Cognitive impairment and resting-state network connectivity in Parkinson's disease

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DISCLOSURE

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ABSTRACT

Previous functional MRI studies have revealed changes in the default-mode network (DMN) in Parkinson's disease (PD). The purpose of this work was to evaluate changes in the connectivity patterns of a set of cognitively relevant, dynamically interrelated brain networks in association with cognitive deficits in PD using resting-state functional MRI.

Sixty-five non-demented PD patients and 36 matched healthy controls (HC) were included. Thirty-four percent of PD patients were classified as having mild cognitive impairment (MCI) based on performance in the three mainly-affected cognitive domains in Parkinson's disease (attention/executive, visuospatial/visuoperceptual and declarative memory). Data-driven analyses through independent-component analysis (ICA) was used to identify the DMN, the dorsal attention network (DAN) and the bilateral frontoparietal networks (FPN), which were compared between groups using a dual-regression approach. Additional seed-based analyses using a-priori defined regions of interest were used to characterize local changes in intra and inter-network connectivity.

ICA results revealed reduced connectivity between the DAN and right frontoinsular cortical regions in MCI patients, which correlated with worse performance in attention/executive functions. The DMN, on the other hand, displayed increased connectivity with medial and lateral occipito-parietal regions in MCI patients; these increases correlated with worse visuospatial/visuoperceptual performance. In line with data-driven results, seed-based analyses mainly revealed reduced within-DAN, within-DMN and DAN-FPN connectivity, as well as increased DAN-DMN coupling in MCI patients.

Our findings demonstrate differential connectivity changes affecting the networks evaluated, which we hypothesize to be related to the pathophysiological bases of different types of cognitive impairment in PD.

INTRODUCTION

In the framework of an integrated model of brain function, neuroimaging studies have demonstrated the relevance of a set of dynamically interrelated brain intrinsic connectivity networks (ICNs) considered to play an important role in cognitive processing: the default-mode network (DMN), the dorsal attention network (DAN) and the frontoparietal networks (FPN) [Sala-Llonch et al., 2012; Seeley et al., 2007; Spreng et al., 2010]. These networks can be evaluated through resting-state functional techniques, and their role as part of the functional substrates of cognitive manifestations of neuropathological processes can be assessed [Smith et al., 2009; Spreng et al., 2010].

Cognitive impairment is an important cause of disability in Parkinson's disease (PD), and patients with mild cognitive impairment (MCI) are at a higher risk of subsequently developing dementia [Williams-Gray et al., 2007], which over time affects around 75% of patients (see [Aarsland and Kurz, 2010]). In a previous study using the same subject sample, we used a graph-theoretical approach to assess changes in global patterns of resting-state functional connectivity and found that the presence of MCI in PD patients was associated with widespread connectivity decrements as well as some increments [Baggio et al., 2014]. Since previous studies in PD have focused on changes affecting the DMN [van Eimeren and Monchi, 2009; Krajcovicova et al., 2012; Rektorova et al., 2012; Tessitore et al., 2012], little is known about how this disease affects other ICNs. Our goal in the present study was to evaluate how connectivity changes affect a set of brain networks – the DMN, the DAN and the bilateral FPN [Spreng et al., 2013]. Specifically, our objective was, in a first step, to assess changes in overall ICN connectivity in the presence of MCI in a large sample of non-demented PD patients through a data-driven independent component analysis (ICA) resting-state functional MRI approach. We also aimed to assess the relationship between changes in patterns of network connectivity and performance in the cognitive functions most frequently affected in Parkinson's disease without dementia, *i.e.*,

attention/executive (A/E), episodic memory and visuospatial/visuoperceptual (VS/VP) [Aarsland et al., 2009; Elgh et al., 2009; Muslimovic et al., 2005]. As a second step, we aimed to evaluate the local patterns of ICN functional connectivity disruption associated with the presence of MCI in PD using an *a priori* seed-based analysis.

MATERIALS AND METHODS

Participants

Eighty-four non-demented PD patients and 38 healthy controls (HC) matched for age, sex and years of education were recruited [Baggio et al., 2014]. The inclusion criterion for patients was the fulfillment of UK PD Society Brain Bank diagnostic criteria for PD [Hughes et al., 2002]. Exclusion criteria were: (i) MMSE <25 or dementia [Emre et al., 2007], (ii) Hoehn and Yahr (HY) score >III, (ii) significant psychiatric, neurological or systemic comorbidity, (iv) significant pathological MRI findings other than mild white-matter hyperintensities in the FLAIR sequence, (v) root-mean-square head motion >0.3 mm translation or 0.6^{o} rotation. Four patients were excluded due to macroscopic movement, 14 due to head motion > 0.3 mm translation or > 0.6^{o} rotation, and one for being an outlier in dual-regression analyses. Two HC were excluded due to microvascular white matter changes, leaving a final sample of 65 PD patients and 36 HC. All patients except one were taking antiparkinsonian medication; all assessments were done in the *on* state. Levodopa equivalent daily dose (LEDD) was calculated as suggested by Tomlinson *et al*. [Tomlinson et al., 2010] Motor disease severity was evaluated using HY staging and the Unified Parkinson's Disease Rating Scale motor section (UPDRS-III). The study was approved by the ethics committee of the University of Barcelona. All subjects provided written informed consent to participate.

Neuropsychological assessment

Attention/executive (backward minus forward digit spans; Trail-Making Test part A minus part B scores; phonemic fluency scores (words beginning with "P" produced in 60 seconds), and Stroop Color-Word Test interference scores), **visuospatial/visuoperceptual** (Benton's Visual Form Discrimination and Judgment of Line Orientation tests) and **memory** (Rey's Auditory Verbal Learning Test total learning and 20-minute free recall scores) functions were tested in all subjects. Z-scores for each test and subject were calculated based on the HC group's means and standard deviations. Expected z-scores adjusted for age, sex and education for each test and subject were calculated based on a multiple regression analysis performed in the HC group [Aarsland et al., 2009]. Subjects were classified as having MCI if the actual z-score for a test was ≥1.5 lower than the expected score in at least two tests in one domain or in one test per domain in at least two domains. As was expected [Muslimovic et al., 2005], most MCI subjects had deficits in more than one function, precluding the creation of patient groups with single-domain impairments. Composite z-scores for each domain were calculated by averaging the age, sex and education-corrected z-scores of all tests within that domain.

