RESEARCH ARTICLE

A divergent breakdown of neurocognitive networks in Parkinson's Disease mild cognitive impairment

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Abstract

Cognitive decline is a major disabling feature in Parkinson's disease (PD). Multimodal imaging studies have shown functional disruption in neurocognitive networks related to cognitive impairment. However, it remains unknown whether these changes are related to gray matter loss, or whether they outline network vulnerability in the early stages of cognitive impairment. In this work, we intended to assess functional connectivity and graph theoretical measures and their relation to gray matter loss in Parkinson's disease with mild cognitive impairment (PD-MCI). We recruited 53 Parkinson's disease patients and classified them for cognitive impairment using Level-1 Movement Disorders Society-Task Force Criteria. Voxel-based morphometry, functional connectivity and graph theoretical measures were obtained on a 3-Tesla MRI scanner. Loss of gray matter was observed in the default mode network (bilateral precuneus), without a corresponding disruption of functional or graph theoretical properties. However, functional and graph theoretical changes appeared in salience network nodes, without evidence of gray matter loss. Global cognition and executive scores showed a correlation with node degree in the right anterior insula. We also found a correlation between visuospatial scores and right supramarginal gyrus node degree. Our findings highlight the loss of functional connectivity and topological features without structural damage in salience network regions in PD-MCI. They also underline the importance of multimodal hubs in the transition to mild cognitive impairment. This functional disruption in the absence of gray matter atrophy suggests that the salience network is a key vulnerable system at the onset of mild cognitive impairment in PD.

KEYWORDS

default mode network, functional neuroimaging, Parkinson's disease, salience network

1 | INTRODUCTION

Progressive cognitive impairment is a major challenge in Parkinson's disease (PD). Mild cognitive impairment in PD (PD-MCI) is considered a transitional state between normal cognition (PD-NC) and Parkinson's disease dementia (PDD) and is considered an independent risk factor for dementia (Aarsland & Kurz, 2010). Research on PD-MCI has progressed substantially since the Movement Disorder Society-Task Force (MDS-TF) defined consensus criteria for PD-MCI (Litvan et al., 2012). However, predicting which PD-MCI patients will develop dementia based on neuropsychological testing alone has proven elusive, and objective biomarkers that allow early diagnosis and progression tracking of cognitive deterioration in PD are needed.

A neural networks perspective (Gratwicke, Jahanshahi, & Foltynie, 2015) could be useful to bridge the gap between pathophysiology and clinical phenotypes. The concept of large-scale brain networks provides a scaffold of connected brain areas serving specific cognitive functions (Menon, 2011). The dysfunction of these large-scale brain networks could identify subjects at risk of dementia before local structural changes appear (Tessitore et al., 2012). Analysis of resting-state via functional MRI (fMRI) is one of the most promising tools in this neural networks perspective. Work by Seeley, Crawford, Zhou, Miller, and Greicius (2009) has shown that neural networks, defined on an fMRI basis, are targeted by particular neurodegenerative diseases (Seeley et al., 2009). This link between neurodegenerative diseases and cognitive function has been further developed into a triple model of cognition (Menon, 2011), comprising the default mode network (DMN), the salience network (SN), and the central executive network (CEN).

The DMN was the first to be described (Greicius, Krasnow, Reiss, & Menon, 2003), corresponding to regions of the medial prefrontal cortex, posterior cingulate, precuneus and lateral and medial prefrontal cortices. It is thought to be responsible of mental processes during resting state, such as self-reflection and screening of internal thoughts. The CEN, composed by areas of the dorsolateral prefrontal cortex and the posterior parietal cortex, is instrumental in cognitive-demanding processes and goal-directed behaviour. Switching between self-directed and stimulus-driven processes is achieved via SN, which is anchored in the insular and anterior cingulate cortices (Seeley et al., 2007). This network serves as a fulcrum that pivots between default and central executive activities.

