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# Altered functional connectivity in the default mode network is associated with cognitive impairment and brain anatomical changes in Parkinson's disease

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ABSTRACT

*Objective:* To assess whether functional neural connectivity is disrupted between the regions of the default mode network (DMN) in Parkinson's disease (PD) and how this connectivity is related to cognition, brain gray matter structure and white matter integrity and diffusivity.
*Methods:* Thirty-seven PD patients and 16 healthy controls were evaluated, using resting-state functional magnetic resonance imaging (MRI), T1-weighted MRI, diffusion-weighted imaging and a battery of cognitive tests. Functional connectivity between the regions of the DMN, specifically in the precuneus, anterior and posterior cingulate, medial prefrontal and temporal and inferior parietal cortices was assessed with seed-to-voxel connectivity; gray matter volume and white matter values were determined using voxel-based morphometry and tract-based spatial statistics.
*Results:* Reduced functional connectivity was observed between the posterior cingulate and medial temporal lobe in PD. Lower cognitive performance, gray matter loss in posterior, medial temporal and parietal areas, and fractional anisotropy reduction in the white matter adjacent to DMN regions were also observed in PD patients compared with healthy controls. Lower DMN functional connectivity correlated with lower verbal and visual memory and visual abilities performance in PD. In addition, lower DMN functional connectivity correlated with lower gray matter volume in the posterior cingulate and precuneus, and with lower white matter fractional anisotropy of the inferior longitudinal and posterior cingulate fasciculi in PD.
*Conclusions:* By combining different neuroimaging techniques and cognitive data, results showed that functional connectivity alteration between the regions of the DMN is associated with lower cognitive performance and gray and white matter abnormalities in PD.


## 1. Introduction

Parkinson's disease (PD) is a neurodegenerative disorder characterized by the progressive development of motor symptoms and cognitive decline, with dementia often occurring in advanced stages of PD [1]. Previously, PD has been related to deficits in executive functions, attention and visuospatial abilities but recent studies also showed that memory is a relevant cognitive deficit in this disease [2]. Previous studies have demonstrated brain anatomical changes [3], cognition task-related functional magnetic resonance imaging (fMRI) changes [4,5] and cognitive impairment in PD [6]. Recently, there has been growing interest in resting-state fMRI studies, as this approach allows the study of the brain's functional networks without requiring participants to perform any task. Moreover, high reproducibility of the findings supports the validity of resting-state fMRI outcome measures as biomarkers [7].

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The default mode network (DMN) is the most studied network in the resting-state and is derived from observations that specific brain regions are more active when the brain is in a wakeful resting-state than during the performance of external tasks. The areas that have been identified as part of the DMN are the medial prefrontal cortex (MPFC), anterior cingulate cortex (ACC), posterior cingulate cortex (PCC), precuneus, medial temporal lobe (MTL) and inferior parietal cortex (IPC) [8]. The relevance of the DMN has been emphasized in several neuropsychiatric diseases [8], but only a few studies have investigated the DMN in the context of PD [9–14]. FMRI studies have confirmed the crucial role played by the DMN in cognitive processing both in normal aging and neurodegenerative disorders [15,16]. In fact, the impairment of PCC and precuneus could be an important marker to distinguish amnestic mild cognitive impairment from healthy aging in the resting-state [17]. However, most neuroimaging studies assessing the DMN only had one single imaging modality making it difficult to investigate structural and functional changes in PD patients. Moreover, studies only assess global cognitive measure instead of extensive cognitive battery. To our knowledge, this is the first study assessing DMN disturbances and its cognitive and brain gray matter (GM) volume and white matter (WM) indexes correlates. Therefore, the first objective of this study was to investigate the resting-state functional connectivity (FC) between the regions of the DMN in PD patients, compared with healthy controls (HC). At the same time, we investigated cognitive differences, and GM volume and WM tracts differences in the DMN areas. The second objective was to explore the cognitive, GM volume and WM correlates of the DMN disturbances in PD. For the first objective, we hypothesized that PD patients would have lower FC, cognitive performance, GM volume and WM. For the second objective, we hypothesized that decreased FC in the DMN would be related to GM atrophy, lower WM, and diminished cognitive performance in PD.