MRI acquisition

Structural T1-weighted images, functional resting-state images and FLAIR images were acquired on a 3T Siemens MRI scanner as previously described [Baggio et al., 2014].

Processing of fMRI

The preprocessing of resting-state images was performed with FSL (http://www.fmrib.ox.ac.uk/fsl/) and AFNI (http://afni.nimh.nih.gov/afni) as previously described [Baggio et al., 2014]. To control for the effect of subject head movement, physiological artifacts (*e.g.*, breathing and vascular) and other non-neural sources of signal variation on the estimation of connectivity, motion correction and regression of nuisance signals (six motion parameters, cerebrospinal fluid and white matter) were performed. To remove the

effects of images corrupted by motion, a *scrubbing* procedure, as suggested by [Power et al., 2012], was applied.

Additionally, individual subject head motion was calculated for translatory and rotatory movements according to the following formula:

$$\frac{1}{M-1}\sum_{i=2}^{M}\sqrt{|x_i - x_{i-1}|^2 + |y_i - y_{i-1}|^2 + |z_i - z_{i-1}|^2},$$

where x_i, y_i and z_i are translations or rotations in the three axes at timepoint *i*, and M is the total number of timepoints (145) [Liu et al., 2008]**.**

Quality control

Despite rigorous head-motion exclusion criteria, rotational head motion was significantly higher in non-MCI (PD-NMCI) patients than in HC (*p*=.028, *post-hoc* Bonferroni test), with no significant differences between HC and PD-MCI patients or between patient subgroups. Head motion data were added as covariates of no interest in intergroup comparisons.

Independent component analysis (ICA) and dual regression analyses

Preprocessed images were analyzed with MELODIC using a temporal-concatenation spatial ICA approach [Beckmann and Smith, 2004]. Functional datasets were decomposed into 25 components, from which those corresponding to the DAN, DMN, right FPN and left FPN were identified through visual inspection. These components were fed into a dual-regression analysis, which uses group ICA maps to extract subject and component-specific time-courses, subsequently used to estimate subject's spatial maps. One-sample t-tests were used to establish each group's maps for each ICN. In order to perform intergroup connectivity analyses, subjects' regression maps for each ICN of interest were compared using a general linear model with non-parametric permutation testing (5000 permutations). A binary mask created from the sum of all groups' thresholded maps for all four networks was used as a search volume for intergroup

analyses to assess intra and internetwork connectivity differences. Individual subjects' GM volume maps (see below) were entered as voxelwise regressors in intergroup comparisons to control for the effect of structural atrophy on connectivity measures; results were similar using global GM volume as a covariate of no interest. In accordance with previous studies that performed multiple comparisons for different brain networks [Agosta et al., 2012; Brier et al., 2012], false-discovery rate (FDR) correction was used for multiple comparisons correction in group comparisons (p<.05); to further control the occurrence of false-positive intergroup results, a cluster-size threshold of 100 voxels was applied to intergroup analyses as in [Agosta et al., 2012].

To evaluate the relationship between connectivity changes and cognitive performance, mean regression coefficients extracted from the clusters of significant MCI-vs.-non-MCI differences were correlated with demographic/clinical variables (age, education, UPDRS, BDI, LEDD). Subsequently, they were correlated with each individual cognitive function scores (A/E, memory, VS/VP) while controlling for the other two functions as well as for rotational and translational head motion. Since LEDD was significantly correlated with intergroup differences in DAN connectivity, this measure was included as a covariate when analyzing this network; results were similar to those without controlling for it.

Processing of structural images

Structural data was analyzed with FSL-VBM [Douaud et al., 2007], a voxel-based morphometry-style analysis. First, structural images were brain-extracted and GM-segmented before being registered to the MNI-152 standard space. The resulting images were averaged to create a study-specific template, to which native GM images were non-linearly re-registered. Second, native GM images were registered to this study-specific template and modulated to correct for local expansion or contraction due to the non-linear component of the spatial transformation. In order to perform intergroup connectivity analyses, voxelwise general linear

model with non-parametric permutation testing (5000 permutations) was applied. FDR was used for multiple comparisons correction (p<.05).

Seed-based functional connectivity analysis using *a priori*-defined regions of interest

In total, 43 nodes (10 DAN, 18 DMN and 15 bilateral FPN nodes; see Table 1) were included using the MNI coordinates described in [Spreng et al., 2013] and 10-mm radius circular masks. Voxels shared by more than one mask were not included in the analyses. Blood-oxygen level dependent signal time series were averaged throughout all voxels inside each region. The connectivity between two nodes was estimated using Pearson's correlation between their mean time series. We used the Jonckheere-Terpstra (JT) test [Bewick et al., 2004], a non-parametric test for ordered differences in 3 or more samples, to assess intergroup differences in functional connectivity between intra and inter-network nodes. Permutation testing (10000 permutations) generating random group affiliation was used to yield a null distribution against which the actual JT statistics were compared to determine statistical significance (p<.05) for each interregional connection.

Sociodemographic/clinical data statistical analyses

Statistical significance threshold was set at p<.05. Pearson's chi-squared test was used to compare categorical variables (hand dominance, sex, HY). Student's t-test was used to compare head motion and clinical data means between Parkinson's disease patients and HC. Three-level one-way ANOVAs were used to compare head motion, clinical and sociodemographic data between HC and patient subgroups.

RESULTS

Table 2 shows sociodemographic, clinical and head motion characteristics for the 3 groups (HC, non-MCI PD patients [PD-NMCI], MCI PD patients [PD-MCI]). Table 3 shows neuropsychological assessment results and group comparisons. Twenty-two patients (33.8%) fulfilled criteria for MCI. No significant intergroup GM volume differences were observed.