Some neurodegenerative diseases show characteristic disruptions in these cognitive networks: Alzheimer's disease (AD) shows reduced DMN connectivity, coherent with a predominant amnesic presentation, whereas frontotemporal dementia shows a predominant SN disruption that is congruent with the diminished social-emotional function (Zhou et al., 2010). Furthermore, some aspects of the clinical phenotype can be ascribed to disruptions of network interaction, such as the impaired moral reasoning in frontotemporal dementia, explained by Chiong et al. (2013) as a loss of SN influence over the DMN during a moral reasoning task.

These three networks have also shown changes related to cognition in PD. A study by Tessitore et al. (2012) in PD-NC shows decreased DMN activity compared to healthy controls, without

evidence of gray matter loss on its territories. In PD-MCI, loss of intra-DMN connectivity has been correlated with cognitive decline (Sala-Illonch, Baggio, Valdeoriola, & Compta, 2015). On the other hand, SN has been linked to nonmotor aspects of PD, given its integrative role of executive, sensorimotor and salience processing (Christopher, Koshimori, Lang, Criaud, & Strafella, 2014). In PD-MCI, loss of D2 dopaminergic receptors in SN territories has been correlated with executive and memory deficits in a small sample of PD-MCI patients (Christopher et al., 2015). The interaction between these large-scale networks has also been probed, showing that changes in network anticorrelations between the SN and the DMN correlate with widespread deficits in attentional, motor, visual, and executive functions (Peraza et al., 2015). However, studies aimed to identify vulnerable traits in these networks at the onset of PD-MCI are still lacking. The decline of SN connectivity in patients who develop PD-MCI and PDD could be a potential marker of cognitive impairment in the early stages of PD. Thus, the characterization and analysis of these early changes in connectivity could be useful for the early detection of PD-MCI. Moreover, early identification of patients at risk for dementia could be key to more accurately selecting participants for clinical trials assessing disease-modifying treatments.

The goal of this study was to analyze early changes in relevant hubs of neurocognitive networks in PD-MCI, using a multimodal approach in a sample of nondemented PD patients. We analyzed (a) functional connectivity and anticorrelations through a region of interest (ROI) analysis of the three neurocognitive networks; (b) graph theory metrics to explore the topological properties of key nodes in these networks; and (c) structural parameters via voxel-based morphometry (VBM) in the regions that showed functional and topological changes. Our main hypotheses were (a) alterations in SN connectivity are key to early detection of PD-MCI; (b) loss of normal anticorrelation patterns between large scale neural networks characterizes PD-MCI; and (c) changes found in functional connectivity cannot be explained by the loss of gray matter volume (GMV).

2 | METHODS

2.1 | Participants

We prospectively recruited 57 patients with idiopathic PD who attended the Movement Disorders Outpatient Unit and who were willing to participate in this study. Inclusion criteria were diagnosis of PD according to the United Kingdom PD Society Brain (Hughes, Daniel, Kilford, & Lees, 1992) and exclusion criteria were (a) presence of dementia, according to the Movement Disorders Society Criteria (Emre et al., 2007); Hoehn & Yahr scale > III; (b) presence of any other significant psychiatric, neurological or unstable systemic comorbidities; (c) pathological MRI findings beyond mild white matter hyperintensities, or not compatible with PD in FLAIR sequence; and (d) presence of head motion or other MRI artifacts. Two patients were excluded because of dementia, and two were excluded after reviewing MRI images for quality control. Patients included in the study were assessed by a multidisciplinary team of neurologists,

neuropsychologists and nurses. All patients were taking a combination of antiparkinsonian drugs. Medication was not changed for this study and all assessments (clinical, neuropsychological, and MRI acquisition) were performed with the patients in the “on” state.

All patients provided written informed consent according to the Declaration of Helsinki. The study was approved by the Ethics Committee for Clinical Research at the Hospital de la Santa Creu i Sant Pau.

