only the higher-order set-switching executive function.

Psychomotor speed/fine motor dexterity was assessed with the Purdue Pegboard Test (Tiffin & Asher, 1948). This test evaluates complex, visually guided coordinated movements in a timed fashion. This test has high test-retest reliability (0.81–0.89; (Buddenberg & Davis, 2000) and construct validity (0.78), as it correlates highly in normal adults with finger tapping and other manual dexterity tasks (Doyen & Carlier, 2002). The performance score indicates the average number of pegs successfully placed within a 30 second trial period. The left and right hands were evaluated in separate trials, and their scores were then averaged to create a composite across hands of psychomotor speed ("Purdue Pegs").

Verbal memory was assessed with the Rey Auditory Verbal Learning Test – 30 minute Delay Recall condition ("RAVLT Recall") (Rey, 1964). Participants recalled as many words as possible from a previously learned list after a 30-minute delay. This test has adequate test-retest reliability overall (0.60–0.70), with the delayed recall score among the more reliable subscores (Mitrushina, Satz, Chervinsky, & D'Elia, 1991).

Neuroimaging Procedure

Each scanning session included twenty minutes of structural imaging sequences followed by resting state data acquisition lasting six minutes and thirty-five seconds, during which the participants were asked to remain still and maintain eyes-open fixation on a projected image of a white cross on a black background. Please refer to Putcha et al., 2015, as well as the supplemental materials for further detail.

Motion correction and ICA-based denoising

From our initial data set of 26 PD and 24 MC participants, we identified and excluded 2 individuals with PD and 4 matched control individuals who demonstrated excess motion (greater than 2mm absolute displacement) from our analysis, using the Artifact Detection toolkit made for SPM8 software. Further details on these procedures can be found in our Supplemental Materials.

Inter-network Functional Coupling

The default mode (DMN), central executive (CEN), and salience networks (SN) were defined using a previously published set of templates from the BrainMap Database (Fox et al., 2005; Laird et al., 2011; Laird, Lancaster, & Fox, 2005). The DMN comprises medial

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prefrontal cortex, posterior cingulate/precuneus cortices, and bilateral posterior parietal cortex. The CEN is divided into left- and right- hemisphere localized CEN; the left-hemisphere localized network (L-CEN) comprises left-lateralized dorsolateral prefrontal cortex and inferior frontal gyrus, as well as posterior parietal cortex, while the right-hemisphere localized network (R-CEN) comprises right-lateralized dorsolateral prefrontal cortex and bilateral posterior parietal cortices. The SN comprises bilateral anterior insula/frontal opercula and the dorsal anterior cingulate gyrus. FSL's dual regression approach was used to calculate the orthogonalized subject specific timecourses and spatial maps for each network of interest within each of our individual subject's data (Beckmann, Mackay, Filippini, & Smith, 2009; Cole et al., 2010; Filippini et al., 2009; Janes, Farmer, Frederick, Nickerson, & Lukas, 2014). Subject-specific timecourses were extracted from the SN, DMN, R-CEN and L-CEN. Correlation coefficients (Pearson's *r*) were computed between the SN and DMN, the SN and CEN (both right and left hemisphere), and between the CEN (both right and left hemisphere) and DMN to determine the extent of inter-network functional coupling at the group level, and subsequently Fisher-*z*-transformed for use in further regression and correlational analyses. For further detail on this analysis, please refer to our previous publication on these findings (Putcha et al., 2015). To investigate if PD disease duration, disease severity, or dopamine replacement medication were related to these inter-network functional coupling measures, correlation coefficients (*r*) were computed between disease duration (number of years), disease severity (Hoehn and Yahr stage), levodopa equivalent dosage, and the functional coupling values (*z)* described above.

Volumetric Analysis

To ensure that volumetric differences between MC and PD participants were not impacting our results, the following analyses were conducted. MP-RAGE images were processed using FreeSurfer (version 5.3.0) (http://surfer.nmr.mgh.harvard.edu). Standard preprocessing of structural volumes produced reconstructions that were used to determine if there were any areas of cortical thinning or subcortical atrophy in the PD group compared to MC using the QDEC utility. We also compared striatal volume between MC and PD groups to determine if there were any volumetric differences.