Data-driven connectivity analysis

The ICA components corresponding to the ICNs of interest were identified in accordance with previous studies [Smith et al., 2009; Veer et al., 2010] and included, among other regions (see Figure 1):

DAN: caudal anterior cingulate gyrus, frontal eye fields, dorsolateral prefrontal areas, temporooccipital junctions and dorsal occipitoparietal regions.

DMN: posterior cingulate gyrus/precuneus, medial prefrontal region, angular gyri and middle/superior frontal gyri.

Right and left FPN: ipsilateral inferior parietal lobule, lateral prefrontal cortex, insula and opercular region, as well as precuneus.

Intergroup comparisons: No significant differences were observed between HC and the collapsed PD patient group for any of the networks analyzed. Statistically significant group differences were observed when stratifying the PD sample into PD-MCI and PD-NMCI subgroups (see Figure 2 and Table 4). Compared with HC, the DAN in PD-MCI showed reduced connectivity (p<.05, FDR-corrected) with widespread, predominantly right-sided, frontal/insular areas. Connectivity reductions of the DAN in PD-MCI compared with PD-NMCI patients were similar, although less extensive, to those seen between PD-MCI and HC, and involved regions that are part of the DAN itself and of the right FPN (see Figure 2 and Table 4).

Compared with HC and with PD-NMCI, PD-MCI showed significant connectivity increases (p<.05, FDR-corrected) between the DMN and posterior cortical regions (see Figure 2 and Table 4). These regions corresponded to areas of the DAN, the left FPN and the DMN itself. No significant connectivity differences were observed between HC and PD-NMCI for any of the ICNs analyzed.

Correlation analyses: Connectivity levels, assessed through the regression coefficients obtained from the clusters of significant differences between PD-MCI and PD-NMCI (DAN and DMN), did not correlate significantly with age, years of education or BDI/UPDRS-III scores. Connectivity levels in the DAN clusters, on the other hand, correlated with LEDD (r=-.34, p=.006).

Partial correlation analyses evaluating the relationship between connectivity levels in the significant PD-MCI-vs.-PD-NMCI comparison clusters and age-, education- and sex-corrected neuropsychological data revealed:

i. significant positive correlation between connectivity in the DAN clusters and A/E (partial-correlation coefficient=.40, p=.001) scores.

ii. negative correlation between connectivity in the DMN clusters and VS/VP scores (partial-correlation coefficient=-.37, p=.004) and MMSE (partial-correlation coefficient=-.32, p=.011) scores.

Seed-based *a priori*-defined connectivity analysis

Visual inspection showed that the *a-priori* masks overlapped with the corresponding regions of the ICNs obtained from ICA. As shown in Figure 3, ordered connectivity reductions (HC>PD-NMCI>PD-MCI) were observed both within and between networks. Intra-network reductions were found mainly in the DMN and the DAN and were characterized by reductions from positive correlation coefficients in HC to values closer to zero in PD-MCI. Most intra-DMN connectivity reductions involved this ICN's midline nodes and their connections with the left

hippocampus, anterior temporal regions and posterior inferior parietal lobules. Intra-DAN reductions were mainly seen between frontal nodes and occipital/parietal nodes. Inter-network connectivity reductions were also observed, mainly affecting connections between the frontal and right insular FPN nodes and occipital/parietal DAN nodes. In HC, these nodes' time series were positively correlated, whereas in PD-MCI they tended to correlate negatively. Connectivity reductions were also seen in a few sparse connections between DAN and DMN nodes.

Connectivity increases (HC<PD-NMCI<PD-MCI) were also present, only affecting internetwork connections. Most such increases were found between midline and frontal/temporal DMN nodes and posterior DAN nodes. As expected, in HC these nodes' time series were negatively correlated. In PD-MCI, they tended to correlate positively (see figure 3).

See Supplementary Table for additional information regarding the interregional connections for which significant ordered connectivity effects were observed.

DISCUSSION

In the present study, we investigated the resting-state functional connectivity of brain ICNs in PD patients according to the presence or absence of MCI using two complementary techniques. As main findings, we observed that PD patients with MCI had a reduction in connectivity between right frontoinsular regions and the DAN, which correlated with A/E performance; and an increased connectivity between posterior cortical regions and the DMN, which correlated with VS/VP scores.

Previous studies have described the association between changes in DMN connectivity and neuropsychological performance in distinct neurological and psychiatric diseases (see [Mevel et al., 2011] and [Whitfield-Gabrieli and Ford, 2012]), but little is known about how changes in internetwork connectivity relate to cognitive decline. Previous fMRI studies show that, during externally-directed cognitive tasks, DAN activity increases whereas DMN activity is reduced; during "rest" or internally-directed/self-referential thoughts, the opposite is observed [Kelly et al., 2008]. The FPN, functionally and anatomically interposed between the main DMN and DAN nodes, has been postulated to flexibly connect to one network or the other depending on attentional task demands, mediating the transition between them [Spreng et al., 2013; Vincent et al., 2008]. This transition appears to be relevant for cognitive task performance [Kelly et al., 2008]. In the current work, PD-MCI subjects displayed reduced connectivity between the DAN and the right anterior insula and adjacent frontal areas, which are regions of the DAN itself and of the right FPN. The relevance of the frontoinsular cortex in cognitive processing has recently been demonstrated (see [Christopher et al., 2014a]). Specifically, this region has been shown to exert a critical and causal role in switching between DAN and DMN across tasks of different modalities as well as in the resting state [Sridharan et al., 2008]. Recent evidence further supports the role played by the DAN and FPN in attentional processes [Hellyer et al., 2014]. We have found that reduced connectivity in this area in PD patients was associated with

worse performance in A/E functions, suggesting that functional right frontoinsular cortical changes play a role in this type of deficit in PD, possibly through the impairment of network-switching mechanisms. We also found connectivity between DAN and right frontoinsular regions to be negatively associated with daily dopaminergic medication dosage. Dopamine synthesis capacity in healthy persons has been shown to correlate with reduced coupling between DAN and FPN, and with increased FPN-DMN coupling, during the resting state [Dang et al., 2012]. Importantly, a recent study found that PD-MCI patients have reduced insular dopaminergic D2 receptors, and that this loss is associated with worse performance in executive functions [Christopher et al., 2014b]. Our findings are in line with previous studies linking A/E deficits and frontostriatal dopaminergic imbalances (see [Cools and D'Esposito, 2011]), and indicate that this type of impairment in PD may be mediated by dopaminergic effects on DAN connectivity.

