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Cerebral correlates of mild cognitive impairment and brain changes related to cognitive rehabilitation in Parkinson's disease

Doctoral thesis presented by María Díez Cirarda,

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PhD Student

María Díez Cirarda

Director

Dr. Naroa Ibarretxe Bilbao

Co-Director

Dr. Javier Peña Lasa

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Director

Dr. Naroa Ibarretxe Bilbao

Co-Director

Dr. Javier Peña Lasa

In Bilbao, January 2018

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la A a la derecha y la izquierda las demás.

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Sin financiación no hay ciencia,

Sin ciencia no hay futuro

Contents

Foreword

This thesis has been presented to obtain the degree of Doctor by the University of Deusto, and is the results of five studies carried out at the Research Group of Neuropsychology of Severe Mental Conditions, at the Department of Methods and Experimental Psychology, Faculty of Psychology and Education, University of Deusto. The following articles have been published in international journals, as a result of the work performed, with a **global impact factor (IF) of 23.563** (ISI Web of Science, Journal Citation Reports).

Paper I

Díez-Cirarda M, Ojeda N, Peña J, Cabrera-Zubizarreta A, Gómez-Beldarrain M, Gómez-Esteban J.C, Ibarretxe-Bilbao N. (2015) Neuroanatomical correlates of Theory of Mind deficit in Parkinson's disease: A multimodal imaging Study. *PloS ONE 10*(11), e0142234. DOI: 10.1371/journal.pone.0142234. [IF = 3.057, Q1 Multidisciplinary Sciences]

Paper II

Díez-Cirarda M, Strafella A.P, Kim J, Peña J, Ojeda N, Cabrera-Zubizarreta A, Ibarretxe-Bilbao N. (2018) Dynamic functional connectivity in Parkinson's disease patients with mild cognitive impairment and normal cognition. *Neuroimage: Clinical, 17*, 847-855. DOI: 10.1016/j.nicl.2017.12.013. [IF = 4.348, Q1 Neuroimaging]

Paper III

Peña J, Ibarretxe-Bilbao N, García-Gorostiaga I, Gomez-Beldarrain M.A, **Díez-Cirarda M,** Ojeda N. (2014) Improving functional disability and cognition in Parkinson disease Randomized controlled trial. *Neurology*, *83*(23), 2167-2174. DOI: 10.1212/WNL.0000000000001043. [IF = 8.185, Q1 Clinical Neurology]

Paper IV

Díez-Cirarda M, Ojeda N, Peña J, Cabrera-Zubizarreta A, Lucas-Jiménez O, Gómez-Esteban J.C, Gómez-Beldarrain M.A, Ibarretxe-Bilbao N. (2017) Increased brain connectivity and activation after cognitive rehabilitation in Parkinson's disease: a randomized controlled trial. *Brain Imaging and Behavior*, *11*(6), 1640-1651. DOI: 10.1007/s11682-016-9639-x. [IF = 3.985, Q2 Neuroimaging]

Paper V

Díez-Cirarda M, Ojeda N, Peña J, Cabrera-Zubizarreta A, Lucas-Jiménez O, Gómez-Esteban J.C, Gómez-Beldarrain M.A, Ibarretxe-Bilbao N. (2018) Long-term effects of cognitive rehabilitation in brain, functional outcome and cognition in Parkinson's disease. *European Journal of Neurology, 25*, 5-12. DOI: 10.1111/ene.13472. [IF = 3.988, Q1 Clinical Neurology]

Glossary of Abbreviations

AD= Axial Diffusivity

ANOVA= Analisis of Variance

ASPARBI= Asociación de Parkinson Bizkaia (Parkinson's disease Association from Bizkay)

BA= Brodmann Area

CG= Control Group

DTI= Diffusion Tensor Imaging

FA= Fractional Anisotropy

FC= Functional Connectivity

fMRI= Functional Magnetic Resonance Imaging

FSL= FMRIB Software Library

GDS= Geriatric Depression Scale

GM= Grey Matter

HC= Healthy Control

LARS= Lille Apathy Rating Scale

LEDD= Levodopa Equivalent Daily Dose

MCI= Mild Cognitive Impairment

MD= Mean Diffusivity

MMSE= Mini Mental State Examination

MRI= Magnetic Resonance Imaging

PD= Parkinson's Disease

PD-MCI= Parkinson's disease patients with Mild Cognitive Impairment

PD-NC= Parkinson's disease patients with Normal Cognition

RD= Radial Diffusivity

REHACOP= Cognitive Rehabilitation Program for Psychosis

rs-fMRI= Resting-state functional Magnetic Resonance Imaging

SPSS= Statistical Package for Social Sciences

TBSS= Tract-Based Spatial Statistics

TFCE= Threshold-free cluster enhancement

ToM= Theory of Mind

UPDRS= Unified Parkinson's disease Rating Scale

VBM= Voxel-Based Morphometry

WHO-DAS= World Health Organization Disability Assessment Schedule

WM= White Matter

I. Abstract

1. Abstract

Parkinson's disease (PD) patients experience cognitive impairment in a wide range of cognitive domains. The brain correlates of diverse cognitive functions have been analyzed in PD but to date no study has assessed the cerebral correlates of theory of mind (ToM) deficit in the disease. In addition, these cognitive deficits in PD have been related with reduced quality of life and functional disability, which progress until dementia occurs in PD. Therefore, research is needed to detect biomarkers of cognitive impairment in the disease. Furthermore, treatment strategies for cognitive decline are needed. However, little is known about the effects of cognitive rehabilitation on cognition, functional outcome and brain changes in PD patients. Additionally, to date, no study has evaluated the long-term effects of cognitive rehabilitation on brain changes in PD.

