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1 **Functional brain networks and cognitive deficits in Parkinson's disease**

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5 **Running title:** Functional network analysis in PD

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1 **ABSTRACT**

2 Graph-theoretical analyses of functional networks obtained with resting-state
3 functional magnetic resonance imaging have recently proven to be a useful approach for the
4 study of the substrates underlying cognitive deficits in different diseases. We used this
5 technique to investigate whether cognitive deficits in Parkinson's disease are associated with
6 changes in global and local network measures. Thirty-six healthy controls (HC) and 66
7 Parkinson's disease patients matched for age, sex and education were classified as having mild
8 cognitive impairment (MCI) or not based on performance in the three mainly-affected
9 cognitive domains in Parkinson's disease: attention/executive, visuospatial/visuoperceptual
10 and declarative memory. Resting-state functional magnetic resonance imaging and graph
11 theory analyses were used to evaluate network measures. We have found that patients with
12 MCI had connectivity reductions predominantly affecting long-range connections as well as
13 increased local interconnectedness manifested as higher measures of clustering, small-
14 worldness and modularity. The latter measures also tended to correlate negatively with
15 cognitive performance in visuospatial/visuoperceptual and memory functions. Hub structure
16 was also reorganized: normal hubs displayed reduced centrality and degree in MCI PD
17 patients. Our study indicates that the topological properties of brain networks are changed in
18 Parkinson's disease patients with cognitive deficits. Our findings provide novel data regarding
19 the functional substrate of cognitive impairment in PD which may prove to have value as a
20 prognostic marker.

21 **Keywords:** Parkinson's disease; cognitive impairment; connectivity; graph theory;
22 fMRI.

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1 **INTRODUCTION**

2 Parkinson’s disease (PD), beyond its hallmark motor symptoms, causes variable
3 degrees of cognitive impairment in a high percentage of patients. The prevalence of cognitive
4 deficits in untreated, newly-diagnosed patients has been described to be between 19 and 24%
5 (Muslimovic *et al.*, 2005; Aarsland *et al.*, 2009). In non-demented patients, the most frequently
6 affected cognitive functions are attention/executive (A/E) (involving attention, working
7 memory, set shifting, planning or inhibition), episodic memory and
8 visuospatial/visuoperceptual (VS/VP) (Foltynie *et al.*, 2004; Muslimovic *et al.*, 2005; Aarsland *et*
9 *al.*, 2009; Elgh *et al.*, 2009). Patients with cognitive impairment that does not significantly
10 interfere with daily life activities, *i.e.*, with mild cognitive impairment (MCI), are at a higher risk
11 of subsequently developing dementia (Janvin *et al.*, 2006; Williams-Gray *et al.*, 2007), which
12 over time affects around 80% of patients (Aarsland *et al.*, 2005). The risk of future dementia
13 appears to vary according to the type of cognitive deficit observed, being higher in patients
14 with cognitive deficits with posterior cortical substrates and not related to dopamine
15 imbalances (Williams-Gray *et al.*, 2009).

16 The study of cognition is increasingly focusing on an integrated model of brain function
17 rather than on the study of individual areas. In this framework, resting-state functional
18 magnetic resonance imaging (fMRI) can be used to detect interregional correlations in blood
19 oxygen level-dependent (BOLD) signal fluctuations (Biswal *et al.*, 1995), considered to reflect
20 baseline neuronal brain activity (Gusnard *et al.*, 2001), which in turn allows the study of
21 intrinsic large-scale brain network organization (Biswal *et al.*, 1995; Fox and Raichle, 2007). In
22 recent years, graph-theory-based complex network analysis, which describes important
23 properties of complex systems by quantifying topologies of their respective network
24 representations (Rubinov and Sporns, 2010), has been increasingly used in the study of the
25 functional and structural organization of the nervous system (Bullmore and Sporns, 2009). For

1 graph-theoretical analysis of neural networks through fMRI, anatomical brain regions are
2 considered as *nodes*, linked by *edges*, which represent the connectivity measured by the
3 temporal correlation of BOLD signal fluctuations between the nodes (Rubinov and Sporns,
4 2010). Network integration and segregation are measured by the *characteristic path length*
5 and the *clustering coefficient*, respectively. Networks which display a balance between these
6 two measures are considered to be *small-world networks* (Sporns and Honey, 2006),
7 characterized by high local specialization (high clustering) and some global “shortcuts” (low
8 path length), allowing fast information transfer with reduced energy expenditure (Rubinov and
9 Sporns, 2010; Karbowski, 2001). Small-world topology has been described in human brain
10 functional (Achard *et al.*, 2006) and structural (Sporns *et al.*, 2007) networks.

11 This approach has been used in the study of large-scale network properties both in
12 healthy subjects (Achard *et al.*, 2006) and in neurodegenerative diseases such as Alzheimer’s
13 disease (Stam *et al.*, 2007; He *et al.*, 2008; Supekar *et al.*, 2008; Lo *et al.*, 2010; Sanz-Arigita *et*
14 *al.*, 2010). Despite ample evidence of changes in connectivity related to motor or cognitive
15 circuits in PD (Ibarretxe-Bilbao *et al.*, 2011; Wu *et al.*, 2011; Hacker *et al.*, 2012; Segura *et al.*,
16 2013), little is known about whole-brain network topology changes associated with this
17 disease. To our knowledge, no published studies addressed graph-theory parameters
18 associated with cognitive deficits in PD.

19 The principal aim of the present work was to explore global and local measures of
20 connectivity and network integration and segregation through a graph-theoretical approach in
21 a large sample of non-demented PD patients using resting-state fMRI. Specifically, we wanted
22 to study how these measures of connectivity would relate to the presence of cognitive deficits
23 in this disease to better understand the functional implications of these deficits on brain
24 function from a network perspective, and also as part of an effort to find neuroimaging
25 markers of cognitive decline and dementia. We hypothesized that PD patients with MCI would

1 have disrupted functional brain topological organization, and that specific types of deficit
2 would be associated with distinct patterns of network disruption.

3

4 **MATERIALS AND METHODS**

5 **Participants**

6 Eighty-four non-demented PD patients and 38 healthy controls (HC) matched for age,
7 sex and years of education were included. Patients were recruited from the Movement
8 Disorders Unit, Hospital Clínic, in Barcelona. HC were recruited from individuals who
9 volunteered to participate in scientific studies at the Institut de l'Envel·liment, Universitat
10 Autònoma de Barcelona. The inclusion criterion for patients was the fulfillment of the UK PD
11 Society Brain Bank diagnostic criteria for PD (Daniel and Lees, 1993). Exclusion criteria were: (i)
12 Mini-Mental State Examination scores less than 25 or the presence of dementia according to
13 the Movement Disorder Society criteria (Emre *et al.*, 2007), (ii) Hoehn and Yahr (HY) score > III,
14 (ii) presence of other significant psychiatric, neurological or systemic comorbidity, (iv)
15 pathological MRI findings other than mild white matter hyperintensities or, in patients,
16 findings not compatible with PD in the FLAIR sequence, (v) root mean square head motion >
17 0.3 mm translation or 0.3 degrees rotation.