RESULTS

No group differences in age, education, male: female ratio, overall mental status, cortical thinning or brain volume

As previously reported in this participant sample (Putcha et al., 2015), MC and PD participants were matched on age ($p>0.2$), education ($p>0.1$), male: female ratio ($X^2 =0.11$, $p > 0.7$), and MMSE scores ($p>0.5$, range 25.7 to 29.7). There were no between-group differences in whole brain cortical thinning or subcortical atrophy ($p>0.05$, Bonferroni corrected), and no group differences in striatal volume after controlling for intracranial volume ($p>0.4$).

Executive functioning

Set-shifting ability was assessed using the Trail Making Test consisting of two subtests (Parts A and B). We found that individuals with PD were impaired in set-shifting ability

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compared to MC individuals on *Trails B* (t=3.14, p=0.003, 95% CI [−9.7, −0.32], Hedges's g_s = 0.95; Figure 1) and *Trails B minus A* (t=2.5, p=0.016, 95% CI [−8.67, −0.16], Hedges's g_s = 0.76). We found no group differences in *Trails A* performance, the measure of simple attention (p > 0.1). Note that higher numbers on Trails indicate longer time to completion (worse performance).

Functional coupling between the SN and DMN (*beta= 0.42, p*= 0.04), but not group membership (*beta*= 0.35, *p*= 0.10), explained a significant amount of variance in *Trails B* performance. There was no significant interaction between group membership and functional coupling between SN and DMN (*beta*= −0.18*, p*= 0.5) in predicting *Trails B* performance. Within-group correlational analysis suggests that performance on this task was significantly related to functional coupling between the SN and DMN in MC participants only (Trails B; *r*= 0.53, *p*= 0.02; Figure 2A), and we did not observe this association in the PD group alone (*r*= 0.20=5, *p*= 0.26; Figure 2A). We found no other significant association between set-shifting ability and functional coupling between any of the other neurocognitive networks.

This analysis was repeated predicting performance on *Trails B minus A*, the composite measure designed to isolate set-shifting from simple attention and visual scanning. We found that functional coupling between the SN and DMN (*beta*= 0.45, *p*= 0.03), but not group membership (*beta*= 0.19, *p*= 0.4), explained a significant amount of variance in Trails *B minus A* performance. There was no significant interaction between group performance and functional coupling between SN and DMN (*beta* = −0.3*, p*= 0.24) in predicting Trails *B minus A* performance. Within-group correlation analysis revealed a significant correlation between SN-DMN functional coupling and the *Trails B minus A* performance in the MC group (*r*= 0.60, *p*= 0.007), but not the PD group (*r*= 0.11, *p*= 0.63).

This analysis was repeated predicting performance on *Trails A,* the measure of simple attention. We found that neither functional coupling between the SN and DMN (*beta= 0.38, p*= 0.07), nor group membership (*beta*= 0.34*, p*= 0.3), predicted *Trails A* performance. The interaction between group performance and functional coupling between SN and DMN did not predict *Trails A* performance (*beta*= −0.05*, p*= 0.8). Within-group correlational analysis did not reveal a significant association between SN-DMN functional coupling and *Trails A* performance in the MC group (r=0.37, p=0.11) or the PD group (r=0.35, p=0.10).

Covarying age and education into Step 1 of a hierarchical linear regression did not change these results and by themselves, these demographic variables did not predict performance on the Trail Making Test, *F(2,39)* = 1.2, *p*= 0.31. There were no other significant main effects of functional connectivity between any of the other neurocognitive network pairs in predicting Trail Making Test performance, though main effect of group was observed across these other models in predicting performance on this test emphasizing group differences on cognitive test performance.

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Psychomotor speed

Psychomotor speed/fine motor dexterity was assessed with the Purdue Pegboard Test. We found that PD participants were impaired on this task compared to MC participants (t=5.32, p<0.001, 95% CI [−7.53 1.75], Hedges's g_s = 1.60; Figure 1).