The present work is composed by five scientific contributions. Firstly, the *first study* aimed to investigate the neuroanatomical correlates of ToM deficit in PD patients. The *second study* assessed the dynamic functional connectivity (FC) and the local/global connectivity in PD patients with mild cognitive impairment (PD-MCI) and with normal cognition (PD-NC). The *third study* evaluated the effects of a cognitive rehabilitation program on cognition and clinical aspects in PD patients. The *fourth study* investigated the structural and functional brain changes related to a cognitive rehabilitation program in these PD patients, and finally, the *fifth study*, assessed the long-term effects of a cognitive rehabilitation on brain, cognition and functionality in PD.

Results revealed presence of ToM deficit in PD that was related to grey and white matter alterations in the prefrontal and parietal lobes. In addition, PD-MCI patients showed dynamic functional brain alterations that were not present in PD-NC. Moreover, PD patients showed increased cognition, decreased functional disability and increased brain functional connectivity and activation after attending a cognitive rehabilitation program. Finally, brain

activity, functionality and cognitive changes after cognitive rehabilitation were maintained after 18 months follow-up.

In conclusion, findings support the presence of ToM deficit in PD patients. In addition, dynamic FC could add relevant information about the neural substrates of MCI in PD. Moreover, cognitive rehabilitation has demonstrated its efficacy on improving cognition, functionality and brain activity in PD patients, and all these improvements may still be present after 18 months.

Keywords: Parkinson's disease, mild cognitive impairment, theory of mind, brain correlates, dynamic functional connectivity, cognitive rehabilitation, brain plasticity, neuroimaging, longitudinal, functional disability.

Resumen

Los pacientes con enfermedad de Parkinson (EP) presentan deterioro cognitivo en varios dominios cognitivos. Los correlatos cerebrales de algunas funciones cognitivas han sido analizados en la EP pero hasta la fecha no se han estudiado los correlatos cerebrales de la función cognitiva teoría de la mente (ToM, *de sus siglas en inglés*). Además, este deterioro cognitivo se han relacionado con una menor calidad de vida y discapacidad funcional, y evoluciona hasta la aparición de demencia en la enfermedad. Por lo tanto, es necesaria más investigación para detectar biomarcadores del deterioro cognitivo y evaluar estrategias para el tratamiento del mismo. Sin embargo hasta la fecha se han llevado a cabo pocos estudios que evalúen la eficacia de un programa integral de rehabilitación cognitiva analizando los cambios cognitivos, funcionales y cerebrales. Además, no se ha publicado ningún estudio que evalúe el efecto a largo plazo de la rehabilitación cognitiva a nivel cerebral en la EP.

El presente trabajo está compuesto por cinco contribuciones científicas. El *primer estudio* investigó los correlatos neuroanatómicos del déficit de ToM en pacientes con EP. El *segundo estudio* evaluó la conectividad funcional dinámica y la conectividad local/global en pacientes con EP con deterioro cognitivo leve y con cognición normal. El *tercer estudio* evaluó los efectos de un programa de rehabilitación cognitiva en la cognición y los aspectos clínicos en pacientes con EP. El *cuarto estudio* investigó los cambios cerebrales estructurales y funcionales relacionados con un programa de rehabilitación cognitiva en pacientes con EP, y finalmente, el *quinto estudio*, evaluó los efectos a largo plazo de esta rehabilitación cognitiva en la cognición, la funcionalidad y los cambios cerebrales en la EP.

Los resultados revelaron la presencia de déficit de ToM en pacientes con EP, y éste correlacionó con alteraciones de la sustancia gris y blanca en los lóbulos prefrontal y parietal. Además, los pacientes con deterioro cognitivo mostraron una conectividad funcional dinámica alterada que no estaba presente en pacientes con EP con cognición normal. Por otra parte,

después de asistir a un programa de rehabilitación cognitiva, los pacientes con EP mostraron un aumento del rendimiento cognitivo, reducción de la discapacidad funcional, así como una mayor conectividad funcional y activación cerebral. Por último, estos cambios a nivel cognitivo, funcional y cerebral se mantuvieron después de 18 meses de seguimiento.

En conclusión, los hallazgos apoyan la presencia del déficit de ToM en pacientes con EP. Además, el análisis de conectividad funcional dinámica podría añadir información relevante sobre los sustratos neuronales de deterioro cognitivo en la EP. La rehabilitación cognitiva ha demostrado ser eficaz en la mejora de la cognición, la funcionalidad y aumentar la actividad cerebral en pacientes con EP, y todas estas mejoras pueden seguir estando presentes después de 18 meses.

Palabras clave: Enfermedad de Parkinson, deterioro cognitivo leve, teoría de la mente, correlatos cerebrales, conectividad funcional dinámica, rehabilitación cognitiva, plasticidad cerebral, neuroimagen, discapacidad funcional, longitudinal.

II. Introduction

2. Introduction

2.1 Parkinson's disease

Parkinson's disease (PD) is the second most common neurodegenerative disease after Alzheimer's disease. Its incidence is directly related to age (Hirsch, Jette, Frolkis, Steeves, & Pringsheim, 2016), being most of the cases diagnosed at around 60 years (Hirsch et al., 2016). Most PD cases are idiopathic, but there is a small percentage of patients (3-5%) who have genetic factors (Klein & Westenberger, 2012). The causes of idiopathic PD are still unknown, but seem to be related to both genetic and environmental influences (Kalia & Lang, 2015). Exposure to pesticides and a head injury have been associated with an increased risk of developing PD, whereas exposure to both factors triples the risk of PD diagnosis (Lee, Bordelon, Bronstein, & Ritz, 2012).