18 All patients except one were taking antiparkinsonian drugs, consisting of different
19 combinations of levodopa, catechol-O-methyl transferase inhibitors, monoamine oxidase
20 inhibitors, dopamine agonists and amantadine. The medication was not changed for the study
21 and all assessments (clinical, neuropsychological and neuroimaging) were done while patients
22 were in the *on* state. Levodopa equivalent daily dose (LEDD) was calculated as suggested by
23 Tomlinson *et al.* (2010). Motor disease severity was evaluated using HY staging and the Unified
24 Parkinson's Disease Rating Scale motor section (UPDRS-III).

1 The study was approved by the ethics committee of the University of Barcelona, and
2 all subjects provided written informed consent to participate.

3 **Neuropsychological assessment**

4 All subjects underwent a neuropsychological battery to assess
5 visuospatial/visuoperceptual, memory and attention/executive functions. The tests
6 administered were as follows (for a full description, see Lezak *et al.*, 2004):

7 **VS/VP functions:** Benton's Visual Form Discrimination (VFD) and Judgment of Line
8 Orientation (JLO) tests. **Memory:** learning and recall memory were assessed using Rey's
9 Auditory Verbal Learning Test (RAVLT) total learning and free recall (after 20 minutes) scores.
10 **A/E functions:** difference between backward and forward digit spans from the Wechsler Adult
11 Intelligence Scale-III Digits subtest; difference between Trail-Making Test (TMT) part A and part
12 B scores; phonemic fluency scores (number of words beginning with the letter "P" produced in
13 60 seconds), and Stroop Color-Word Test (SCWT) interference scores.

14 The Beck Depression Inventory II (BDI) and the MMSE were also administered to all
15 subjects.

16 **MRI acquisition**

17 Images for all subjects were obtained with a 3T MRI scanner (MAGNETOM Trio,
18 Siemens, Germany), using an 8-channel head coil. The scanning protocol included a resting-
19 state, 5-minute-long functional gradient-echo echo-planar imaging sequence (150 T2*-
20 weighted volumes, TR=2 s, TE=19 ms, flip angle=90°, slice thickness=3 mm, FOV=240 mm, in
21 which subjects were instructed to keep their eyes closed, not to think of anything in particular
22 and not to fall asleep), a high-resolution 3D structural T1-weighted MPRAGE sequence
23 acquired sagittally (TR=2.3 s, TE=2.98 ms, 240 slices, FOV=256 mm; 1 mm isotropic voxel) and a
24 T2-weighted axial FLAIR sequence (TR=9 s, TE=96 ms).

1 **Processing of resting-state fMRI data**

2 The preprocessing was carried out using FSL-5.0 (<http://www.fmrib.ox.ac.uk/fsl/>) and
3 AFNI (<http://afni.nimh.nih.gov/afni>). Briefly, it included removal of the first 5 volumes to allow
4 for T1 saturation effects, skull stripping, grandmean scaling and temporal filtering (bandpass
5 filtering of 0.01-0.1 Hz). To control for the effect of subject head movement, physiological
6 artifacts (*e.g.*, breathing and vascular) and other non-neural sources of signal variation on the
7 estimation of functional connectivity, motion correction (using FSL's MCFLIRT) and regression
8 of nuisance signals (six motion parameters, cerebrospinal fluid and white matter) were
9 performed.

10 Head motion was calculated separately for translatory and rotatory movements
11 according to the following formula:

12
$$\frac{1}{M-1} \sum_{i=2}^M \sqrt{|x_i - x_{i-1}|^2 + |y_i - y_{i-1}|^2 + |z_i - z_{i-1}|^2}$$

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

15 **Quality control**

16 From the initially recruited sample, four patients were excluded due to macroscopic
17 movement artifacts and 14 due to head motion > 0.3 mm translation or > 1° rotation. Two
18 controls were excluded due to microvascular white matter changes, leaving a final sample of
19 66 PD patients and 36 HC. Despite rigorous head motion exclusion criteria, rotational head
20 motion was significantly higher (t=3.304, p =.001) in the patient (mean=.044°, standard
21 deviation (SD)=.035) than in the control group (mean=.028°, SD=.011). Evaluating patient
22 subgroups, rotational head motion was found to be significantly higher in non-MCI patients
23 than in controls (p =.028, *post-hoc* Bonferroni test). No significant differences were found

1 between controls and MCI patients or between patient subgroups. No significant intergroup
2 differences were found in translational motion (see Table II).

3 **Atlas-based definition of nodes**

4 We used the AAL atlas (Tzourio-Mazoyer *et al.*, 2002), the parcellation scheme most
5 frequently used in fMRI graph-theory studies (Tijms *et al.*, 2013), to parcellate the cerebral
6 gray matter into 45 regions of interest (ROI) per hemisphere (see Table I). Non-linear
7 registration using FNIRT (<http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FNIRT>) was used to transform the
8 AAL ROIs to each subject's T1-weighted image space; subsequently, a linear registration
9 (Jenkinson *et al.*, 2001) was applied to bring the ROIs from each subject's T1-weighted to
10 native functional space.

11 **Network computation and parameters**

12 BOLD signal temporal series were averaged throughout all voxels within each ROI
13 (Biswal *et al.*, 1995). The connectivity between two ROIs was estimated using Pearson's
14 correlation between their timeseries. A 90x90 matrix for each subject was thus obtained,
15 representing all the edges. Networks were constructed using only positive r values (Tian *et al.*,
16 2007; Wang *et al.*, 2011; Chen *et al.*, 2013). Because there is no agreement on the selection of
17 a threshold to define biologically relevant connections, we used a sparsity (S – existing number
18 of edges in a graph divided by the number of all possible edges) threshold to create a set of
19 undirected graphs, using correlation strength as edge weights, for each subject (Bassett and
20 Bullmore, 2006; Zhang *et al.*, 2012), while minimizing the effects of overall connectivity
21 differences (Achard and Bullmore, 2007). Sparsity is a measure of network density; using it as a
22 threshold to networks with equal numbers of nodes such as in the present study ensures that
23 all subjects' networks will also have the same number of edges, making them more suitable for
24 comparisons (van Wijk *et al.*, 2010). We evaluated the consistency of the global measures over
25 a range of sparsities ($5\% \leq S \leq 25\%$, at 2.5% steps) (Wang *et al.*, 2009; Fornito *et al.*, 2010;

1 Bullmore and Bassett, 2011). Since a similar trend for intergroup differences was observed
2 over the range of thresholds for global measures, only results using an S of 15% are reported
3 for regional measures analysis.

4 The obtained networks were analyzed in terms of their global (or whole-brain)
5 characteristics, as well as regional/local (or nodal) measures (for a more detailed, see Rubinov
6 *et al.*, 2010) using the Brain Connectivity Toolbox (Rubinov and Sporns, 2010). The parameters
7 evaluated were the following:

8 Local/regional measures (of a node):

9 *Clustering coefficient* is the number of connections between a node's neighbors
10 divided by the number of possible such connections, or the probability that a node's neighbors
11 are also connected to each other, indicating how close they are to forming a clique.

12 The *local efficiency* of a node is calculated as the global efficiency of the subgraph
13 formed by this node's neighbors. It is a measure of clustering and indicates the capacity of this
14 subgraph to exchange information if that node is eliminated (Achard and Bullmore, 2007).

15 *Node's connectivity degree*: number of edges linked to a node (*i.e.*, number of
16 input/output connections). This measure can be interpreted as a node's accessibility.