2.2 | Cognitive assessment

For the diagnosis of PD-MCI, we employed the Level-1 Task Force criteria, which provide an assessment of global cognition and precise cut-off scores for PD-MCI. A cut-off score of 83 points or less for the total PD-CRS score has been shown to provide high sensitivity and specificity for the diagnosis of PD-MCI (Fernández de Bobadilla et al., 2013). Compared to Level-2 criteria, a clear cut-off score using a properly validated test of global cognitive function in PD populations is less influenced by the various neuropsychological tasks used by different research groups. We also administered a comprehensive neuropsychological battery that included two neuropsychological tests per cognition domain. These tests were used to identify subtypes of PD-MCI, outline their potential neural correlates, and to explore the link between graph theoretical parameters and cognitive subdomains. Attention and working memory were assessed using the Digit Span Forward and Trail Making Test-A; executive dysfunction was measured using the Trail Making Test-B and phonemic fluency; visuospatial function was determined by the Rey-Osterrieth complex figure (ROCFT) and the Visual Object and Space Perception Battery (VOSP; number location); language function was evaluated using the Boston Naming Test and Token Test; and memory function was assessed using the Free and Cued Selective Reminding Test (FCSRT) and ROCFT.

2.3 | MRI acquisition

MRI scans were acquired in a 3-Tesla Philips Achieva station. T1-weighted images were acquired using a specific axial T13D-MPRAGE MRI (TR/TE 500/50 ms, flip angle = 8°, field of view (FOV) 23 cm, with in-plane resolution of 256 × 256 and 1 mm slice thickness). Resting-state BOLD images during 12 min were also obtained. (TR = 2000 ms, FOV 240 mm, voxel size 3 mm, TE = 30 ms, flip angle 78°).

2.4 | Voxel-based morphometry

GMV imaging data were obtained from T1-weighted images using a VBM approach in SPM12. The processing pipeline method is described in detail in our previous work (Martinez-Horta et al., 2016). Briefly, the original T1-MRI images were segmented to obtain their corresponding gray matter tissue probability maps. These maps were then spatially normalized into MNI space using DARTEL. Isotropic smoothing (FWHM = 8 mm) was then applied.

The GMV images were individually smoothed and entered into a voxelwise, second-level, two-sample *t*-test between PD-NC and PD-MCI patient groups to determine GMV differences. This statistical

model included age, sex, UPDRS-III, and total intracranial volume as covariates of no interest. Results were considered significant using $p < 0.05$ false discovery rate (FDR) corrected and a minimum extent of 100 contiguous voxels.

2.5 | Functional connectivity analysis

Functional connectivity was analyzed using CONN v14p software and its standard processing pipeline (described in depth in (Whitfield-Gabrieli & Nieto-Castanon, 2012)).

The set of functional brain networks described in (Shirer, Ryali, Rykhlevskaia, Menon, & Greicius, 2012) and available at https://findlab.stanford.edu/functional_ROIs.html was introduced in CONN to explore connectivity changes within these regions in our sample. In particular, we focused on the DMN, SN, and CEN ROI. A detailed depiction of each ROI is provided in Figure S7.

A ROI-to-ROI analysis between the network components was performed from the Z-score connectivity matrices of each subject. Both intragroup (PD-NC, PD-MCI) and intergroup (PD-NC vs. PD-MCI) connectivity patterns were studied and compared; using age, sex and UPDRS-III as nuisance covariates. Significance was set at $p < 0.05$ corrected for multiple comparisons (FDR).

2.6 | Graph theoretical analysis

Graph theoretical measures were computed and compared across groups using a connectivity cost threshold of 0.15, which in our sample represented the best combination of global and local efficiency, and thus, of small-worldness. The adjacency matrices were built using both one- and two-way edge thresholds to account for the possible effects of negative correlations. We analyzed the seven parameters offered by Conn toolbox (global efficiency, local efficiency, betweenness centrality, average path length, clustering coefficient, cost, and node degree). Age, sex, and UPDRS-III were used as covariates of no interest within all group analyses. Results were considered significant at $p < 0.05$ FDR-corrected.