In the present study, PD-MCI subjects displayed increased connectivity between the DMN and occipito-parietal lateral and medial cortical regions that are components of the left FPN, the DAN and the DMN itself. Seed-based analyses also revealed that the increased connectivity between DMN and posterior DAN nodes in PD-MCI was characterized by the loss of the negative correlation normally observed between these regions. Despite variable findings regarding the DMN in PD, the most frequently described connectivity changes involve abnormal patterns of activation and deactivation of the precuneus/PCC during rest and cognitive tasks [van Eimeren and Monchi, 2009]. In the current study, posterior DMN connectivity increments were seen to be associated with worse VS/VP performance. Seed-based analyses revealed reduced within-DMN connectivity, a finding in line with a recent resting-state fMRI study that evaluated cognitively unimpaired PD patients [Tessitore et al., 2012]. As in the present study, connectivity changes affecting posterior cortical regions correlated with performance in visuospatial/visuoperceptual tests. These findings are in line with and complement previous structural neuroimaging studies addressing the neuroanatomical bases of such deficits in PD [Pereira et al., 2009]. Furthermore, previous evidence suggests that task-positive frontoparietal

networks and the DMN competitively connect with visual areas during visual tasks, and that the degree of decoupling of the DMN with these structures predicts task performance [Chadick and Gazzaley, 2011]. Our findings suggest that changes in connectivity between the DMN and posterior cortical areas belonging to the DAN and the FPN may be part of the substrates of VS/VP deficits in PD through a disruption of these dynamic-coupling mechanisms.

A positive association between resting-state DMN connectivity with lateral parietal areas has previously been observed with the administration of levodopa in healthy subjects [Cole et al., 2013], suggesting that dopaminergic imbalances in PD may play a part in connectivity between the DMN and posterior cortical regions. In our sample, however, DMN connectivity increases were not associated with LEDD and were seen to correlate with VS/VP deficits, which are not related to dopaminergic neurotransmission [Lange et al., 1992]. Longitudinal studies have shown that, unlike dopamine-related deficits, impairments with posterior cortical bases are predictors of future dementia in PD [Williams-Gray et al., 2007; Williams-Gray et al., 2009]. Data from a longitudinal PET study found that reduced glucose metabolism in occipital and posterior cingulate regions heralded future conversion to dementia [Bohnen et al., 2011], emphasizing the importance of posterior cortical changes as predictors of dementia in PD. We hypothesize that such connectivity increases are secondary to the cortical dysfunctions that lead to progressive cognitive decline and, ultimately, dementia. It remains to be studied whether posterior connectivity or metabolic changes are related to the pathologic cortical changes that appear to be critical for the development of dementia in PD, such as synucleinopathy or Alzheimer's-type pathology [Compta et al., 2011].

One possible limitation of our study is that, despite the rigorous head motion exclusion criteria and preprocessing steps aimed at minimizing the effect of motion artifacts, we cannot guarantee that our results were not influenced to some degree by them. Nonetheless, the identified effects were detected in the PD-MCI sample, which had less pronounced head motion

than PD-NMCI. Additionally, cognitive measures correlated with network connectivity in the PD sample, but did not correlate with severity of head motion. These observations indicate that our results have actual biological origins. Furthermore, in order to evaluate the effects of specific types of cognitive impairment, patients would ideally be stratified according to the deficits found. In the present study, most MCI patients had multi-domain deficits, precluding the creation of subgroups.

The present study shows that cognitive decline in PD is associated with different patterns of connectivity changes affecting large-scale brain ICNs, even in the absence of significant structural degeneration. These findings suggest that network changes, mainly characterized by the loss of intra-network connectivity and an increase in the connectivity between networks that normally display anti-correlated activities, are part of the neural substrate underlying cognitive deficits in PD. These findings indicate, for the first time, the involvement of resting-state networks other than the DMN in these deficits. Moreover, our results give further support to the hypothesis that the brain networks studied play a role in the neural processing of distinct neuropsychological functions. Future, longitudinal studies may help clarify if internetwork connectivity measures can be used as predictors of cognitive decline in PD.

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Figure 1. Resting-state networks of interest.

Left-sided images: maps obtained from independent component analyses (ICA) of the whole sample. Right-sided images: group-level maps obtained from dual-regression analyses ($p<.05$, FDR corrected). DAN: dorsal attention network; DMN: default mode network; FPN: frontoparietal network. The right hemisphere is displayed on the left side of axial and coronal views.

Figure 2. Data-driven analysis intergroup connectivity comparisons.

Left side: clusters of significant ($p<.05$, FDR-corrected; 100-voxel threshold) connectivity group differences for Parkinson's disease patients with mild cognitive impairment (PD-MCI) versus healthy controls (HC) or patients without mild cognitive impairment (PD-NMCI) for the dorsal attention network (DAN) and the default mode network (DMN). FDR-corrected *p* values are color-coded according to the bar at the top. MNI Y and Z coordinates of the slices shown are indicated. Right side: scatterplots showing the correlation between connectivity values (*regression coefficients obtained from the clusters of significant PD-MCI *vs.* PD-NMCI differences) and age-, sex- and education-corrected z-scores in attention/executive (A/E) and

visuospatial/visuoperceptual (VS/VP) functions in the PD patient group. *r*: partial correlation coefficient. The right hemisphere is displayed on the left side.

Figure 3. Seed-based connectivity analysis results.

Left side: schematic representation of the interregional connections where significant ($p<.05$) ordered connectivity changes were observed. Network affiliation of the nodes shown as well as of the internodal connections are indicated in the legend above. Abbreviations refer to those described in Table 1. Right side: plots showing r coefficient levels according to group for the connections where significant effects were found, according to the network affiliation of the involved nodes. Only intra or internetwork changes comprising more than 3 connections are plotted. DAN: dorsal attention network; DMN: default mode network; FPN: frontoparietal

network; HC: healthy controls; PD-NMCI: Parkinson's disease patients without mild cognitive impairment; PD-MCI: Parkinson's disease patients with mild cognitive impairment.