17 *Betweenness centrality* (BC) is the number of shortest paths between any two nodes
18 that go through a given node, and indicates the importance of that node to the network.

19 Brain *hubs* are highly connected or central nodes (Sporns *et al.*, 2007), which play an
20 important role in global network communication (Achard *et al.*, 2006). These nodes tend to
21 have numerous (high degree) and relevant (high BC) connections (Ottet *et al.*, 2013). For each
22 subject group, nodes were scored according to the sum of their rank position in BC and node
23 degree. The 20% highest-scoring nodes were classified as hubs.

1 Global measures

2 The *clustering coefficient* of a network is defined as the average of the clustering
3 coefficients of all nodes in the network. It quantifies the local interconnectivity of a network
4 and reflects functional segregation, or the ability for specialized processing within densely
5 interconnected groups of brain regions.

6 *Characteristic path length*, defined as the average of the shortest path length or
7 distance between any pair of nodes in a network. The minimum path length between two
8 nodes is the smallest number of edges that must be traversed to connect them. Lower values
9 indicate higher routing efficiency, as information exchange involves fewer steps.

10 *Small-world coefficient*: this measure is defined as the ratio of the average clustering
11 coefficient to the characteristic path length divided by the ratio of the same measures of
12 equivalent random networks (Humphries and Gurney, 2008). Small-world networks usually
13 have small-world coefficients greater than 1.

14 *Global efficiency*: measures the ability of a network to transmit parallel information at
15 the global level. It inversely correlates with path length but is not susceptible to the presence
16 of disconnected nodes.

17 *Modularity*: indicates the degree to which a network can be subdivided into well-
18 delineated modules made up of densely interconnected nodes with few intermodular
19 connections, and which may represent network functional subcomponents (Grossberg, 2000).
20 For the study of the distribution of network modules by group, mean group functional
21 matrices were constructed with the ratio of mean to standard deviation of all subjects'
22 matrices as proposed by Chen *et al.* (2013) to minimize intersubject variation in edge
23 connectivity strength (see formula in Supplementary Materials).

1 The mean network global connectivity was calculated as the mean of all positive
2 interregional timeseries correlation r values. This measure was calculated for the
3 unthresholded correlation matrices as well as for the networks constructed after applying each
4 sparsity threshold (from 200 edges at 5% sparsity to 1001 at 25% sparsity). Cutoff r values
5 were calculated as the r coefficient of the weakest edge included in each subject's thresholded
6 correlation matrix for each S threshold. For intergroup comparisons in interregional
7 connectivity strengths, r coefficients were converted to z coefficients using Fisher's r to z
8 transformation.

9 **Neuropsychological data analysis**

10 Initially, z scores for each test and subject were calculated based on the HC group's
11 means and standard deviations. Expected z scores adjusted for age, sex and education for each
12 test and each subject were calculated based on a multiple regression analysis performed in the
13 HC group (Aarsland *et al.*, 2009).

14 We classified subjects as having MCI if the actual z score for a given test was at least
15 1.5 lower than the expected score in at least two tests in one domain or in at least one test per
16 domain in at least two domains. As was expected (Muslimovic *et al.*, 2005), most such subjects
17 had deficits in more than one function, precluding the creation of patient groups with single-
18 domain impairments.

19 **Statistical analyses**

20 All statistical analyses were performed using SPSS Statistics 20.0.0 (Chicago, IL,
21 <http://www-01.ibm.com/software/analytics/spss/>). Statistical significance threshold was set at
22 $p < 0.05$. Pearson's chi-square test was used to compare categorical variables (hand dominance,
23 sex, HY stage). Student's t -test was used to compare head motion, clinical and connectivity
24 data means between patients and controls. Three-level one-way ANOVAs were used to

1 compare head motion, clinical and sociodemographic data between HC and patient subgroups
2 (non-MCI, MCI). Three-level one-way analyses of covariance were used to compare network
3 measures (normally distributed) between HC and patient subgroups while controlling for
4 variables that presented intergroup differences in the previous step. Significance p values were
5 adjusted using *post-hoc* Bonferroni tests considering the number of intergroup comparisons.
6 Test statistics and significance levels are given in Supplementary Table II. To study the effects
7 of different types of deficits on the evaluated network parameters in the PD group, the entire
8 patient sample was analyzed through linear regression models entering the difference
9 between expected and actual z scores for each of the three cognitive domains assessed plus
10 relevant normally-distributed variables that significantly correlated with these scores as
11 independent variables. Non-normally distributed variables were analyzed using Spearman rank
12 correlations, Mann-Whitney tests and Kruskal-Wallis tests.

13

14 **RESULTS**

15 **Sociodemographic and clinical features**

16 Twenty-three patients (34.8%) fulfilled criteria for MCI. Table II shows
17 sociodemographic, clinical and head motion data and the corresponding group comparisons.
18 Supplementary table I shows the results of neuropsychological assessment and group
19 comparisons.

20 **Mean connectivity changes**

21 No significant intergroup differences were observed for global mean connectivity
22 values (Supplementary Table II). The exploratory analysis of correlation strengths over all
23 edges, controlling for the effect of rotational head movement, revealed that the collapsed
24 sample of PD patients had several widespread connectivity decrements, most often affecting

1 interlobular edges, as well as some increments, mainly in interlobular prefrontal connections
2 (see Supplementary Figs. 1 and 2). The analysis of PD subgroups revealed that MCI patients
3 had widespread reductions compared with HC; connectivity increases were also present,
4 mostly involving shorter-range frontal and temporal links (see Fig. 1 and Supplementary Fig. 2).
5 Non-MCI patients were also seen to have some connectivity reductions compared with HC
6 mainly involving connections between frontal, occipital and parietal areas. A more detailed
7 description of the pattern of interregional connectivity changes in PD subgroups can be found
8 in Supplementary Figure 3. No significant group differences in cutoff r coefficients were
9 observed for any of the sparsity thresholds applied (see Supplementary Figure 4).

10 **Global network topological parameters**

11 The networks of HC and both PD subgroups displayed small-world and modular
12 characteristics (see Fig. 2). No significant differences were found for any of the global
13 measures when comparing HC and the collapsed PD-patient group at any of the sparsity
14 thresholds applied, with or without controlling for differences in BDI scores and rotational
15 head motion.

16 Global measures analysis revealed that MCI patients presented significantly higher
17 small-world and modularity coefficients than HC and non-MCI patients (see Fig. 2 and
18 Supplementary Table II). Clustering coefficients were higher in MCI than in non-MCI patients at
19 stricter thresholding (see Fig. 2 and Supplementary Table II).

20 **Community structure and hub distribution**

21 Figure 3 shows the nodes that ranked highest in clustering coefficient and BC in each
22 group and were therefore classified as hubs, as well as the modular structure identified in each
23 group. Mean brain networks in the three groups were decomposed into four basic modules:
24 fronto-parietal, insulo-operculo-striatal, fronto-parieto-parahippocampal and occipito-

1 temporal (see Fig. 3). In HC, an additional module composed of the thalami was identified. A
2 significant group effect was found for the number of modules (Kruskal-Wallis $H=6.756$,
3 $p=.034$); Bonferroni-corrected post-hoc Mann-Whitney tests showed a tendency for more
4 modules in MCI patients than in HC ($p=.069$) (see Figure 3). The number of modules did not
5 correlate significantly with motion parameters.