Functional coupling between the SN and DMN (*beta*= −0.52, *p*= 0.001), but not group membership (*beta*= −0.21, *p*= 0.2), explained *Purdue Pegboard* performance. We also found a significant interaction between group membership and functional coupling between SN and DMN (*beta= 0.69, p= 0.002).* However, the Sobel test of mediational significance suggests that group membership does not mediate this relationship *(Sobel t*= 1.18, *p*= 0.23). Within-group correlational analysis within the MC group alone revealed a significant association between *Purdue Pegboard* performance and coupling between the SN and DMN (*r*= −0.68, *p*= 0.001; Figure 2B), and no association in the PD group alone (*r*= 0. 27, *p*= 0.23; Figure 2B).

Age and education in Step 1 of a hierarchical linear regression did predict performance on Purdue Pegboard Test (*F(2,39)* = 4.1, *p*= 0.02). Over and above this effect, we still observed a significant main effect of group membership (*beta* = −0.35, *p*=0.03), a significant main effect of functional coupling between the SN and DMN (*beta* = −0.45, *p*=0.005*),* and a significant interaction between group and functional coupling (beta = 0.56, *p*=0.01). There were no other significant main effects of functional connectivity between any of the other neurocognitive network pairs (SN-CEN, CEN-DMN) in predicting *Purdue Pegboard* performance, though a main effect of group was observed across these other models in predicting performance on the Purdue Pegboard Test emphasizing group differences on cognitive test performance.

Verbal memory retrieval

Verbal memory retrieval was assessed using the Rey Auditory Verbal Learning Test – 30 minute Delay Recall condition. The PD group showed poorer performance than the MC group (t=2.21, p=0.04, 95% CI [−7.97 1.21], Hedges's g_s = 0.62; Figure 1).

Functional coupling between the SN and DMN (*beta= −*0.48, *p*= 0.024), but not group membership (*beta* = −0.04, *p*= 0.8), explained a significant amount of variance in *RAVLT delayed recall* performance. The interaction between group membership and SN-DMN functional coupling did not significantly predict performance on the RAVLT delayed recall (*beta* = 0.47, *p*=0.08*).* Within-group correlational analysis examining the MC group separately revealed a significant association between performance on *RAVLT delayed recall* and functional coupling between the SN and DMN (*r*= −0.52, *p*= 0.02; Figure 2C), and no such association within the PD group (*r*= 0.03, *p*= 0.9; Figure 2C).

Age and education in Step 1 of a hierarchical linear regression did not change these results and by themselves, these demographic variables did not explain a significant amount of variance in predicting cognitive performance on the RAVLT delayed recall condition (*F(2,39)* = 6.5, *p*= 0.5). There were no other significant main effects of functional connectivity between any of the other neurocognitive network pairs in predicting RAVLT

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verbal delayed recall performance (SN-CEN, p> 0.5; CEN-DMN, p> 0.2), though main effect of group was observed across models in predicting performance on this test.

Associations with disease and levodopa equivalent dosage (LED)

No measures of functional coupling were related to disease duration, disease severity (Hoehn and Yahr stage), or levodopa equivalent dosage (LED). No cognitive measures were related to LED. Psychomotor speed (Purdue Pegboard) was the only cognitive measure score related to disease duration (r=−0.45, p=0.04), such that longer disease duration was related to worse performance.

Between-groups inter-network functional coupling

Across all subjects, L-CEN was significantly and negatively correlated with the DMN (r= −0.45, p=0.002) and positively correlated with the SN (r=0.66, p<0.001). As previously reported in this participant sample (Putcha et al., 2015), inter-network functional coupling was significantly different between groups, such that SN coupling with R-CEN was diminished in PD compared to MC (t= 2.45, p=0.019, 95% CI [−7.63 0.43], Hedges's g_s = 0.69), and R-CEN coupling with DMN was aberrantly positive in PD compared to the expected anti-correlation between these networks observed in the MC group (t=−2.06, p=0.04, 95% CI [−8.08 −0.001], Hedges's g_s = 0.59).

Surprisingly, here we did not observe differences in functional coupling between the SN and DMN in the PD group compared to the MC group (p>0.6), and there were no significant correlations between cognitive performance and functional coupling between any of the three neurocognitive networks within the PD group alone. We did not find any evidence that functional coupling between any of the other neurocognitive networks predicts task performance in any of the regression models conducted.