The description of the disease made by James Parkinson in 1817 only reported the motor disturbances. The core motor symptoms that characterize the disease are rigidity, tremor, bradykinesia (akinesia) and postural instability. In addition, freezing of gait (difficulty to initiate or continue walking) and flexed posture have been included in the cardinal motor symptoms of the disease (Xia & Mao, 2012). Nowadays, it is known that this neurodegenerative process produces a wide range of motor and non-motor symptoms in PD patients, hence, PD is considered a multiple system neurodegenerative disorder (Tolosa, Gaig, Santamaria, & Compta, 2009).

2.2 Neuropathology of PD

When the onset of first motor symptoms occur, dopaminergic denervation is already present in the disease, occurring in 60% in neurons of the striatum and it is estimated that approximately 50–60% of dopaminergic neurons are already lost in the substantia nigra pars compacta (Ross et al., 2004).

PD motor symptoms start with the neurodegeneration of the nigro-striatal pathway. The loss of dopaminergic neurons in the substantia nigra produces a reduction in the activation of the thalamo-cortical activity which triggers PD symptomatology (Del Tredici, Rub, De Vos, Bohl, & Braak, 2002). Briefly, in healthy subjects, the dopaminergic neurons in the substantia nigra produce the activation (D1-receptors, direct pathway) or inhibition (D2 receptors- indirect pathway) of the striatum that excites or inhibits the globus pallidus, which connects with the thalamus. The direct pathway produces an excitatory effect, and the thalamus sends information to the cortex. The indirect pathway produces an inhibitory effect. The correct combination of the direct and indirect pathways makes the thalamus send adequate information to the cortex (Bravo, Rangel-Barajas, & Garduño, 2014). In PD patients, the loss of dopaminergic neurons in the substantia nigra, produces an absence of activation of the direct pathway, consequently the thalamo-cotical activity is reduced. This produces one of the most common motor symptoms in PD, the bradykinesia (Bravo et al., 2014) (see Figure 1).

Figure 1: Dopaminergic Direct and Indirect Pathways. Modified after (Bravo et al., 2014)