Table 1. Anatomical regions used as network nodes for seed-based connectivity analyses.

Region	**Left hemisphere/midline**		**Right hemisphere**	
	Network	Abbreviation	Network	Abbreviation
Frontal eye fields	**DAN**	**DA l FEF**	**DAN**	**DA r FEF**
Inferior precentral sulcus	**DAN**	**DA l iPCS**	**DAN**	**DA r iPCS**
Middle temporal motion complex	**DAN**	**DA l MT**	**DAN**	**DA r MT**

Superior occipital gyrus	**DAN**	**DA l SOG**	**DAN**	**DA r SOG**
Superior parietal lobule	**DAN**	**DA l SPL**	**DAN**	**DA r SPL**
Anterior medial prefrontal cortex	**DMN**	**DMN amPFC**		
Dorsal medial prefrontal cortex	**DMN**	**DMN dmPFC**		
Posterior cingulate cortex	**DMN**	**DMN pCC**		
Precuneus	**DMN**	**DMN PCu**		
Ventral medial prefrontal cortex	**DMN**	**DMN vmPFC**		
Anterior temporal lobe	**DMN**	**DMN l aTL**	**DMN**	**DMN r aTL**
Hippocampal formation	**DMN**	**DMN l HF**	**DMN**	**DMN r HF**
Inferior frontal gyrus	**DMN**	**DMN l IFG**	**DMN**	**DMN r IFG**
Posterior inferior parietal lobule	**DMN**	**DMN l pIPL**	**DMN**	**DMN r pIPL**
Superior frontal gyrus	**DMN**	**DMN l SFG**	**FPN**	**FP r SFG**
Superior temporal sulcus	**DMN**	**DMN l STS**	**DMN**	**DMN r STS**
Temporal parietal junction	**DMN**	**DMN l TPJ**	**DMN**	**DMN r TPJ**
Dorsal anterior cingulate cortex	**FPN**	**FP daCC**		
Medial superior prefrontal cortex	**FPN**	**FP msPFC**		
Anterior inferior parietal lobule	**FPN**	**FP l aIPL**	**FPN**	**FP r aIPL**
Anterior insula	**FPN**	**FP l aINS**	**FPN**	**FP r aINS**
Dorsolateral prefrontal cortex	**FPN**	**FP l dlPFC**	**FPN**	**FP r dlPFC**
Middle frontal gyrus BA 6	**FPN**	**FP l MFG BA6**	**FPN**	**FP r MFG BA6**
Middle frontal gyrus BA 9	**FPN**	**FP l MFG BA9**	**FPN**	**FP r MFG BA9**
Rostrolateral prefrontal cortex	**FPN**	**FP l rlPFC**	**FPN**	**FP r rlPFC**

Resting-state networks to which each node belongs is indicated: DAN (dorsal attention network), DMN (default mode network) or FPN (frontoparietal network).

Table 2. Sociodemographic, clinical and head motion characteristics of participants with intergroup comparisons.

	HC	**PD**		
	n=36	Non-MCI n=43	MCI n=22	**Test stats/*p***
Age (yrs.)	63.4 (10.5)	64.0 (9.8)	66.1 (12.2)	.473/.624
Sex (female:male)	17:19	20:23	8:14	.431/.806 χ

Years of education	10.3 (4.0)	10.8 (5.1)	8.8 (4.0)	2.178/.119
MMSE	29.70 (.47)	29.35 (0.90)	28.50 (1.22)	**13.285/<.001**
Hand dominance (r:l)	34:2	42:1	22:0	2.429/.657 χ
BDI	5.81 (5.66)	8.9 (6.1)	11.5 (6.6)	**6.357/.003**
Age at onset (yrs.)	-	57.8 (10.2)	56.8 (13.5)	.340/.735 †
Disease duration	-	6.1 (4.4)	9.3 (5.5)	**2.523/.014** †
LEDD	-	646.7 (419.2)	951.9 (498.2)	**2.604/.011** †
HY (1:2:3)	-	20:21:2	3:15:4	**8.315/.016** χ
UPDRS-III	-	14.1 (7.5)	18.2 (8.7)	**1.927/.059** †
Number of outlier timepoints	4.0 (2.6)	3.9 (2.6)	5.3 (3.4)	2.016/.139
Head rotation (degrees)	.03 (.01)	.05 (.04)	.04 (.03)	**3.586/.031**
Head translation (mm)	.08 (.05)	.07 (.04)	.07 (.05)	.349/.706

Results are presented in *means (SD)*. Statistically significant results (p<.05) are marked in bold. *MMSE*: mini-mental state examination. *BDI*: Beck's Depression Inventory-II scores. *Disease duration*: duration of motor symptoms, in years. *LEDD*: Levodopa equivalent daily dose, in mg. HY: Hoehn and Yahr scale. *Test stats*: F-statistics, Pearson's chi-squared (χ) or Student's *t* (†). *Post-hoc* analyses showed significant differences between MCI patients and HC for BDI, between MCI patients and both HC and non-MCI patients for MMSE scores, and between non-MCI patients and healthy controls for head rotation (p<.05, Bonferroni correction).

Table 3. Neuropsychological performance results for healthy controls and Parkinson's disease patients according to MCI status.