6 **Local network topological parameters**

7 To assess the reorganization of local topological measures (node degree, BC, nodal
8 clustering coefficient and local efficiency) in the subgroups of PD patients, we correlated the
9 mean nodal values for the HC group and the differences between each individual subject's
10 value and the mean value in HC (Achard *et al.*, 2012). This strategy allows the analysis of
11 whether changes in nodal parameters in the patient groups are related to their respective
12 values in HC, and also provides a visual representation of increases or decreases in these
13 properties in individual nodes. Intergroup comparisons of z-transformed correlation
14 coefficients revealed that, for BC, both PD subgroups had significantly more negative
15 correlations than HC, indicating that hubs tend to lose centrality, and nodes which normally
16 have low centrality undergo the most significant increases ($F=11.090$, $p<.001$; post-hoc
17 Bonferroni test: PD-MCI>HC $p<.001$, PD-non-MCI>HC $p=.001$) in PD patients. For node degree,
18 a similar effect was found in PD-MCI compared with HC ($F=4.429$, $p=.014$; post-hoc Bonferroni
19 test: PD-MCI>HC $p=.011$) (see Fig. 4). No significant differences in correlation coefficients were
20 found for measures of nodal clustering coefficient and local efficiency.

21 Figures 4 and 5 show the distribution of mean changes in nodal parameters as a
22 function of mean values in HC for both PD subgroups. Differences between MCI patients'
23 values and HC's for clustering coefficient and local efficiency were more often positive,
24 indicating a tendency for increased clustering, especially for nodes that in HC belong to the
25 occipito-temporal or the fronto-parietal modules (see Fig. 5).

1 **Effect of types of cognitive deficits on topological measures**

2 VS/VP scores did not correlate significantly with A/E or memory scores, with
3 clinical/demographical variables such as age, education, LEDD, disease duration or UPDRS-III or
4 BDI scores, or with head motion parameters; a simple regression model was therefore used to
5 evaluate the corresponding cognitive function. A/E scores significantly correlated with memory
6 scores ($r=.31$, $p=.011$); the latter, in turn, also correlated significantly with age ($r=-.34$, $p=.006$)
7 and LEDD ($r=-.27$, $p=.027$). These variables were entered as independent variables in the
8 analysis of A/E and memory functions in a multiple regression model.

9 Regression analyses performed in the patient group revealed that composite z scores
10 for VS/VP and memory correlated negatively with clustering, modularity and small-world
11 coefficients over a range of thresholds (see Fig. 6). A/E scores, on the other hand, did not
12 correlate significantly with global measures at any of the thresholds applied.

13 At the regional level, measures of clustering (clustering coefficient and local efficiency),
14 degree and BC had mainly negative correlations with VS/VP scores, predominantly in temporal
15 and parietal cortices, as well as with basal ganglia, thalamus and medial temporal nodes
16 (see Figure 6 and Supplementary Table III). Memory scores were likewise seen to correlate
17 with local parameters predominantly in frontal and temporal areas. Memory scores correlated
18 negatively with measures of clustering in prefrontal and medial temporal regions. Node degree
19 correlated with these scores in frontal and occipital areas (see Figure 6 and Supplementary
20 Materials). Significant nodal correlates for A/E scores were found mainly in frontal regions. BC
21 in several frontal areas correlated both positively and negatively with these scores (see Figure
22 6 and Supplementary Table III).

23 No significant correlations were found between HC scores in any of the 3 cognitive
24 domains assessed and global network measures at any of the thresholds applied.

1

2 **DISCUSSION**

3 In the current study, we evaluated brain network topologies associated with the
4 presence of cognitive deficits in a large sample of non-demented, treated PD patients through
5 resting-state fMRI. We thresholded subjects' correlation matrices to construct weighted,
6 undirected networks composed of identical numbers of nodes and edges. Our findings suggest
7 that graph-theoretical approaches can evidence cerebral functional network reorganization in
8 PD patients in association with cognitive deficits and may prove useful as imaging biomarkers
9 of cognitive decline in this disease. Our main findings were that MCI PD patients' functional
10 connectomes had increased modularity and *small-worldness*. Although more advanced disease
11 may partially account for these changes, regression analyses controlling for clinical confounds
12 showed that global parameters of clustering, modularity and *small-worldness* were negatively
13 associated with performance in VS/VP and memory functions. These findings suggest that the
14 presence of cognitive impairments is per se associated with network topological
15 reorganization in non-demented PD patients.

16 In the present study, widespread long-range connectivity decreases were observed in
17 the PD group, most notably in patients with MCI. In this group, these decrements were seen to
18 affect connections between all major cortical and subcortical areas. Connectivity increases of a
19 possible compensatory nature were also observed, mainly affecting shorter connections within
20 the frontal and temporal lobes. The presence of both decreased and increased edge strength
21 explains the absence of intergroup mean global connectivity differences. Previous resting-state
22 functional connectivity fMRI studies in PD have found connectivity increases and decreases
23 depending on the networks or circuits studied. Wu *et al.* (2009), in a study addressing motor
24 network connectivity, described increases in the *off* state which were normalized after
25 levodopa administration. In another study, the same group found both increments and

1 decrements in the rostral supplementary motor area's connectivity compared with HC (Wu *et*
2 *al.*, 2011). More recently, Tessitore *et al.* (2012) described functional connectivity decreases
3 between regions of the default mode network (in parietal cortical and medial temporal areas)
4 and the rest of the same network in cognitively preserved PD patients. Recent evidence
5 indicates that white matter degeneration plays a role in PD-related cognitive impairment
6 (Agosta *et al.*, 2012; Baggio *et al.*, 2012; Hattori *et al.*, 2012). Studies using genetic animal
7 models suggest that primary axonopathy is part of the PD pathological process (Li *et al.*, 2009;
8 see also Burke and O'Malley, 2013). We hypothesize that the observed connectivity
9 decrements result from structural connectivity deficits due to neurite dysfunction, and that
10 these changes contribute to cognitive impairment in PD. No group differences were found in
11 the measures of integration (characteristic path length and global efficiency) assessed in the
12 present study, probably due to the strengthening of alternative pathways. Nonetheless, this
13 hypothesis would merit testing through the combined analysis of connectivity patterns and
14 white matter integrity. Evidence from animal studies using genetic models also indicates that
15 α -synuclein aggregates lead to impairments in neurotransmitter release and subsequent
16 synaptic dysfunctions, further contributing to connectivity impairments (Scott *et al.*, 2010).

17 The overall topographic distribution of the network modules was preserved in the PD
18 group, although brain modularity was seen to be increased in patients with MCI. This finding is
19 probably related to the increases in these patients' local interconnectedness (*i.e.*, higher nodal
20 clustering coefficients and local efficiency), which were found to preferentially involve nodes
21 that normally belong to the occipito-temporal and fronto-parietal modules, and which also
22 lead to increases in the calculated small-world coefficients. It could be speculated that the
23 increments in local interconnectivity result from shorter-range, within-module compensatory
24 plasticity mechanisms as a response to long-range connectivity loss or primary cortical
25 pathology (Compta *et al.*, 2011).