DISCUSSION

There were two main findings in this study. First, we found evidence of cognitive dysfunction across domains of executive functioning, psychomotor speed, and verbal memory delayed recall in a group of non-demented individuals with PD compared to age- and education- matched control participants, replicating what has been previously reported (Barone et al., 2011; Kudlicka, Clare, & Hindle, 2011). Our novel finding is that functional coupling between the salience network (SN) and the default mode network (DMN) predicts performance in all three cognitive domains regardless of group membership. Within-group analysis suggest this finding may be more robust in the control participants, as the significant correlations between SN-DMN functional coupling and performance on each of these measures were observed in the MC participants, but not in PD alone. The results suggest that functional coupling between the SN and DMN is important for successful cognition across domains. We postulate that PD-related striatal disruption may lead to abnormal network dynamics, exacerbating cognitive dysfunction as the disease progresses.

Cognitive impairment in early stages of PD is present in many individuals, but is often under-recognized using routine screening methods (Mamikonyan et al., 2009). In the present study we found evidence of cognitive deficits across tests of executive functioning,

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psychomotor speed, and verbal memory recall in PD individuals with MMSE scores that were comparable to those of age- and education- matched control participants. Successful cognitive performance on these tasks requires switching between externally and internally salient stimuli, resulting in anti-correlated network coupling between the SN and the DMN. Our findings demonstrate that successful performance on tasks requiring a high level of cognitive control is related to anti-correlated intrinsic functional coupling between the SN and DMN.

Large-scale functional networks exert coordinated effects across distributed cortical areas during many different cognitive functions (Bressler & Menon, 2010). In particular, the three core neurocognitive networks examined here (SN, DMN, CEN) are thought to interact dynamically to influence cognitive task performance (Fox, Snyder, Vincent, & Raichle, 2007; Seeley et al., 2007; Sridharan et al., 2008). The SN plays the critical role of responding to external events that are behaviorally salient, and switching between activation of the DMN and CEN (Menon & Uddin, 2010). The SN becomes dysfunctional in PD as its key nodes, the anterior insula and dorsal anterior cingulate cortex, become direct targets of PD-related striatal disruption (Christopher, Koshimori, Lang, Criaud, & Strafella, 2014; Christopher, Marras, et al., 2014). This suggests that striatal dysfunction directly impacts the functional integrity of the insula, and therefore the SN, in individuals with PD.

Interactions between the SN and the DMN are crucial in the control of attention required for demanding cognitive tasks. In healthy young adults, greater anti-correlation between the SN and DMN has been associated with more efficient cognitive control (Kelly, Uddin, Biswal, Castellanos, & Milham, 2008). Failures of DMN deactivation have been associated with reduced sustained attention (Weissman, Roberts, Visscher, & Woldorff, 2006), and are observed across many neurological diseases (Leech & Sharp, 2014). In PD, it is proposed that as the SN becomes dysfunctional it is no longer able to suppress DMN activity effectively (Bonnelle et al., 2012; Jilka et al., 2014). Decreased intra-network DMN connectivity in PD at rest was associated with decreased processing speed and increased time on tasks requiring a high level of cognitive control (Disbrow et al., 2014), suggesting that DMN integrity is critical for efficient cognition. Compared with cognitively intact individuals, individuals with PD who have mild cognitive impairment also demonstrated dopaminergic deficits within the SN and DMN that have been associated with disrupted memory retrieval (Christopher et al., 2015).

Surprisingly, we did not observe group differences in functional coupling between the SN and DMN. This may be explained by the fact that we examined functional coupling between timecourses across entire networks, rather than focusing on each of the individual nodes comprising each network. Previous work has established decreased functional connectivity within just the posterior nodes of the DMN (medial temporal lobes and inferior parietal cortices) but not within the anterior node (medial prefrontal cortex) (Tessitore et al., 2012). Further, the medial prefrontal cortex has demonstrated comparable task-related deactivations compared with control participants, while the posterior cingulate cortex showed less deactivation during task than expected (van Eimeren, Monchi, Ballanger, & Strafella, 2009). These findings suggest that the posterior DMN nodes in particular may be dysfunctional. Investigations into the functional coupling between the SN and these posterior hubs of the

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DMN may reveal the dysfunctional coupling we hypothesized. Future longitudinal follow-up investigations would also help to elucidate the progression of network-level cortical changes over time.