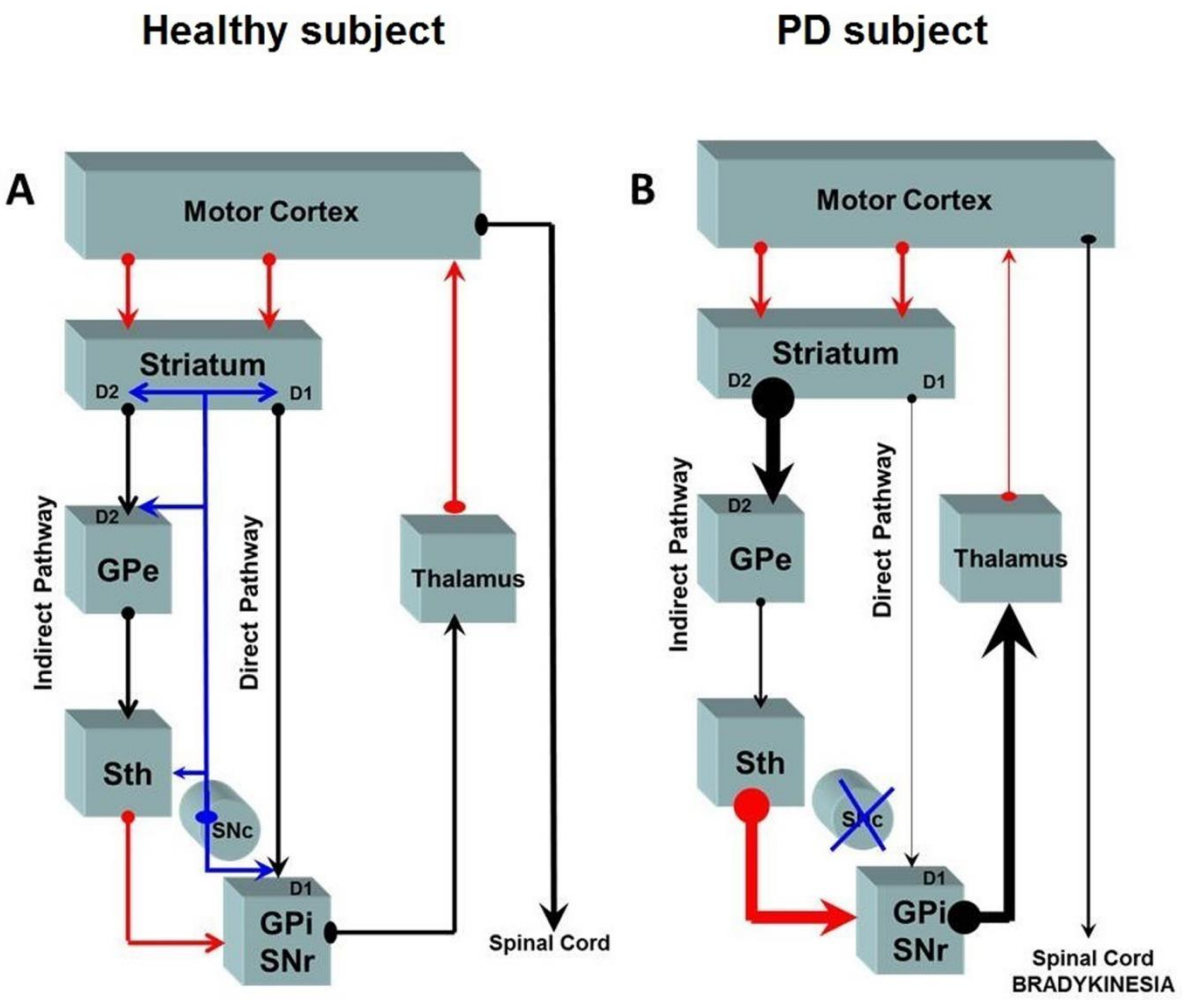


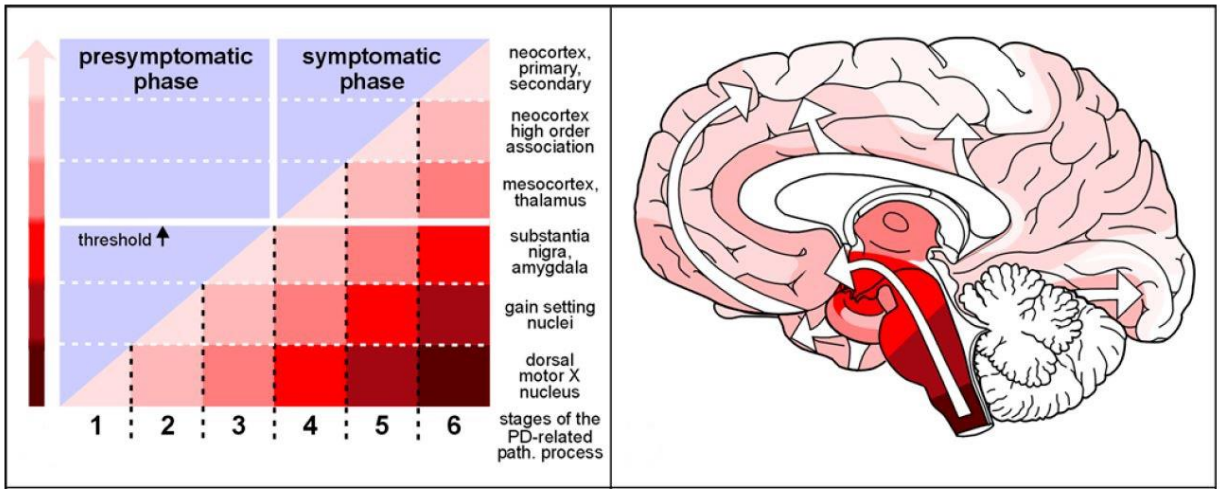
Figure 1 Legend: Dopaminergic pathways in healthy subjects A), and in PD subjects B). Blue arrows represent dopamine pathways; Red arrows represent excitatory pathways (GABA); Black arrows represent inhibitory pathways (glutamate). D1= dopamine receptor; D2= dopamine receptor; GPe= External globus pallidus; GPi= Internal globus pallidus; SNr=Substrancia nigra pars reticularis; SNc= Substrancia nigra pars compacta; Sth= Subthamalic nucleus.

However, other brain areas are also involved in the PD neurodegeneration process, starting even before the substantia nigra degeneration, such as the olfactory tract, the locus ceruleus, the reticular nuclei of the brainstem, the dorsal motor nucleus of the vagus, as well as the basal nucleus of Meynert, the amygdala and the hippocampus are also affected in PD (Del Tredici et al., 2002; Ferrer, 2009). All these areas present Lewy bodies, which main component is the alfa-synuclein, even before alterations of the substantia nigra (Del Tredici et al., 2002). In addition, similar protein aggregations known as Lewy neurites are usually localized in neural projections in the same brain areas (Ferrer, 2009).

In addition, metabolic deficits have also been identified as contributory factor in the pathogenesis of PD, including oxidative stress, abnormal gene regulation, aggregation and mitochondrial abnormalities (Ferrer, 2009).

The whole neuropathological process of PD was described by Braak and colleagues in 2003, and was divided into 6 stages (Braak, Rüb, Gai, & Del Tredici, 2003). *Stage 1* is characterized by early lesions in the olfactory bulb and the dorsal motor nucleus of the vagus nerve; *stage 2* begins when the lesions appear in the lower raphe nuclei, locus coeruleus and reticular nucleus; *stage 3* includes the degeneration of the amygdala and substantia nigra pars compacta; the first cortical lesions appear in *stage 4*, located at the anteromedial temporal cortex; *stage 5* is characterized by the atrophy of the secondary somatomotor areas and prefrontal cortex; finally, *stage 6* of the disease involves cortical degeneration of the whole brain, including the primary somatosensory areas and premotor areas. These stages have been divided into the "presymptomatic *phase*" (from *stage* 1 to *stage* 3) and the "symptomatic phase" (from *stage 4 to stage 6*) (Braak, Ghebremedhin, Rüb, Bratzke, & Del Tredici, 2004) (See Figure 2).

Figure 2. Progressive stages of PD symptomatology. Modified after (Braak et al., 2004)



2.3 Motor and non-motor symptoms

PD is considered a multiple system neurodegenerative disorder, characterized by parkinsonism but also non-motor symptoms (Tolosa et al., 2009). Indeed, some non-motor symptoms have been suggested to appear even before motor symptoms, such as olfactory loss, cognitive impairment, sleep disturbances, mood disorders, dysautonomia, excessive sweating and fatigue (Pont-Sunyer et al., 2015; Tolosa et al., 2009).

The first non-motor symptom to appear in PD is olfactory loss (Haehner et al., 2009), corresponding to *stage* 1 of the Braak staging scheme for PD (Braak et al., 2004). The prevalence of smell loss in PD ranges from 45% (Ansari & Johnson, 1975) to 90% (Doty, Deems, & Stellar, 1988). The high prevalence of this symptom makes it a good clinical biomarker for early diagnosis (Ross et al., 2008). Another common non-motor symptom in PD is sleep disorder, as approximately 30% of PD patients suffer from sleep problems (Hu et al., 2015). In addition, 25% of patients also suffer from hallucinations, which are usually related to antiparkinsonian treatments (Fenelon, Mahieux, Huon, & Ziegler, 2000). Presence of visual hallucinations has also been associated with a higher risk of developing dementia (Ibarretxe-Bilbao et al., 2010). Mood disorders could appear from 2 to 10 years before motor

symptoms (Pont-Sunyer et al., 2015), and the most common ones are apathy (Pagonabarraga, Kulisevsky, Strafella, & Krack, 2015) and depression (Aarsland, Påhlhagen, Ballard, Ehrt, & Svenningsson, 2012). Finally, dysautonomia is also common occurrence in PD. Symptoms of autonomic failure in patients with PD include constipation, urinary incontinence and heat or cold intolerance (Goldstein, 2003).