We also extracted the values of node degree for each patient, and wherever significant differences were found between cognition groups, these measures were entered into a correlation analysis alongside parameters of global cognition (PD-CRS) or the appropriate neuropsychological measures related to that node (for instance, anterior insulae-executive function). With these parameters, we ran a correlation analysis of the whole PD sample using SPSS software and Microsoft Excel for visual plotting.

3 | RESULTS

3.1 | Clinic and sociodemographic data

Fifty-three patients with early-to-mid stages of PD were included (age 68.4 ± 7 years; disease duration 6.4 ± 3 years, UPDRS III 23.5 ± 9). Thirty-four patients were classified as PD-NC and nineteen as PD-MCI. Groups did not differ in terms of education, disease duration,

TABLE 1 Clinical and sociodemographical data of patients according to cognition status based on level-I criteria

	Cognitive status		<i>p</i> value
	PD-NC	PD-MCI	
<i>N</i>	34	19	
Age, year	65.8 ± 6.7	73 ± 4.5	<0.01
Sex, % men	69% 24/34	52% male, 10/19	0.11
PD onset, year	6.4 ± 3	6.3 ± 3.2	0.9
Education, year	13 ± 4.3	11 ± 4.61	0.07
Laterality, % left	47% left	42% left	0.8
PD-CRS total score	98.8 ± 10	72.7 ± 7	<0.01
UPDRS III	22.6 ± 8.8	29 ± 7	<0.01
H&Y	1.9 ± 0.7	2 ± 1.01	0.57
LEDD	681 ± 363	597 ± 237	0.31

Note. Clinical and sociodemographical data according to neuropsychological testing.

Abbreviations: H&Y, Hoehn and Yahr rating scale; LEDD, Levodopa equivalent daily dose; PD-CRS, Parkinson's disease cognitive rating scale; PD-MCI, Parkinson's disease mild cognitive impairment; PD-NC, Parkinson's disease normal cognition; UPDRS III, unified Parkinson's disease rating scale.

disease severity, or levodopa equivalent daily dose (LEDD), but showed differences in age, sex, and UPDRS III score. These parameters were therefore introduced as covariates in the analyses between

the two groups. Regarding cognitive subdomains, the 19 PD-MCI patients were classified as multiple-domain according to Level-2 criteria (see Table 1). Thus, we could not describe the imaging findings for specific PD-MCI subtypes (such as disexecutive-predominant PD-MCI vs. visuospatially predominant PD-MCI).

3.2 | VBM results

With the restrictive criteria controlled for FDR, PD-MCI patients showed significantly less gray matter in the bilateral precuneus and the posterior cingulate cortex than PD-NC patients (Figure 1). No increases in gray matter were observed in the PD-MCI group compared to PD-NC.

3.3 | Functional connectivity: ROI to ROI intrinsic connectivity

We tested connection strength and node relevance for each network in both PD-MCI and PD-NC groups. We then analyzed SN connectivity. In PD-NC patients, SN showed the highest coherence between the left anterior insula (AI) and right AI ($T = 18.3$). Other statistically significant relations were found between the two supramarginal (Sm) gyri ($T = 17.14$). In PD-MCI patients, the strongest connectivity was observed between the right and left mid-frontal cortices

FIGURE 1 Voxel-based morphometry showing decreases in gray matter volume in PD-MCI compared to PD-NC patients, according to the PD-CRS classification (for a statistical threshold of $p < 0.05$ corrected for multiple comparisons). The main areas of volume reduction are located in the bilateral precuneus and the posterior cingulate cortex. Abbreviations: PD-CRS, Parkinson's disease cognitive rating scale; PD-MCI, Parkinson's disease mild cognitive impairment; PD-NC, Parkinson's disease normal cognition [Color figure can be viewed at wileyonlinelibrary.com]