## 2. Methods

### 2.1. Participants

The study included 37 PD patients recruited from the Department of Neurology at the Galdakao Hospital and from the PD Biscay Association (ASPARBI). We also included 16 HC who were acquaintances of the patients, matched with the patients by age, gender and years of education. PD patients were enrolled in the study if they fulfilled the UK PD Society Brain Bank diagnostic criteria, as assessed by a neurologist specialized in movement disorders. Other inclusion criteria were as follows: (i) age between 45 and 75 years; (ii) Hoehn and Yahr disease stage $\leq 3$; and (iii) Unified PD Rating Scale (UPDRS) evaluated by the neurologist. The exclusion criteria were as follows: (i) the presence of dementia, as defined by the DSM-IV-R and the Movement Disorders Society clinical criteria for PD dementia; (ii) scores of <24 on the Mini Mental State Examination; (iii) the presence of other neurological illness or injury or atypical parkinsonism; (iv) unstable psychiatric disorders; (v) PD patients with visual hallucinations, as assessed by the Neuropsychiatric Inventory Questionnaire; and (vi) diagnosis of depression or a depression score of >5, as evaluated with the Geriatric Depression Scale. WM hyperintensity ratings were calculated twice by the same neuroradiologist using the Fazekas Scale based on T1-weighted images. One patient was taking no medication, and 36 were on anti-Parkinsonian treatment as follows: Levodopa (L-dopa) monotherapy (n = 4); combination of L-dopa and a dopamine agonist (n = 5); monoamine oxidase type B (MAO-B) inhibitors monotherapy (n = 1); combination of L-dopa and MAO-B (n = 5); combination of L-dopa, a dopamine agonist and MAO-B (n = 9); combination of dopamine agonist and MAO-B (n = 4); combination of a dopamine agonist and anticholinergics (n = 2); combination of glutamate agonists in combination with others (n = 4); and catechol-*O*-methyltransferase (COMT) inhibitors in combination with others (n = 2). Participants were symptomatically stable and evaluated during the "ON" period. Their Levodopa equivalent daily dose (LEDD) was registered. The clinical and sociodemographic characteristics of the study sample are shown in Table 1.

### 2.2. Ethics statement

The study protocol was approved by the Ethics Committee at the Health Department of the Basque Mental Health System in Spain. All subjects were volunteers and provided written informed consent prior to their participation in the study.

### 2.3. Cognitive evaluation

The cognitive battery included tests to evaluate processing speed, verbal fluency, verbal and visual learning and memory, visual abilities and executive functioning. All cognitive measures were converted into *z* scores, based on the pooled PD group, and all composite cognitive domains maintained satisfactory internal consistency. Processing speed (Cronbach $\alpha = 0.86$) was quantified, based on the Trail Making Test–A and Salthouse Letter Comparison Test. For verbal fluency ($\alpha = 0.89$), semantic and phonetic fluency tests were used. For verbal learning and memory ($\alpha = 0.92$), learning and long-term recall performance on the Hopkins Verbal Learning Test (version 2) was utilized. For visual learning and memory ($\alpha = 0.97$), learning and long-term recall performance on the Brief Visual Memory Test (version 1) was used. For visual abilities, the Drawing Test (order and copy) and Visual Objects and Space Perception Battery (incomplete letters and cubes) were used ($\alpha = 0.76$). Executive functioning ($\alpha = 0.73$) was determined, based on the WAIS-III Indirect digits and the Stroop test, using the word color and interference scores.

**Table 1**
Sociodemographic, clinical and neurological characteristics of the study sample.

| | PD (n = 37) | HC (n = 16) | Statistics | *p* |
|---|---|---|---|---|
| Age (years) | 67.97 (6.18) | 65.13 (6.78) | $t = 1.45$ | 0.141 |
| Gender (male) | 22 (59.50%) | 12 (75.00%) | $\chi^2 = 1.17$ | 0.279 |
| Years of education | 10.24 (4.81) | 12.27 (4.30) | $t = -1.85$ | 0.069 |
| Fazekas Scale | 0.51 (0.69) | 0.67 (0.90) | $\chi^2 = 2.89$ | 0.235 |
| Fazekas 0 | 22 (59.46%) | 10 (62.50%) | | |
| Fazekas 1 | 11 (29.73%) | 2 (12.50%) | | |
| Fazekas 2 | 4 (10.81%) | 4 (25.00%) | | |
| UPDRS | | | | |
| Mental State | 1.86 (1.47) | – | – | – |
| Daily living activities | 10.28 (6.27) | – | – | – |
| Motor exam | 21.72 (10.29) | – | – | – |
| Treatment complications | 2.75 (2.88) | – | – | – |
| Total score | 36.61 (17.27) | – | – | – |
| LEDD | 808.59 (536.81) | – | – | – |
| Years of disease evolution | 6.96 (5.61) | – | – | – |
| Age of disease onset (years) | 61.01 (8.44) | – | – | – |
| Hoehn and Yahr Scale | 1.89 (.45) | – | – | – |
| Stage 1 | 5 | – | – | – |
| Stage 1.5 | 3 | – | – | – |
| Stage 2 | 26 | – | – | – |
| Stage 2.5 | 1 | – | – | – |
| Stage 3 | 2 | – | – | – |

Note: Values are expressed as the mean (Standard deviation), unless otherwise stated.
Abbreviations: PD = Parkinson's disease; HC = Healthy controls; UPDRS = Unified Parkinson Disease Rating Scale; LEDD = Levodopa Equivalent Daily Dose.