One of the primary findings of this study was that functional coupling between the SN and the DMN predicts cognitive performance across multiple cognitive domains. In contrast, we did not observe an association between cognitive performance and SN-CEN interactions, as hypothesized. In our previous paper (Putcha et al, 2015), we reported on alterations in intrinsic SN-CEN and CEN-DMN functional coupling between MC and PD. In this follow up study, we examined associations between functional coupling and cognitive performance, and did not find a link between cognition and SN-CEN coupling, but we did with SN-DMN connectivity. This finding is in line with recent work emphasizing the role of the DMN over the CEN in highly demanding cognitive tasks (Disbrow et al., 2014; Duan et al., 2012). In contrast with the DMN, nodes within the CEN are not a major site of dopamine deficiency in PD (Christopher et al., 2015) and the CEN does not demonstrate intra-network connectivity changes compared to healthy control participants in early stages of PD (Disbrow et al., 2014). Taken together, this evidence suggests that although the CEN is an important network for efficient cognition (Menon, 2011), coupling between the SN and DMN is of primary importance in supporting cognitive performance in both healthy aging and PD.

It is worth noting that PD participants in this study were evaluated during peak levels of dopaminergic medications, which limits our ability to address questions related to the effects of dopamine on neurocognitive network interactions in the absence of medication effects. These results should be regarded as conservative. In addition, dopaminergic medications used to treat Parkinson’s disease have been shown to affect striatal activity, but not cortical activity (Martinu, Degroot, Madjar, Strafella, & Monchi, 2012). Although our measure of levodopa equivalent dosage (LED) did not correlate significantly with any measure of functional coupling or with cognitive performance, we cannot completely rule out the possibility that dopamine medication is related in some way to the association between functional network coupling and cognitive performance in our PD group. There is some evidence that dopaminergic therapy diminishes DMN integrity (Krajcovicova, Mikl, Marecek, & Rektorova, 2012). However, examining the network connectivity of individuals with PD on their typical medication regimens has great utility as most patients experience cognitive dysfunction and disrupted activities in daily living even during peak medication states (Narayanan, Rodnitzky, & Uc, 2013). It is also worth noting that dopamine replacement therapy does not ameliorate cognitive disturbances specific to attentional set-shifting and other aspects of executive functioning (Lewis, Slabosz, Robbins, Barker, & Owen, 2005; Poletti & Bonuccelli, 2013), which are subserved by the neurocognitive networks examined in our present study. We also acknowledge the possibility that the low doses of anxiolytic and antidepressant medications could also have an effect on functional network disruption, though it is unlikely as only three PD participants were receiving these medications and our results did not change when excluding them.

We provide evidence in this study of functional coupling between SN and the DMN relating to cognitive task performance. This finding may be more robust in our healthy older adults,

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as this association was observed strongly in the MC group alone but not in the PD group. We postulate that as these PD participants progress in disease severity, dysfunctional neurocognitive network interaction specific to the SN and DMN may underlie the progression of cognitive deficits ultimately leading to dementia. This work supports previous investigations highlighting the SN and DMN as networks critical for supporting high-level cognitive functioning, which has clinical implications for non-pharmacological treatment. With converging evidence suggesting that these networks become vulnerable in early stages of PD progression, the SN and DMN represent potential targets of non-invasive treatment approaches, such as repetitive transcranial magnetic stimulation, which may serve to improve quality of life and extend independence in daily living.