FIGURE 2 Summary of functional connectivity results. All tests shown met a $p < 0.05$ FDR-corrected threshold. (a) One sample t -test comparison of salience and default mode networks across PD cognition showed less connection strength in key SN nodes in PD-MCI patients. (b) Anticorrelations between salience and default mode networks showed a reduction in quantity and strength. (c) Group comparison, showing greater connectivity of SN in PD-NC, and increased connectivity of SN and DMN in PD-MCI. Abbreviations: DMN, default-mode network; PD-MCI, Parkinson's disease mild cognitive impairment; PD-NC: Parkinson's disease normal cognition; SN: salience network [Color figure can be viewed at wileyonlinelibrary.com]

($T = 13.74$), while connectivity between the two insulae ($T = 8.3$) and the two supramarginal gyri ($T = 10.3$) decreased.

The DMN showed a less stark contrast between cognitive states. In PD-NC patients, strong connections bound posterior elements of the DMN, such as both precuneus ($T = 27.36$) and those with posterior cingulate cortex (PCC, $T = 19.4$). In PD-MCI, similar connections remained between left and right precuneus ($T = 16.7$), and between bilateral precuneus and PCC ($T = 13.3$). Thus, though decreases in network connectivity were also apparent in the DMN, the overall network structure (i.e., which nodes were the most connected) remained similar. The depiction of SN and DMN connectivity is shown in Figure 2a. A more detailed connectivity table is provided in Figures S1 and S2.

CEN followed a similar functional pattern, with mild differences between cognitive states. The strongest connections in both PD-NC and PD-MCI groups were found between mid-frontal cortices and ipsilateral angular gyri.

3.4 | Functional connectivity: Differences between cognition groups

Network intrinsic connectivity provides an initial overview of the changes between groups, but to properly outline differences in cognitive networks between PD-NC and PD-MCI patients, we followed the same criteria for ROI selection and entered our data in a two-sample t -test. Results are shown in Figure 2c. Details of individual connections are available in Figure S3.

Network coherence analysis showed greater connectivity between the two anterior insulae, anterior cingulate cortex and right supramarginal gyrus in PD-NC patients than in PD-MCI patients. PD-MCI patients showed greater functional coupling between hubs of normally anticorrelated DMN and SN-CEN hubs: while an increased connectivity was observed between the right anterior insula (SN) and both the posterior cingulate cortex (DMN) and left angular cortex (DMN), no connectivity differences within DMN hubs were found between groups.

Interestingly, when GMV of the precuneus was introduced as a nuisance covariate in order to explore the link between structural and functional findings, no differences in intrinsic SN connectivity could be established between the two groups (Figure S8). However, introducing the LEDD did not result in significant changes in the group comparisons (Figures S10 and S11).

3.5 | Functional connectivity: Anticorrelations

In the anticorrelation analysis, ROIs pertaining to both SN and DMN were chosen for comparisons using a one-tailed, one-sample *t*-test in both cognition groups. Results are shown in Figure 2b, and connectivity measures are shown in Figure S4.

In PD-NC patients, main anticorrelations appeared between right AI and PCC ($T = -9.8$), and between right AI and left angular gyrus ($T = -7.6$). Thus, anticorrelated regions in the PD-NC group featured a more anterior insular cluster and a posterior DMN-related group of

nodes structured around PCC, precuneus, and left angular cortex. In PD-MCI patients, however, the volume and intensity of these anticorrelations were drastically reduced, and though a posterior, DMN-centered cluster persisted, few anticorrelations between these hubs and insular SN survived the statistical threshold.

3.6 | Graph theoretical analysis

As described in Section 2, we analyzed seven graph theory parameters: global efficiency, local efficiency, betweenness centrality, average path length, clustering coefficient, cost, and node degree. Figure 3 shows the results of NC > MCI contrasts.