	HC n=36 mean (SD)	PD-NMCI n=43 mean (SD)	PD-MCI n=22 mean (SD)	**F/*p***
VFD	29.61 (2.70)	29.09 (2.34)	26.50 (3.45)	**9.550/<.001**
JLO	23.94 (3.99)	23.12 (3.93)	19.50 (5.23)	**7.926/.001**
RAVLT total	44.67 (6.05)	44.47 (9.08)	33.55 (7.93)	**16.866/.001**
RAVLT retrieval	9.08 (2.10)	8.58 (2.64)	6.05 (2.94)	**10.645/<.001**
Digits backwards minus forwards	-1.69 (1.16)	-1.81 (1.03)	-1.23 (1.07)	2.663/.075
Stroop interference	-2.42 (8.96)	-.97 (9.92)	-3.31 (5.62)	.553/.577
TMT A-B	-50.17 (23.93)	-57.33 (29.58)	-142.35 (104.00)	**22.340/<.001**
Phonemic fluency	16.57 (5.03)	16.40 (4.962)	11.82 (5.44)	**7.183/.001**
VS/VP z-score	-.012 (.572)	-.169 (.601)	-.989 (.880)	**16.169/<.001**
Memory z-score	-.010 (.818)	-.092 (1.028)	-1.365 (1.156)	**15.157/<.001**
A/E z-score	.027 (.537)	-.022 (.519)	-.776 (.996)	**12.077/<.001**

Results are presented as *means (SD)*. *PD-NMCI*: Parkinson's disease patients without MCI; *PD-MCI*: patients with MCI; *VFD*: visual form discrimination test; *JLO*: judgment of line orientation test; *RAVLT*: Rey's auditory verbal learning test; *Digits backwards minus forwards*: difference between backward and forward digit spans; *TMT A-B*: difference between Trail Making Test parts A and B; *VS/VP*: visuospatial/visuoperceptual; *A/E*: attention/executive. Z-scores for cognitive domains refer to the difference between actual z-scores and expected age, sex and education-adjusted z-scores, averaged throughout the tests within that domain. For all significant F-test comparisons, *post-hoc* analyses showed that MCI patients' scores were

significantly worse than non-MCI patients' and healthy controls', with no significant differences between the latter (p<.05, *post-hoc* Bonferroni test).

Table 4. Clusters of significant intergroup connectivity differences (p<.05, FDR-corrected; 100-voxel threshold).

	Region	MNI coordinates of maximum (*x y z*)	Cluster volume (mm^3)	Mean cluster t value	Peak FDR-corrected *p*-value
DAN HC>PD-MCI	Superior frontal gyri, right middle/inferior frontal gyri, right precentral gyrus, right anterior/middle insula	21 36 -15	65,988	2.196	0.005
	Right middle temporal gyrus, temporo-occipital junction	60 -57 -6	4,158	2.831	0.005
	Left caudate nucleus, left putamen	-12 0 18	3,159	2.389	0.005
	Thalami	-6 -15 -3	3,105	1.990	0.009
DAN PD-NMCI>PD-MCI	Right inferior frontal gyrus, frontal operculum, anterior/middle insula	57 12 3	7,938	2.561	0.038
	Right middle temporal gyrus, temporo-occipital junction	60 -30 -27	3,294	2.642	0.038
DMN HC<PD-MCI	Bilateral dorsal precuneus, posterior cingulate gyrus, superior occipito-parietal junctions and superior occipital gyri, left superior parietal lobule	-33 -66 18	42,957	2.418	0.034
	Left temporo-occipital junction	-57 -69 -12	4,860	2.349	0.034

DMN PD-NMCI<PD-MCI	Bilateral dorsal precuneus, posterior cingulate gyrus, superior occipito-parietal junctions and superior occipital gyri, left superior parietal lobule, left temporo-occipital junction	-57 -21 -27	74,007	2.300	0.009

DAN: dorsal attention network; DMN: default mode network; HC: healthy controls; PD-MCI: Parkinson's disease patients with mild cognitive impairment; PD-NMCI: Parkinson's disease patients without mild cognitive impairment.

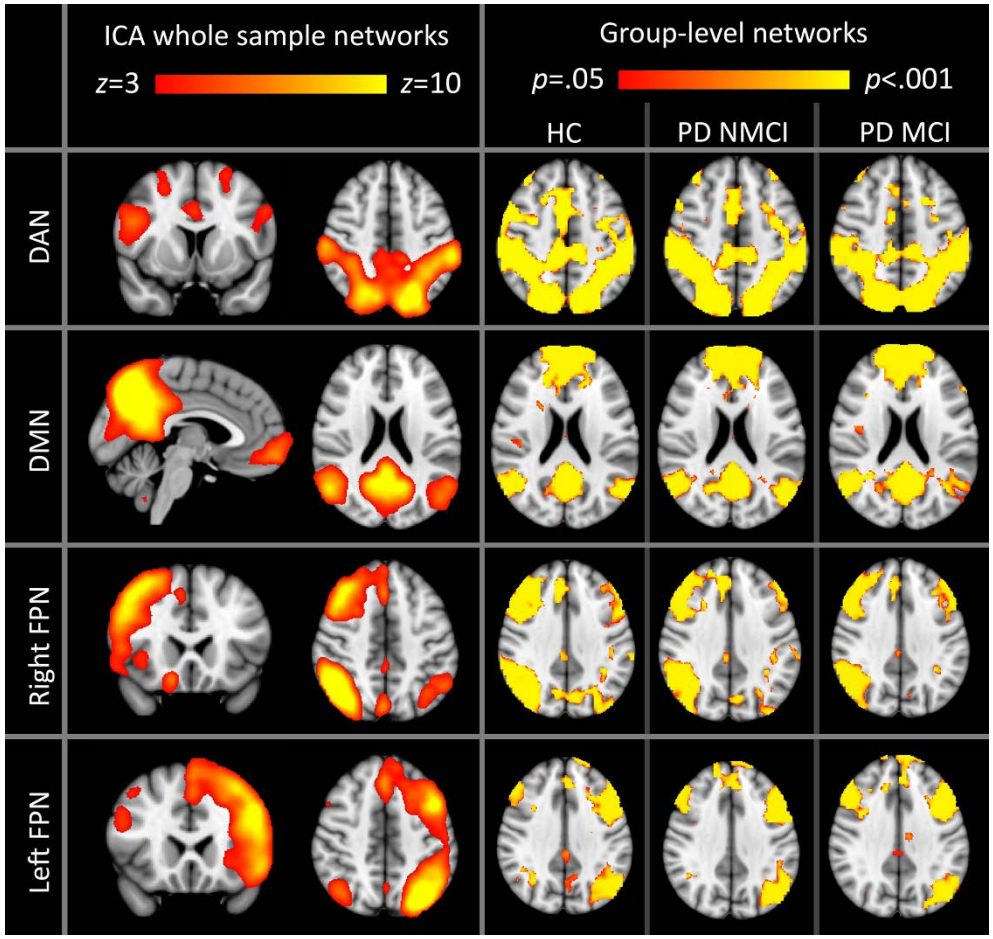
ICA whole sample networks
z=3
z=10
Group-level networks
p=.05
p<.001
HC
PD NMCI
PD MCI
DAN
DMN
Right FPN
Left FPN