1 We also evaluated changes in parameters that identify the most relevant nodes to
2 information traffic, *i.e.*, network hubs. We found that PD, especially in the presence of
3 cognitive deficits, was associated with a reorganization of hub structure, characterized by
4 reduced importance – as measured by BC and degree – of nodes that are normal hubs and
5 increased importance of nodes that normally have low network relevance. The increase in
6 *hubness* was most noticeable in prefrontal nodes, several of which were classified as hubs only
7 in the PD subgroups. Our findings indicate that, in PD, hubs may be especially vulnerable to the
8 degenerative pathogenic process that amounts to cognitive impairment, as has been described
9 in Alzheimer's disease (Stam *et al.*, 2009) and hypothesized to be derived from these region's
10 higher metabolic activity (de Haan *et al.*, 2012). Considering the relevance of Alzheimer's type
11 pathology in the genesis of cognitive deficits in PD (Compta *et al.*, 2011), a common
12 mechanism could underlie these changes in both diseases.

13 The analysis of topological patterns associated with specific types of deficits revealed
14 that VS/VP and memory deficits, although not mutually correlated, were associated with the
15 same global parameters that were altered in MCI patients. A/E deficits, on the other hand, did
16 not correlate with global network measures. Dopaminergic antagonism has been seen to
17 reduce both global and local efficiency in healthy subjects (Achard and Bullmore, 2007). PD
18 patients off medication (*i.e.*, in a state of dopamine deficiency) have also been described to
19 have reduced global and local efficiency (Skidmore *et al.*, 2011). The extrapolation of these
20 data to treated Parkinson's disease subjects is not straightforward, however, as these patients
21 are not in a consistent hypodopaminergic state. Midbrain dopaminergic neuron loss
22 progresses heterogeneously (Damier *et al.*, 1999). Affected areas thus coexist with spared
23 areas, which may ultimately suffer dopaminergic overstimulation or *dopamine overdose* as a
24 result of antiparkinsonian treatments (Gotham *et al.*, 1986). Longitudinal population-based
25 studies indicate that the presence of deficits related to dopamine imbalance in PD does not
26 increase the risk of subsequent dementia, whereas deficits with posterior-cortical, non-

1 dopaminergic bases are markers of worse cognitive prognosis (Williams-Gray *et al.*, 2007;
2 Williams-Gray *et al.*, 2009). The role played by primary cortical pathology in cognitive
3 impairment and in the development of dementia in PD, which according to post-mortem
4 studies can be related to synucleinopathy as well as to Alzheimer's-type pathology (Fields *et*
5 *al.*, 2011; Compta *et al.*, 2011; see also Ferrer, 2009), is likely to explain these associations.
6 VS/VP deficits in PD appear to be independent from dopamine imbalances (Lange *et al.*, 1992)
7 and are accompanied by temporo-parieto-occipital gray matter atrophy (Pereira *et al.*, 2009).
8 And although striatofrontal circuit disruptions are considered to play a part in declarative
9 memory deficits associated with PD (Dujardin *et al.*, 2001), recent work has described
10 structural hippocampal changes associated with these impairments (Apostolova *et al.*, 2012;
11 Carlesimo *et al.*, 2012; Beyer *et al.*, 2013; Pereira *et al.*, 2013). The global changes observed in
12 the present study to be associated with MCI and with VS/VP and memory deficits may,
13 therefore, reflect primary white-matter changes as well as the gray-matter pathological
14 processes responsible for more severe cognitive decline and conversion to dementia. Future
15 longitudinal studies are needed to establish if these changes have predictive value for worse
16 cognitive outcomes. The regional network reorganization associated with A/E deficits, on the
17 other hand, may be a reflection of the dopamine imbalances affecting frontal areas, a finding
18 compatible with the known relationship between these impairments and frontostriatal
19 dopaminergic imbalances (see Cools and D'Esposito, 2011). These data provide valuable
20 evidence about the different pathological implications of distinct types of neuropsychological
21 impairment in PD.

22 The results found in the present study do not conform to the patterns described in
23 Alzheimer's disease, currently the best-studied neurodegenerative process. Graph theory
24 studies in this disease with different methodological approaches have yielded variable results
25 (see Tijms *et al.*, 2013), but studies using resting-state fMRI have described reduced (Supekar
26 *et al.*, 2008) or unchanged (Sanz-Arigita *et al.*, 2010) clustering coefficients. Characteristic path

1 lengths have been described to be reduced in patients with AD (Sanz-Arigita *et al.*, 2010) and
2 increased in patients at risk for this disease (Wang *et al.*, 2013). Our findings of increased
3 segregation and modularity with no significant changes in integration may therefore be more
4 specific of cognitive impairment in PD.

5 One possible limitation of the present work is that patients were evaluated in the *on*
6 state, *i.e.*, under the influence of dopaminergic medication. As previous work has shown
7 (Achard and Bullmore, 2006), dopaminergic manipulations impact measures of network
8 efficiency. Besides the constraint of conceivably more severe motion artifacts in the *off* state,
9 with subsequent effects on functional connectivity estimations (van Dijk *et al.*, 2012), we
10 wanted to study cognitive deficits and their substrate as they occur in patients' daily lives – *i.e.*,
11 under the effect of their usual medication. In this way, we expect our findings can be
12 extrapolated to the clinical setting and can be more useful in future efforts to establish
13 neuropsychological and neuroimaging biomarkers for dementia. Additionally, despite the
14 rigorous head motion exclusion criteria and preprocessing steps aimed at minimizing the effect
15 of motion artifacts, we cannot guarantee that our results were not influenced to some degree
16 by them. Nonetheless, the fact that connectivity changes were more significant in the MCI
17 group – which displayed less pronounced head motion than the non-MCI group – indicates
18 that the observed effect has actual biological origins.

19 In conclusion, our results indicate that complex network analysis through resting-state
20 fMRI is a useful method for the investigation of functional changes related to cognitive decline
21 in Parkinson's disease. This study suggests that MCI in PD is accompanied by increases in
22 network modularity and small-world coefficients, as well as by changes in network hub
23 regions. Additionally, cognitive deficits in PD are accompanied by network disruptions
24 characterized by the weakening of long-range connections alongside increases in local
25 connectedness. The observed pattern of these changes and their anatomical distribution

1 indicates that they may be part of the distinct substrates underlying different types of PD-
2 related cognitive impairment. Future longitudinal studies could provide relevant information
3 about the potential use of specific changes in network parameters as predictors of subsequent
4 cognitive decline.

5

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7

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19 **FIGURE LEGENDS**

20 Figure 1. Comparisons of interregional connectivity strength between HC and Parkinson's
21 disease subgroups.

1 Top row: mean connectivity matrices according to group (Pearson's r coefficients, indicated in
2 the color bar) for all pairs of ROIs. Bottom row: edges with significant *post-hoc* group
3 differences ($p < .05$) in z correlation values are marked in color. Bottom left: non-MCI versus
4 MCI patients; bottom middle: HC vs. MCI patients; bottom right: HC vs. non-MCI patients.
5 Color bars indicate *post-hoc* Bonferroni test p values according to direction of differences.
6 Anatomical regions, ordered in roughly anterior-posterior sequence and grouped according to
7 lobes or subcortical structures, are numbered in the vertical and horizontal axes according to
8 Table I. *CS*: corpus striatum; *thal*: thalamus.

9

10 Figure 2. Small-world, modularity and clustering coefficients (vertical axis) as a function of
11 sparsity thresholds (horizontal axis) for HC and Parkinson's disease subgroups.