In keeping with previous connectivity results, the main findings in GT measures were found in SN hubs. Both anterior insulae and both supramarginal gyri showed a greater node degree and cost in PD-NC patients than in PD-MCI patients. Local efficiency was also higher in the right anterior insula in the PD-NC group. No differences were found in

FIGURE 3 Summary of graph theory findings. In direct contrasts between PD-NC and PD-MCI patients, node degree was higher in the anterior insulae and supramarginal gyri in the PD-NC group ($p < 0.05$, FDR-corrected). Global cognition (PD-CRS) and executive scores were correlated with node degree in the right anterior insula. Visuospatial function (VOSP number location) was correlated with node degree in the right supramarginal gyrus. Abbreviations: PD-CRS, Parkinson's disease cognitive rating scale; PD-MCI, Parkinson's disease mild cognitive impairment; PD-NC, Parkinson's disease normal cognition; VOSP, visual object and space perception battery [Color figure can be viewed at wileyonlinelibrary.com]

the remaining parameters analyzed for this statistical threshold. Connectivity values for node degree can be found in Figure S5.

GT analysis showed changes in node degree of key hubs pertaining to the SN. These regions were also identified as connectivity hubs in the FC analysis. We therefore tried to explore the clinical significance of node degree values by correlating them with neuropsychological performance (Figure 3). We chose relevant nodes from the previous analysis (right anterior insula, right supramarginal gyrus) and selected tests for global cognition (total PD-CRS score), executive function (Trail Making Test B) and visuospatial skills (VOSP number location). We found a positive correlation between global PD-CRS score and right AI node degree ($r = 0.456$, $p = 0.001$). Regarding executive and visuospatial functions, node degree in right AI correlated with TMT-B ($r = -0.447$, $p = 0.001$), and VOSP number location correlated with node degree in the right supramarginal cortex ($r = 0.305$, $p = 0.02$).

4 | DISCUSSION

In the present work we aimed to identify the features that characterize early disruption of cognitive networks in PD-MCI. First, we found that loss of GMV was restricted to DMN nodes, consistent with previous literature (Mak et al., 2015; Weintraub et al., 2012). Second, we

observed intrinsic coupling, anticorrelations, and topological properties of core SN nodes to be specifically lower in PD-MCI patients than in PD-NC patients. Third, changes in topological properties—such as node degree—in SN hubs correlated with impairment in global cognitive function, executive, and visuospatial tasks.

Interestingly, we uncovered divergent trends in structural and functional disruptions of cognitive networks in PD-MCI patients. While functional changes appeared in SN hubs in the absence of gray matter loss, DMN showed reductions of GMV in the precuneus and posterior cingulate cortex, with no functional or topological differences (Figure 4). These findings could have two interpretations. On the one hand, decreased functional connectivity in the SN and the loss of gray matter in the precuneus of the DMN could be independent phenomena that reflect the different rate of deterioration of structural and functional features of brain networks. This would be the most immediate conclusion, since loss of gray matter and functional connectivity decline do not overlap in any of these large-scale networks. However, given the lack of functional connectivity differences between PD-NC and PD-MCI, when the tests are controlled by the GMV of the precuneus (Figure S8), these two phenomena might seem to be linked in PD-MCI. When GMV in the precuneus declines, so does connectivity in the PD-MCI group, but when volume loss is regressed out, the intrinsic connectivity of the SN is not statistically different between groups. This strengthens the notion that

FUNCTIONAL AND STRUCTURAL CHANGES ACCORDING TO TASK FORCE LEVEL I (PD-CRS)

FIGURE 4 A summary of functional, topological, and structural findings of this study. The functional changes in the hub of the SN are shown in red in the insular, anterior cingulate and supramarginal cortices. Decreases in gray matter volume in the precuneus are outlined in blue. Abbreviation. SN, salience network [Color figure can be viewed at wileyonlinelibrary.com]

functional connectivity changes could be driven by structural changes in other large-scale networks. It is perhaps explained by absence of changes in connectivity between salience and DMNs in the PD-MCI > PD-NC contrast. This increased connectivity between antagonical networks, which reflects the loss of anticorrelations in PD-MCI, remains similar regardless of GMV in the precuneus (Figure S9).