Cognitive impairment is an important non-motor symptom due to its prevalence among PD patients (20-50%) (Muslimovic, Post, Speelman, & Schmand, 2005; Yarnall et al., 2014), its relationship with quality of life and functional disability (Leroi, McDonald, Pantula, & Harbishettar, 2012) and its role in the progression to dementia (Hely, Reid, Adena, Halliday, & Morris, 2008; Hoogland et al., 2017). Cognitive deficits will be extensively discussed in the 2.6 section of the introduction.

2.4 Diagnosis

The diagnosis of PD is usually based on the UK PD Society Brain Bank clinical diagnostic criteria, which includes both inclusion and exclusion criteria (Hughes, Daniel, Kilford, & Lees, 1992). After the PD diagnosis, two tests are widely used to evaluate the evolution of the disease: The Unified PD Rating Scale (UPDRS) (Martinez-Martin et al., 1994) and the Hoehn and Yahr scale (Hoehn & Yahr, 1967). Both scales show a high correlation between them (Martinez-Martin et al., 1994). The UPDRS is composed of 42 items divided into four subscales: Mentation, Activities of Daily Living, Motor section and Treatment complications. The Motor section subscale of the UPDRS is the most widely used by researchers and clinicians. The Hoehn and Yahr scale measures motor dysfunction and was first divided into 5 stages (Hoehn & Yahr, 1967). Later, the modified Hoehn and Yahr scale included intermediate stages between them, describing a total of 7 stages (Goetz et al., 2004) (see Table 1).

Table 1. Equivalence between original and modified Hoehn and Yahr stages of the disease.

	Hoehn and Yahr Scale (5 stages)	**Modified Hoehn and Yahr Scale (7 stages)**
Stage 1	Unilateral involvement only usually with minimal or no functional disability	Unilateral involvement only
Stage 1.5		Unilateral and axial involvement
Stage 2	Bilateral or midline involvement without impairment of balance	Bilateral involvement without impairment of balance
Stage 2.5		Mild bilateral disease with recovery on pull test
Stage 3	Bilateral disease: mild to moderate disability with impaired postural reflexes; physically independent	Mild to moderate bilateral disease; some postural instability; physically independent
Stage 4	Severely disabling disease; still able to walk or stand unassisted	Severe disability; still able to walk or stand unassisted
Stage 5	Confinement to bed or wheelchair unless aided	Wheelchair bound or bedridden unless aided

2.5 Treatment

The standard treatment for motor symptoms in PD is pharmacological treatment (Connolly & Lang, 2014). The most common pharmacological treatment is Levodopa, a drug that supplies the loss of dopamine in the disease. It is a very effective treatment, but it loses its efficacy as the disease progresses. Dopamine agonists are another common pharmacological treatment in PD, usually used as the initial treatment for young PD patients. Other treatments against PD motor symptoms are inhibitors of monoamine oxidase B (MAO-B), catechol-O-methyltransferase (COMT) inhibitors, and anticholinergics (Connolly & Lang, 2014). When pharmacological treatments begin to lose efficacy, a surgical procedure is a common option that has been shown efficacy. The surgical intervention commonly used in PD is deep brain stimulation (Okun, 2012).

These treatments (pharmacological and surgical) have shown to be effective against motor symptomatology, however, cognitive impairment and other non-motor symptoms are

still present in the disease. Treatment strategies are needed to diminish these symptoms but to date, no pharmacological treatments have demonstrated efficacy on the reduction of cognitive dysfunctions (Petersen et al., 2014). On the contrary, non-pharmacological therapies, such as cognitive rehabilitation, have demonstrated some efficacy against cognitive decline (Petersen et al., 2014), hence the importance of the cognitive rehabilitation approach in PD treatment.

2.6 Cognitive impairment

Cognitive impairment is a common non-motor symptom in PD. The percentage of PD patients with cognitive impairment could range from 20% to 50% (Yarnall, Rochester, & Burn, 2013) and PD patients might develop cognitive impairment from the early stages of the disease (Muslimovic et al., 2005; Yarnall et al., 2014). These cognitive deficits deteriorate with the progression of the disease until dementia occurs in up to 80% of the patients after 20 years of follow-up (Hely et al., 2008; Hoogland et al., 2017).

Traditionally, cognitive deficits in PD have been related to a dysexecutive syndrome, due to the deterioration of the circuitry that connects the frontal cortex with subcortical structures (Litvan, Mohr, Williams, Gomez, & Chase, 1991). The incidence of cognitive deficits in PD in a newly diagnosed cohort was first presented in 2004, in a study that showed that 36% of PD patients experienced cognitive impairment classified as fronto-striatal impairment, temporal impairment or global deterioration (Foltynie, Brayne, Robbins, & Barker, 2004). Another study with newly diagnosed PD patients indicated that cognitive impairment was present in diverse cognitive domains, such as attention, language, executive functions, visuospatial ability and memory, although performance in most of the domains was determined by memory and executive functions (Muslimovic et al., 2005). A later study identified a twofold increase in mild cognitive impairment (MCI) in PD patients compared to healthy controls (HC), which affected a wide range of cognitive domains, while the largest

effect size was noted for verbal memory (Aarsland et al., 2009). Interestingly, memory deficits in PD have been traditionally related to impairment in the retrieval process, but learning is also altered in the disease (Chiaravalloti et al., 2014). Furthermore, cognitive deficits related to alterations in posterior brain areas, such as visuospatial or semantic fluency, have been found to play a relevant role in the dementing process in PD (Williams-Gray, Foltynie, Brayne, Robbins, & Barker, 2007).