Figure 1

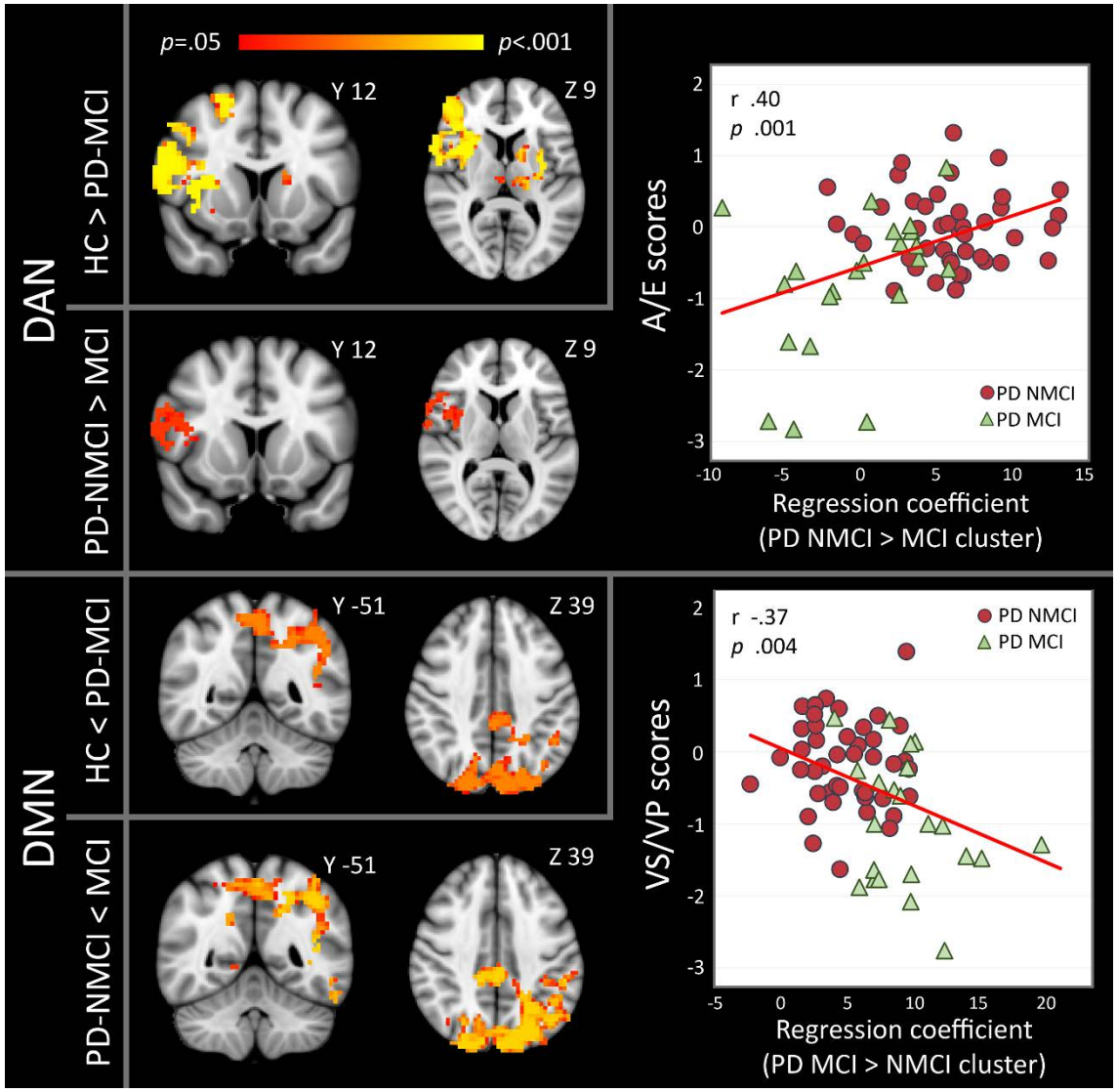
DAN
HC > PD-MCI
p=.05
p<.001
Y 12
Z 9
PD-NMCI > MCI
Y 12
Z 9
A/E scores
r .40
p .001
PD NMCI
PD MCI
Regression coefficient
(PD NMCI > MCI cluster)
DMN
HC < PD-MCI
Y -51
Z 39
PD-NMCI < MCI
Y -51
Z 39
VS/VP scores
r -.37
p .004
PD NMCI
PD MCI
Regression coefficient
(PD MCI > NMCI cluster)