Furthermore, this study attempted to establish a link between the initial neuropsychological features of PD-MCI and network disruption in these early stages of cognitive impairment. According to the dual syndrome hypothesis (Kehagia, Barker, & Robbins, 2012; Pagonabarraga et al., 2008), the addition of posterior cortical dysfunctions over a progressive dysexecutive syndrome—the consequence of gradual dopamine denervation, cholinergic deficits, and cortical atrophy—appears to be the neuropsychological hallmark leading to dementia. Accordingly, although PD-MCI patients in our sample mainly showed impairment in executive functions, signs of network dysfunction were widespread, involving networks encompassing both prefrontal and posterior cortical structures. Functional connectivity decay, aberrant network synchronization, and loss of properties such as nodal degree affected both executive and visuospatial hubs of the SN. These findings are in accordance with previous data (Christopher et al., 2014) indicating that loss of dopamine not only affects fronto-striatal loops, but also leads to extensive changes in the SN, especially at the level of the anterior insula and connected areas such as the supramarginal gyrus. Thus, disruptions in networks subserving posterior cortical functions can be found in PD-MCI, even when they are not clinically evident, as subdomain analyses showed no impairment in visuospatial or mnemonic performance.

As a first step in this work, we conducted a VBM analysis to detect areas of gray matter loss in PD-MCI. These regions showing reduced gray matter correspond to the main hubs of the DMN, namely, the posterior cingulate cortex and precuneus. Previous studies comparing PD-NC and PD-MCI have found a pattern of reduced gray matter in precuneus, PCC and perihippocampal gray matter (Mak et al., 2015; Weintraub et al., 2012) or no significant differences (Melzer et al., 2012). Cortical thinning studies also show changes in cuneus, fusiform, and temporal cortices (Pagonabarraga et al., 2013; Segura et al., 2014). However, studies in PD cognition show that structures of the DMN, such as medial temporal and inferior parietal cortices, exhibit functional changes well before gray matter loss appears (Sala-Illonch et al., 2015). The study by Tessitore et al. (2012) showed a similar phenomenon, where PD-NC patients showed functional disruption of the DMN without proportional gray matter loss in this network; interestingly, in their final remarks the authors suggest that frontoparietal networks could play a role in maintaining normal cognition in PD-NC patients. In our sample, DMN regions showed reduced gray matter in PD-MCI patients, but there were no differences in functional connectivity compared to PD-NC patients. This is in contrast with SN regions, which showed a marked alteration in connectivity and GT parameters without evidence of structural changes. Thus, decreases observed in SN functional connectivity cannot be explained as a result of gray matter loss. In summary, DMN disruption without gray matter loss could be a feature of PD-NC, and a similar

process of disrupted connectivity but preserved SN gray matter could mark the transition to PD-MCI.