12 * indicates significant differences between HC and MCI patients ($p < .05$, *post-hoc* Bonferroni
13 test); § indicates significant differences between non-MCI and MCI patients ($p < .05$, *post-hoc*
14 Bonferroni test). SW: small-world coefficient.

15

16 Figure 3. Community structure and hub distribution according to group.

17 Colors in nodes and links correspond to the modules indicated at the top of the figure. Black
18 nodes in the HC group represent the thalami. Only intramodular edges are shown. Mean
19 number of modules and standard deviations per group are shown at the right. Nodes classified
20 as hubs in each group are listed, as well as the communities to which they belong in each
21 group's mean network.

22

1 Figure 4. Changes in measures of node degree and BC in non-MCI and MCI PD patients relative
2 to HC as a function of HC's means.

3 Left side: mean differences between PD-non-MCI and HC (A, C) and between PD-MCI and HC
4 (B, D) for node degree (K) (A, B) and betweenness centrality (BC) (B, D) are plotted against the
5 mean values in the HC group (horizontal axes) for all nodes. Nodes classified as hubs in the
6 control group are numbered (see Table I). Colors indicate the modules to which each node
7 belongs in HC as indicated at the top of the figure. Right side: correlation between HC's mean
8 values for K (above) and BC (below) (horizontal axes) and the individual differences between
9 subjects' values in the corresponding parameters and mean HC values (vertical axes). Mean r
10 correlation values and standard deviations according to group are shown.

11

12 Figure 5. Changes in nodal parameters of segregation in non-MCI and MCI PD patients relative
13 to healthy controls as a function of HC's means.

14 Mean differences between PD-non-MCI and HC (A, C) and between PD-MCI and HC (B, D) for
15 node nodal clustering coefficients (C) (A, B) and local efficiency ($eLoc$) (B, D) are plotted against
16 the mean values in the HC group (horizontal axes) for all nodes. Nodes classified as hubs in HC
17 are numbered (see Table I). Colors indicate the modules to which each node belongs in the HC
18 group as indicated at the top of the figure.

19

20 Figure 6. Relationship between network parameters and composite scores for memory and
21 VS/VP functions.

22 A: Significant linear regression analysis results for global measures and VS/VP (top) and
23 memory (bottom) z scores. β – standardized beta regression score. B: Regions where regional

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1 measures correlated significantly with A/E, memory or VS/VP scores. Top row: negative
2 correlations; bottom row: positive correlations. *C*: clustering coefficient; *Mod*: modularity; *SW*:
3 small-world coefficient; *eLoc*: local efficiency.