Other complex cognitive functions have also been found to be impaired in PD. Decision-making ability, defined as the ability to modify choice behavior depending on reward contingencies (short or long-delay), has been widely examined in PD patients using the Iowa Gambling task. Studies using the Iowa Gambling task showed a dysfunctional decision-making pattern in PD patients compared to HC (Poletti, Cavedini, & Bonuccelli, 2011). Another cognitive functions that has been found impaired in PD is the recognition of emotions in facial expressions which may occur at the early stages of the disease (Ibarretxe-Bilbao et al., 2009).

2.6.1 Social cognition

Most studies that assessed cognitive impairment in PD were focused on attention, memory, executive functions or verbal fluency. However, little is known about social cognitive impairment in PD. Studies suggest that PD patients also suffer from deficits in social cognitive abilities, including theory of mind (ToM) deficit (Bodden et al., 2010; Kawamura & Koyama, 2007; Monetta, Grindrod, & Pell, 2009; Santangelo et al., 2012). In addition, ToM has been found to be impaired from the early stages of the disease (Kawamura & Koyama, 2007; Santangelo et al., 2012). ToM was first described as the ability to make inferences about others' mental states for the first time by Premark and Woodruff (Premack & Woodruff, 1978). More recently, ToM has been characterized as the ability to understand and

predict another's beliefs, intentions, emotions, behavior and knowledge (Bodden et al., 2010; Santangelo et al., 2012). Interestingly, ToM deficit has been demonstrated to have an impact in patients' quality of life (Bodden et al., 2010; Santangelo et al., 2012). ToM has been related with other cognitive functions such as executive functions and working memory and the correct performance in these two cognitive domains enhance the ToM performance (Costa et al., 2013; Monetta et al., 2009). However, contradicting results have also been reported, suggesting the need to further explore this relationship (Bodden, Dodel, & Kalbe, 2010; Yu & Wu, 2013).

Regarding the neuroanatomical correlates of ToM, previous studies suggested a relationship with the mirror-neuron system, whose core regions are located in the rostral part of the inferior parietal lobe, the precentral gyrus and the inferior frontal gyrus (Rizzolatti & Craighero, 2004). Magnetic Resonance imaging (MRI) studies have described a core network for ToM that includes the medial prefrontal cortex, bilateral posterior temporo-parietal junction (Carrington & Bailey, 2009; Schurz, Radua, Aichhorn, Richlan, & Perner, 2014) and the superior temporal sulcus (Carrington & Bailey, 2009). Other regions, such as the precuneus and the anterior cingulate cortex, are also associated with ToM performance (Carrington & Bailey, 2009). These findings are supported by previous studies in schizophrenia (Schurz et al., 2014) and healthy adults (Carrington & Bailey, 2009; Rizzolatti & Craighero, 2004; Schurz et al., 2014). These anatomical areas related to ToM are known to be progressively impaired in PD (Poletti, Enrici, Bonuccelli, & Adenzato, 2011; Poletti, Enrici, & Adenzato, 2012). However, to date, there are no studies in PD assessing the neuroanatomical correlates of ToM deficit using MRI, which is one of the objectives of the present thesis.

2.6.2 MCI classification

Due to the importance and to the high prevalence of cognitive deficits in PD, a classification of MCI has been proposed by the Movement Disorders Society, with specific guidelines for MCI diagnosis in PD (PD-MCI) (Litvan et al., 2012). The diagnosis of PD-MCI has been described as a stage between normal cognition and dementia, characterized by the presence of cognitive deficits not normal for a given age (Goldman & Litvan, 2011). The classification for PD-MCI could be performed with two types of cognitive assessments (Litvan et al., 2012). The first type of assessment, also called by the authors "level I", is based on an abbreviated assessment or a global cognitive scale such as the Montreal Cognitive Assessment. The "level II" type of assessment represents a comprehensive assessment and should include two tests per cognitive domain and evaluate the five cognitive domains: attention and working memory, executive functions, language, memory and visuospatial ability. The PD-MCI classification differentiates between single-domain MCI, which is diagnosed when only one cognitive domain is impaired, and multiple-domain MCI, when two or more cognitive domains are impaired (Litvan et al., 2012). This subtype classification could help clinicians to adjust and adequate treatments for PD patients (Geurtsen et al., 2014; Litvan et al., 2012).

The presence of cognitive impairment in PD patients has been associated with an increased age at disease onset, longer disease duration and severity of motor symptoms (Aarsland et al., 2010). Moreover, cognitive impairment has been shown to be related to reduced quality of life and functional disability in PD (Leroi et al., 2012; Rosenthal et al., 2010). Additionally, a relationship has been suggested between clinical symptoms and cognitive deficits in PD patients. For example, the presence of cognitive deficits in the disease has been associated with depressive symptoms (Gustafsson, Nordstrom, & Nordstrom, 2015). In addition, the apathetic symptomatology is a common symptom in PD (Pagonabarraga et al.,

2015) that has been linked to the development of cognitive deficits and the evolution to dementia in PD (Dujardin, Sockeel, Delliaux, Destée, & Defebvre, 2009).