According to our data, then, SN dysfunction appears as an intrinsic feature of mild cognitive impairment in PD. Previous knowledge points towards a buffering role of SN in the initial stages of cognitive decline: core processing regions of SN receive dopaminergic input from the mesocortical pathway, which originates in the ventral tegmental area (VTA). Studies comparing the dorsal and ventral dopaminergic pathways showed that, in the early stages of PD, the VTA is relatively spared compared to the substantia nigra pars compacta (Javoy-Agid, Taquet, Ploska, Cherif-Zahar, & Ruberg, 1981), constituting a surplus of dopaminergic innervation for the insular cortex. When this source is finally exhausted, signaled by a decrease in D2 receptors, cognitive decline occurs (Christopher et al., 2015). Besides preferential innervation, the pivotal role of the insular cortex in SN also lies in its multiple connections with sensorimotor, emotional (hippocampus, amygdala, orbitofrontal cortex), and executive hubs (Christopher et al., 2014; Menon & Uddin, 2010). Through these connections, the insula allows the SN to select salient stimuli and dynamically direct the interplay of other large scale networks (Nomi et al., 2016). We found that these functions are impaired in the transition to PD-MCI: network coherence is diminished, anticorrelations with DMN are lost, and the degree of key nodes is lowered. These measures could represent a link between neuropsychological decline and network disruption. Furthermore, the dysexecutive syndrome observed in our PD-MCI patients, perhaps emerging from impaired SN switching, could be hiding the incipient failure of large scale systems.

Besides the interplay between large scale networks, hubs identified in GT analysis underlined the relevance of both the anterior insulae and supramarginal gyrii. The latter has been linked to awareness of space through integration of visual, proprioceptive and vestibular information (Kheradmand, Lasker, & Zee, 2015). Both regions, therefore, are able to integrate multimodal information, the versatility of which might be useful when other network hubs start to fall apart. Indeed, the successive failure of different networks in each stage of the disease—DMN in PD-NC, SN in PD-MCI—seems to follow a model of cascading network failure, as recently proposed for DMN in AD (Jones et al., 2015). In this framework, the first affected are the posterior components of DMN, which shift processing burden to frontal, unaffected regions of the network. As disease progresses and amyloid starts to accumulate, the disintegration of the vulnerable posterior hubs propagates through the network, causing a collapse similar to a cascading failure in a power grid. In PD, DMN hubs could also be the first to show disruptions in early, cognitively-unimpaired patients, but as disease progresses, it is the disruption in SN hubs which seem to signal the onset of PD-MCI.

Defining the “early-failing” regional hubs for each neurodegenerative syndrome could be fruitful in the early detection of cognitive impairment. Based on our findings, the anterior insulae and supramarginal gyrii appear to be two such hubs in PD. Both regions show marked decreases in connectivity in PD-MCI, and we were able to link the loss of node degree with diminished executive and visuospatial

cognitive scores. As we move from the localizationist paradigms onto a networks perspective, one of the stepping stones is the fact that large scale networks are differently targeted by neurodegenerative syndromes (Seeley et al., 2009). In fact, the clinical manifestations that give each entity its features (such as memory loss in Alzheimer's, or the dysexecutive syndrome in PD) probably stem from the networks that are initially perturbed. It seems logical, thus, that we continue our biomarker quest by probing those regions that might be "first responders" when large-scale networks begin to unravel.

We acknowledge some limitations of our study. First, the sample size limits the scope of our findings. Second, the lack of an age-matched healthy cohort dampens possible claims of network compensation in PD-NC patients, which merits further studies. However, we believe the main results of this study pertain to the specific interface between PD-NC and PD-MCI, and thus offer new insights into this stage of PD. Third, all scans were performed in the "on" state, therefore some of the results might be influenced by treatment regime; however, daily equivalent levodopa dose was not significantly different between the cognitive groups, and including this parameter as a nuisance covariate did not result in meaningful differences. Finally, the cross sectional nature of this study makes further longitudinal studies desirable in order to test the accuracy of our findings. On the other hand, our results are coherent with previous knowledge in connectomic literature, both in PD and in other neurodegenerative diseases, and they show a substantial agreement between diverse modalities of neuroimaging and neuropsychological assessment, using standard neuroimaging pipelines and stringent, FDR-corrected analyses.

In summary, the present findings indicate that multimodal assessment captures divergent phenomena affecting cognitive networks at the onset of PD-MCI. Atrophy in DMN nodes is not mirrored by functional disruption, while early decline in global cognition, executive and visuospatial performance can be linked to functional disruption centered in SN hubs.

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