4

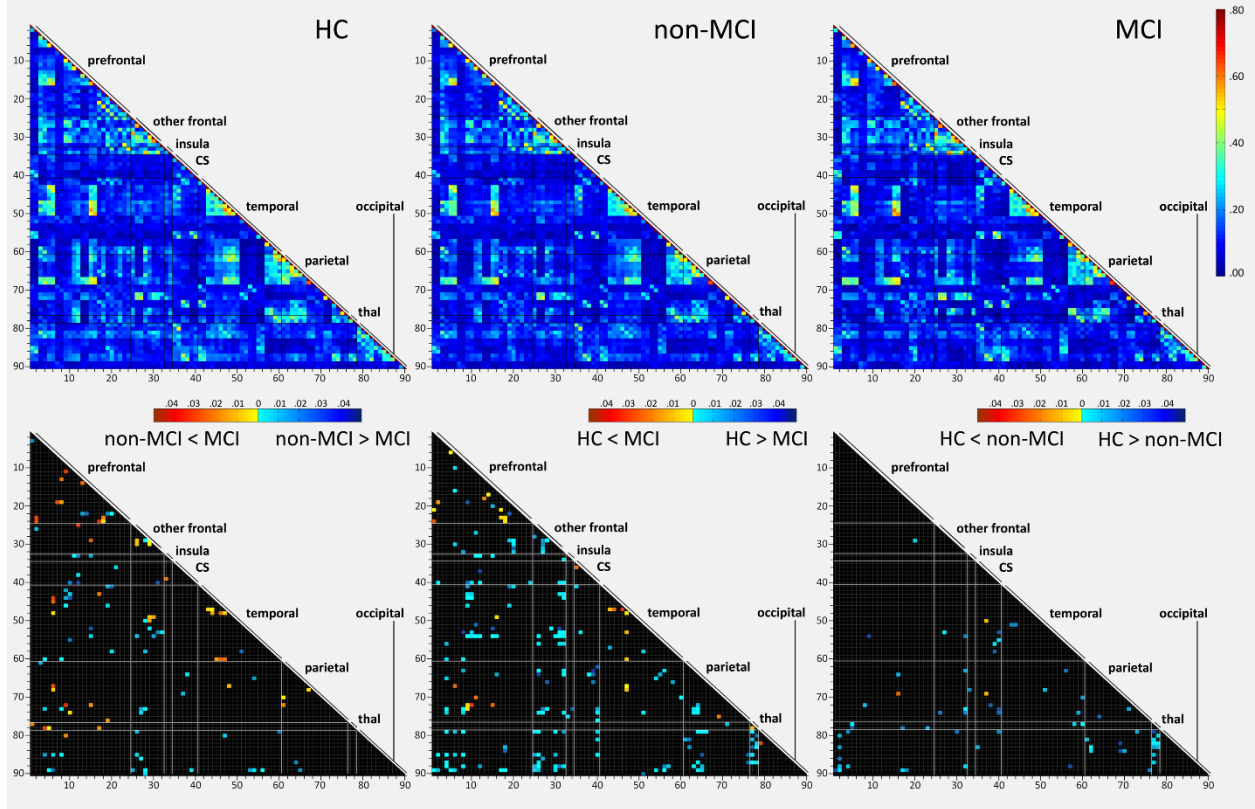


Figure 1

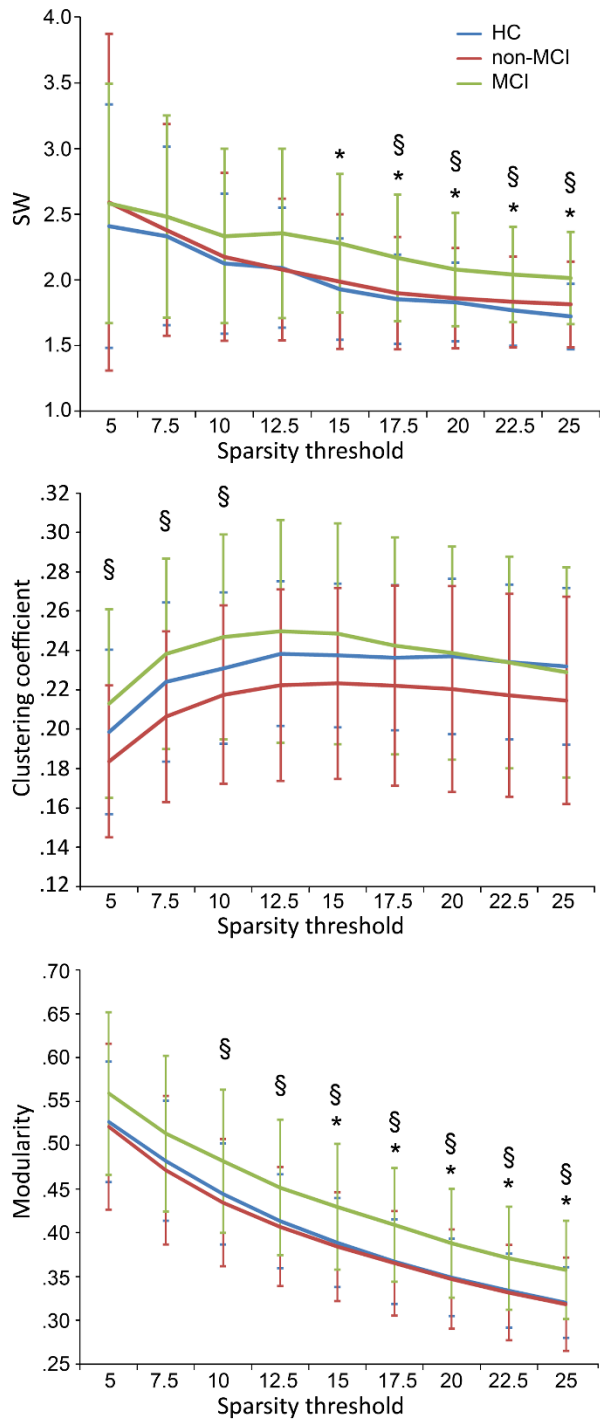


Figure 2

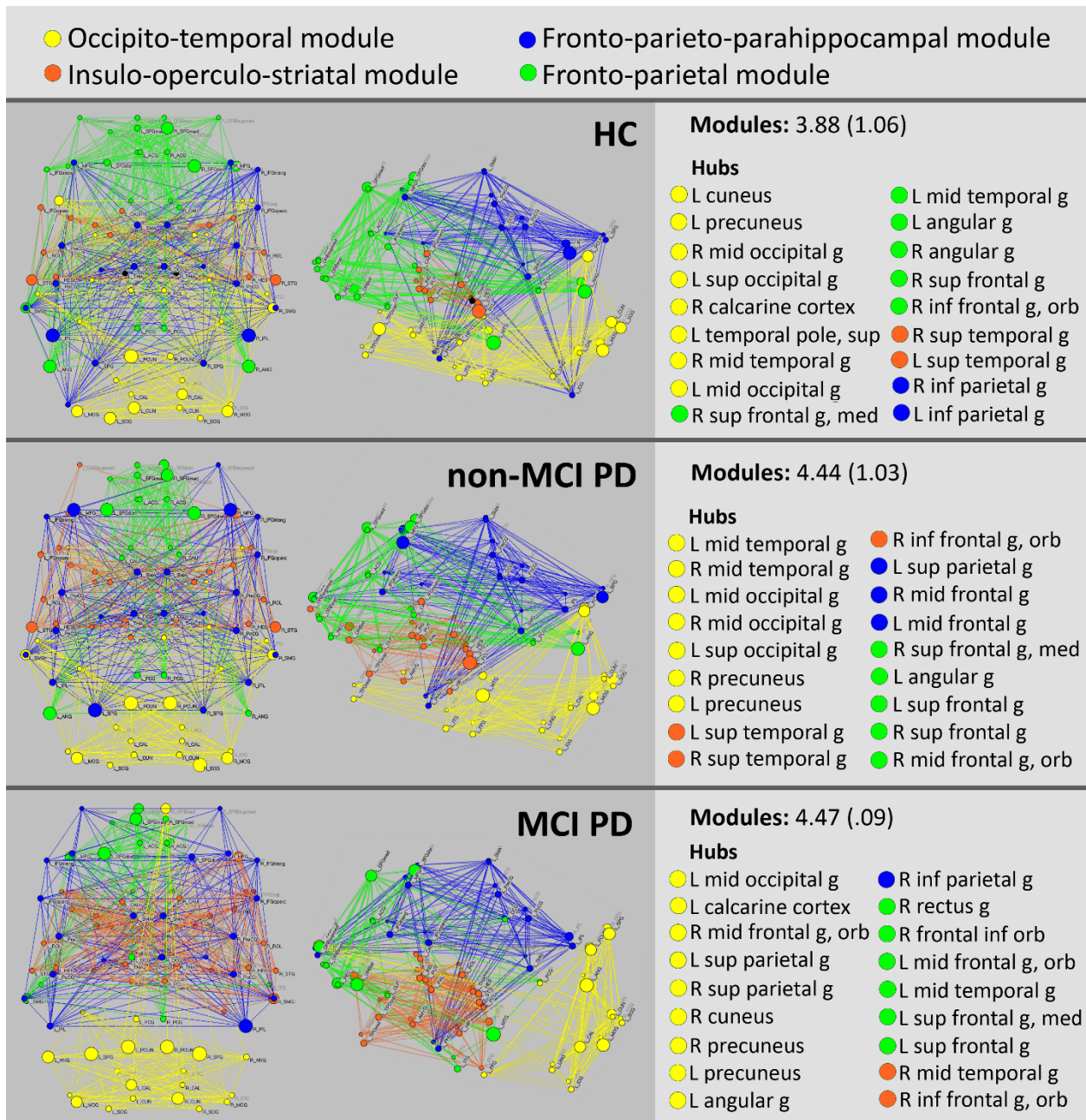


Figure 3

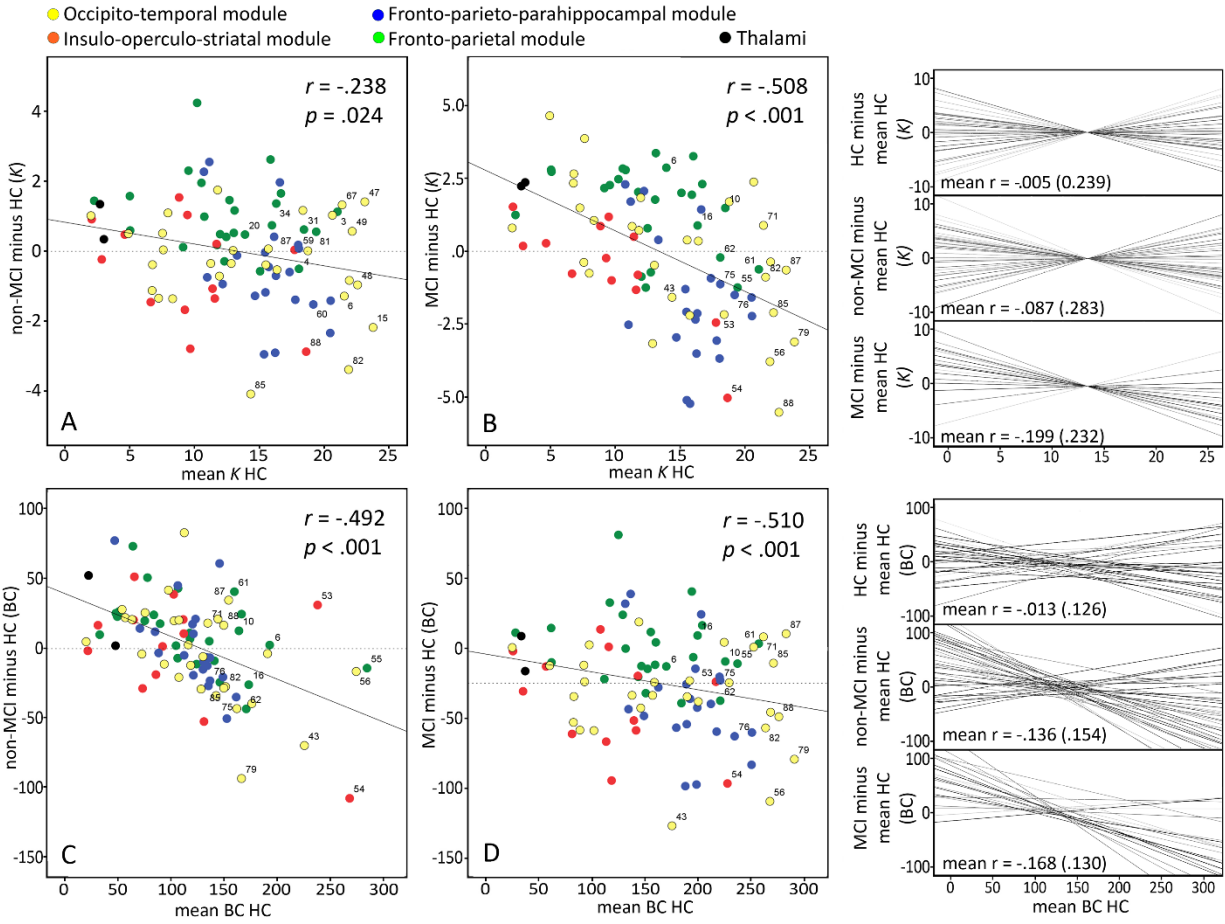


Figure 4

- Occipito-temporal module