2.6.3 Progression of cognitive impairment

These cognitive deficits present in patients with PD deteriorate with the progression of the disease, until dementia occurs after 10 to 20 years (Hely et al., 2008; Williams-Gray et al., 2013). A study followed newly diagnosed PD patients over time, and found that after 20 years, dementia was present in up to 80% of PD (Hely et al., 2008). In addition, recent studies showed that the presence of MCI diagnosis in PD patients, contributes to the development of dementia (Hoogland et al., 2017), and results support that MCI could be considered as a prodromal stage for dementia in PD (Johnson, Langford, Garnier-Villarreal, Morris, & Galvin, 2016). The incidence of dementia in PD has been found to be six times higher than the incidence in healthy people (Emre, 2003). With the progression of the disease, cognitive deterioration is accompanied by grey matter (GM) volume loss (Ramírez–Ruiz et al., 2005), white matter (WM) alterations (Zhang, Wu, Tosun, Foster, & Schuff, 2016) and functional brain changes (Huang et al., 2007; Segura et al., 2013). When dementia occurs in PD patients, cortical degeneration has been extended to frontal, temporal, parietal and occipital areas (Mak, Su, Williams, & O'Brien, 2015).

2.7 Cerebral correlates of cognitive impairment

Magnetic resonance imaging (MRI) studies have demonstrated structural (Duncan et al., 2016; Ibarretxe-Bilbao, Junque, Marti, & Tolosa, 2011) and functional (Cabeza & Nyberg, 2000; Christopher & Strafella, 2013) cerebral correlates of the impairment of different cognitive domains in PD.

Cognitive impairment in PD has been related to GM atrophy (Duncan et al., 2016; Melzer et al., 2012) in the frontal, temporal and parietal cortex, but also in the hippocampus, amygdala and putamen (Duncan et al., 2016; Melzer et al., 2012). Specifically, executive dysfunction have been correlated with frontal deterioration, differentiating between the anterior cingulate cortex, which controls the initiative and inhibition; the orbitofrontal cortex, which has been related to decision-making; and the dorsolateral prefrontal cortex, which has been associated with problem solving (Hanna-Pladdy, 2007). The brain correlates of decision-making measured with the Iowa Gambling task have also been analyzed, and results have shown a strong correlation with the lateral orbitofrontal cortex in PD (Ibarretxe-Bilbao et al., 2009; Kobayakawa, Tsuruya, & Kawamura, 2017). In addition, memory impairment in PD patients has been associated with a deterioration of the hippocampus (Bouchard et al., 2008; Bruck, Kurki, Kaasinen, Vahlberg, & Rinne, 2004; Carlesimo et al., 2012; Ibarretxe-Bilbao et al., 2008) and amygdala (Junqué et al., 2005). Semantic fluency has been related to frontal, temporal and cerebellar brain areas in PD (Pereira et al., 2009b). Visuospatial ability has been correlated mostly with the parietal and occipital lobes in patients with PD, and visuoperceptive ability has shown correlates with occipital, frontal and subcortical areas in PD patients (Pereira et al., 2009a).

PD patients with MCI have shown widespread cerebral WM deterioration (Duncan et al., 2016; Matsui et al., 2007; Zheng et al., 2013). Executive dysfunctions in PD have been related to atrophy in the anterior WM tracts (Melzer et al., 2013), as well as in tracts located in the parietal lobe (Matsui et al., 2007). Memory impairment in PD patients has been related to anterior WM deterioration (Melzer et al., 2013). Also, attention and working memory have been associated with the anterior and posterior tracts (Melzer et al., 2013).

In addition, resting-state functional MRI (rs-fMRI) is a non-invasive method that shows reliability and high reproducibility to easily explore the functional activity of the

different brain networks (Biswal et al., 2010; Van Den Heuvel, Martijn P & Pol, 2010). To date, most rs-fMRI studies in PD have investigated functional connectivity (FC) patterns as a static phenomenon. Functional MRI (fMRI) studies have demonstrated that cognitive impairment in PD is related to functional brain deterioration, during resting-state and during cognitive tasks inside the scanner (Christopher & Strafella, 2013; Olde Dubbelink et al., 2014). During resting-state, PD patients with MCI usually showed reduced functional connectivity compared with PD patients without MCI and HC (Amboni et al., 2015; Gorges et al., 2015). Most of the connectivity alterations were found within the default-mode network (Gorges et al., 2015), within the frontoparietal network (Amboni et al., 2015) and within the dorsal attention network, but inter-network alterations were also identified between default-mode network and dorsal attention network and between the dorsal attention network and frontoparietal network (Baggio et al., 2015).

Moreover, PD patients showed brain activation dysfunctions during cognitive fMRI tasks inside the scanner. For example, during a Wisconsin card sorting task that measures planning, execution and cognitive flexibility, PD patients showed less deactivation in different areas of the default-mode network, and even reversed patterns of activation and deactivation compared to HC (van Eimeren, Monchi, Ballanger, & Strafella, 2009). PD patients also showed decreased brain activation in frontal and occipital areas and decreased deactivation in the default-mode network during a recognition memory fMRI task (Ibarretxe-Bilbao et al., 2011). Moreover, another study evaluated the brain activity during a verbal two-back working memory task and found reduced activation in bilateral striatal and frontal regions in PD patients (Ekman et al., 2012). Additionally in the same study, PD with MCI also showed reduced activation in the right dorsal caudate nucleus and the bilateral anterior cingulate cortex compared with PD patients without MCI (Ekman et al., 2012). Furthermore, another study assessed the brain activity during an emotional processing task in PD patients

and found increased brain activation in the medial prefrontal lobe that could compensate the reduced activation in the striatal area compared to HC (Moonen et al., 2017).