Figure 2

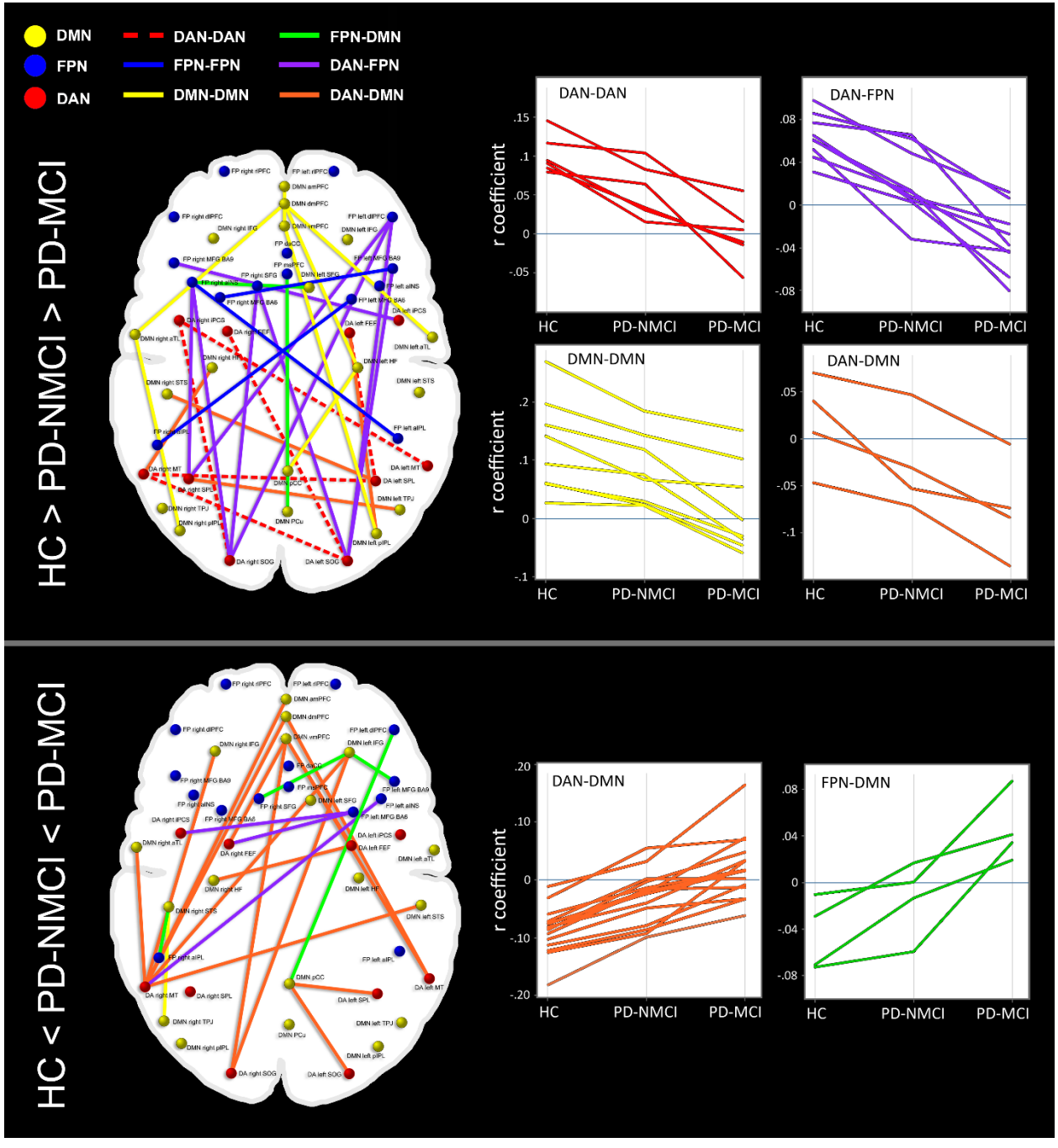
DMN
FPN
DAN
DAN-DAN
FPN-FPN
DMN-DMN
FPN-DMN
DAN-FPN
DAN-DMN
HC > PD-NMCI > PD-MCI
HC < PD-NMCI < PD-MCI
r coefficient
HC
PD-NMCI
PD-MCI

Figure 3

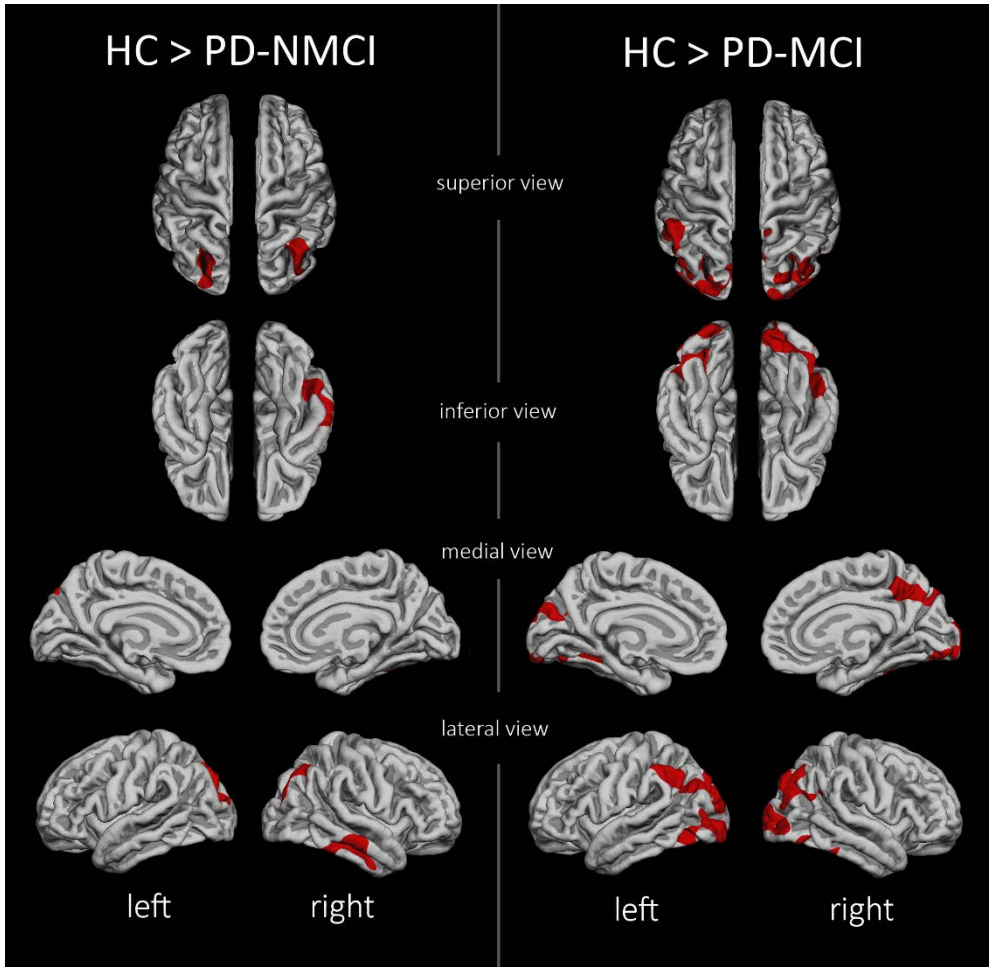

Figure 4