- Fronto-parieto-parahippocampal module
- Thalami
- Insulo-operculo-striatal module
- Fronto-parietal module

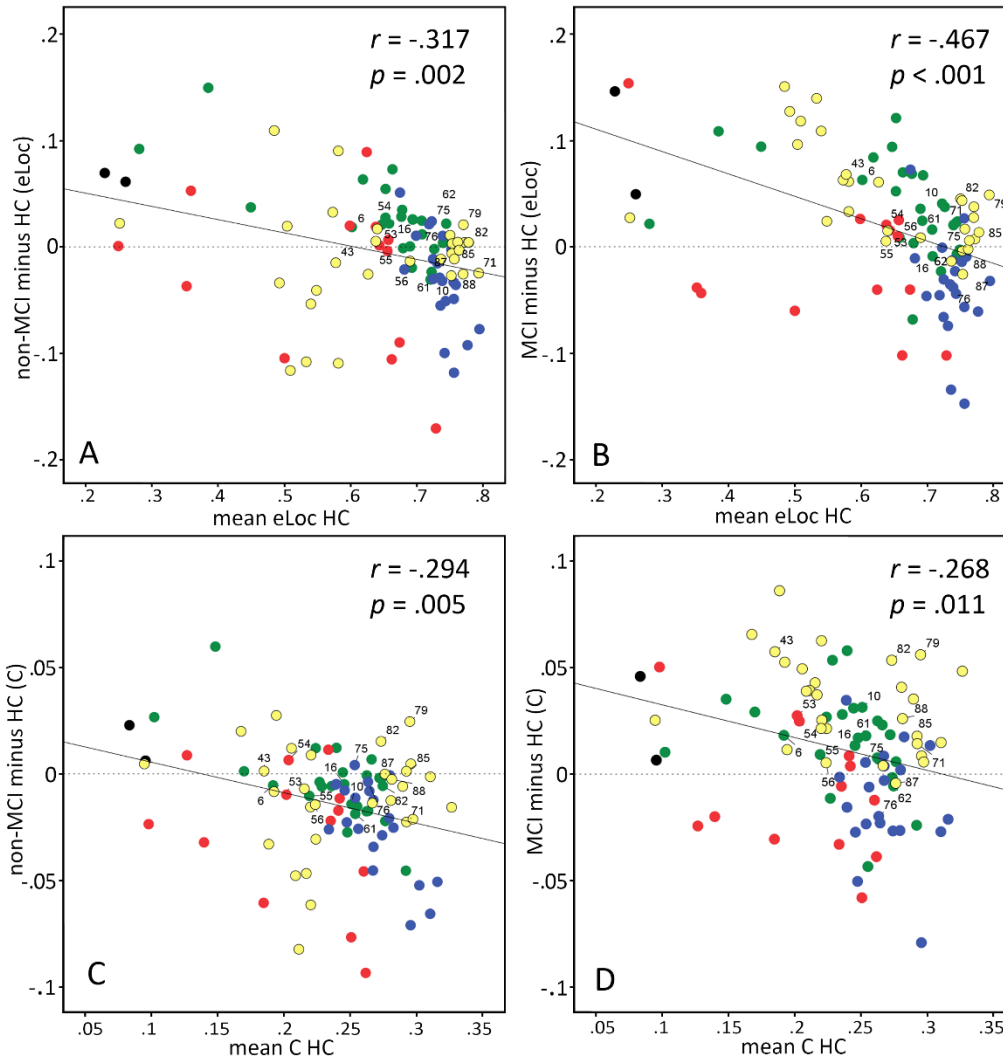
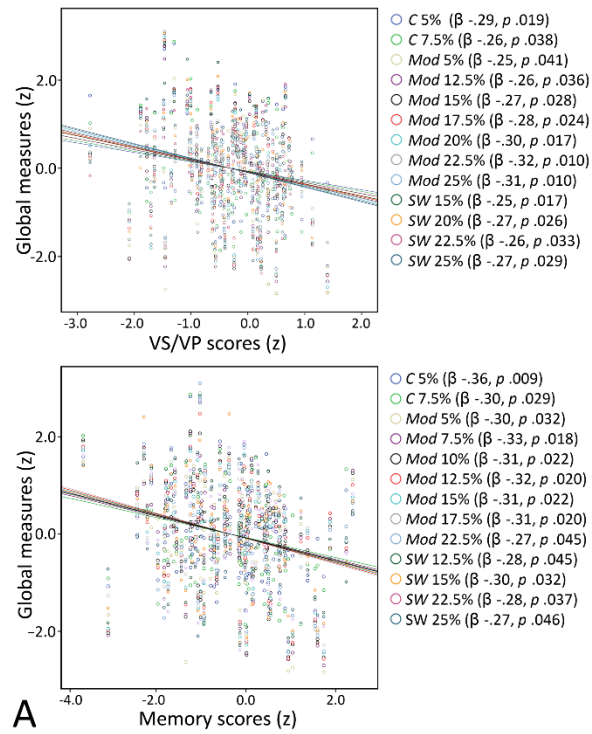


Figure 5



A

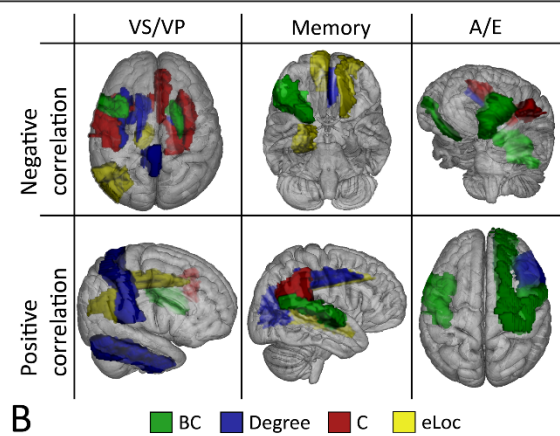


Figure 6