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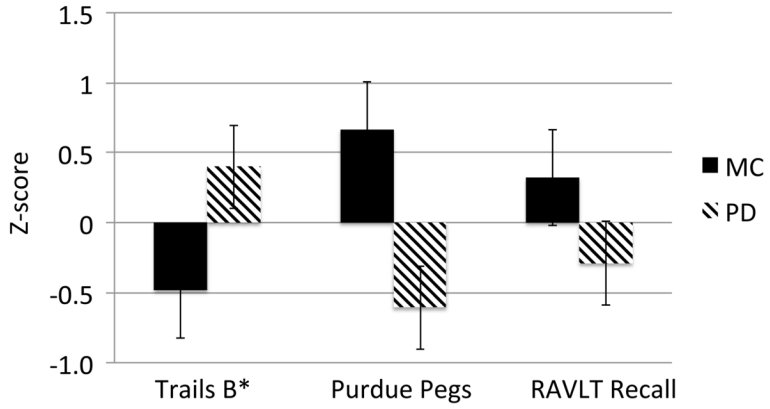

Figure 1. Cognitive performance

PD participants performed significantly worse than MC participants across multiple cognitive domains, including executive function (Trail Making Test Part B; t= -3.14, p=0.003), psychomotor processing speed (Purdue Pegboard; t=5.3, p<0.001), and delayed verbal recall (RAVLT 30 minute Delay Recall; t=2.05, p=0.04). *Negative Trails B scores indicate better (faster) performance on this test.

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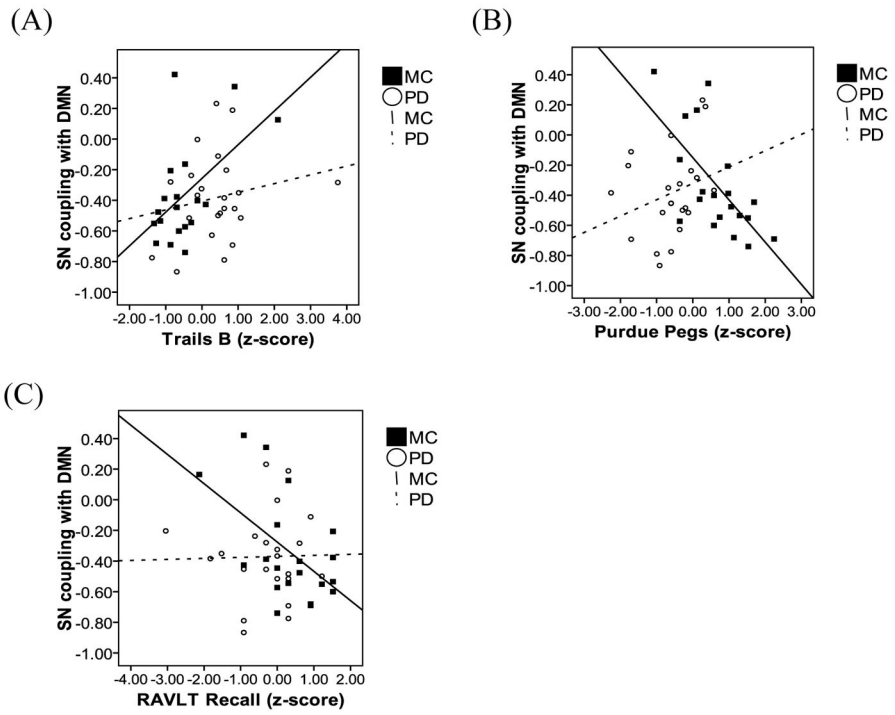

Figure 2. SN coupling with DMN relates to cognition in MC but not PD

Functional coupling between the Salience Network (SN) and the Default Mode Network (DMN) is related inversely to better cognitive performance in MC across all three cognitive domains: *(A)* Executive function (Trail Making Test- Part B; r= 0.53, p=0.02), *(B)* Psychomotor Processing Speed (Purdue Pegboard; r= −0.68, p=0.001), and *(C)* Verbal Memory Recall (RAVLT 30-minute Delay; r= −0.52, p=0.02). This association suggests that anti-correlations between the SN and DMN are related to better cognitive performance in MC. There are no significant associations between cognitive performance and functional coupling between these networks in PD. Each data point represents an individual participant.

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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)	--

Values presented in the table are means ± standard deviations, unless otherwise noted.

* Indicates group differences at a significance level of $p<0.05$,

** $p < 0.005$.

MMSE: Mini-Mental State Examination. UPDRS: Unified Parkinson's Disease Rating Scale. BDI-II: Beck Depression Inventory, 2nd Edition. BAI: Beck Anxiety Inventory.