More recently, rs-fMRI studies have shown that FC may actually vary during the acquisition time (i.e. dynamic FC) (Allen et al., 2014; Calhoun, Miller, Pearlson, & Adalı, 2014; Hutchison et al., 2013). A widely applied method for temporal dynamic FC analysis is the sliding time window method (Allen et al., 2014; Damaraju et al., 2014; Du et al., 2016; Hutchison et al., 2013). This method divides acquired rs-fMRI into windows and calculates the variation of FC across those windows. The results represent the dynamic characteristic of FC. Given that static FC has helped to understand the cerebral correlates of cognitive impairment in PD, a dynamic FC approach may add relevant information as it represents more accurately the dynamic nature of the brain (Calhoun et al., 2014; Cohen, 2017; Hutchison et al., 2013), and has helped clarifying brain activity patterns and relationships with key symptoms in psychiatric disorders (Damaraju et al., 2014; Du et al., 2016; Rashid et al., 2016). Therefore, a dynamic approach to study FC may help clarify the neurobiological substrates of presence of MCI in PD. To date, only one dynamic FC study has been recently published in PD, and showed dynamic FC alterations in PD patients compared to HC (Kim et al., 2017).

2.8 Cognitive rehabilitation

Due to the importance of cognitive deterioration in the progression of PD, intervention strategies are needed to treat cognitive decline. Among treatments against cognitive impairment, cognitive rehabilitation has proven to be the most effective in improving cognition (Petersen et al., 2014). Cognitive rehabilitation can be defined as a behavioral treatment for cognitive impairment based on the restoration, compensation and optimization

of the cognitive functions that targets cognitive skills, but also daily functioning (Bahar-Fuchs, Clare, & Woods, 2013; Wykes & Spaulding, 2011).

2.8.1 Cognitive and functional changes after cognitive rehabilitation

The efficacy of cognitive rehabilitation programs on improving cognition has been demonstrated in PD through several randomized controlled studies (Cerasa et al., 2014; Edwards et al., 2013; París et al., 2011; Petrelli et al., 2014; Sammer, Reuter, Hullmann, Kaps, & Vaitl, 2006; Zimmermann et al., 2014). However, these cognitive rehabilitation studies in PD patients differ in: 1) the number of cognitive domains trained; 2) the duration of the rehabilitation (from 4 weeks to 13 weeks); 3) the frequency of the sessions (1-3 sessions per week); 4) the duration of the sessions (30-90 minutes per session); 5) the format (Group-based or individual); and 6) the modality (paper/pencil or computer-based exercises) (Hindle, Petrelli, Clare, & Kalbe, 2013; Leung, 2015).

Table 2 shows a summary of cognitive rehabilitation studies that meet the following criteria: 1) They were randomized controlled trials; 2) The experimental group attended a cognitive rehabilitation program; and 3) The experimental group attended only the cognitive rehabilitation program and not a combination of therapies (e.g. cognitive training + motor training).

Table 2: Summary of the randomized controlled trials assessing the efficacy of cognitive rehabilitation programs in PD Retrieved from (Díez-Cirarda, Ibarretxe-Bilbao, Peña, & Ojeda, in press)

Authors	Sample	H&Y	Cognitive rehabilitation program				Results*
			Duration	Paper-Pencil (P) Computerized (C)	Cognitive domains trained	Format (Group/Home)	
Sammer et al. (2006)	**26 PD** 12 CR 14 CG	2-3	10sessions 30min/session	P	• Working memory • EF	Group	**Improvements** • EF
París et al. (2011)	**28 PD** 16 CR 12 ACG	1-3	4 weeks 3 times/week 45min/session	P + C "SmartBrain Tool"	• Attention • Working memory • Memory • Psychomotor speed • EF • Visuospatial ability • Language • Calculation skills • Culture	Group + Home	**Improvements** • Attention • Information processing speed • Visual memory • Visuospatial ability • Visuoconstructive ability • Semantic Fluency • EF
Edwards et al. (2013)	**73 PD** 32 CR 42 CG	1-3	3 months 3 times/week 1h/session	C "InSight Software"	• Information processing speed	Home	**Improvements** • Cognitive speed of processing
Cerasa et al. (2014)	**15 PD** 8 CR 7 ACG	1-3	6 weeks 2 times/week 1h/session	C "RehaCom"	• Attention • Information processing	Group	**Improvements** • Attention • Processing speed • Short-term working memory
Zimmermann et al. (2014)	**39 PD** 19 CR 20 ACG	2[a]	4 weeks 3 times/week	C "CogniPlus"	• Attention • Working memory • EF	Group	• ACG improved Attention compared to CR.
Petrelli et al. (2014)	**43 PD** CR-structured CR-unstructured CG	1-3	6 weeks 2 times/week 90min/session	P "NEUROvitalis"	• Attention • Memory • EF	Group	**Improvements** • Working memory • Short-term memory

CR=cognitive rehabilitation; CG= control group; ACG= Active control group; EF= Executive functions; H&Y=Hoehn and Yahr.
*Results are reported only for repeated measures ANOVA (group x time) interaction effect. [a] Median

Traditionally, the main target of cognitive treatments has usually been cognitive improvement; however, a promising finding in PD is that cognitive rehabilitation programs not only improve cognitive functions but also could have an impact on functional outcome (Walton, Naismith, Lampit, Mowszowski, & Lewis, 2017). That is, benefits from cognitive treatments can be transferred to other variables that have not been trained directly during the cognitive program. Depressive symptomatology is one of the clinical symptoms that has been usually evaluated in the studies focused on the efficacy of cognitive programs in PD, but despite some significant changes, the overall results point to an absence of efficacy in reducing depression symptomatology after treatment (Leung, 2015). However, the absence of significant results could be related to the exclusion of patients with depression diagnosis or with severe symptoms of depression prior to participation.

PD patients usually present functional disability, which is usually related to cognitive decline in PD (Leroi et al., 2012; Rosenthal et al., 2010). Functional disability is defined by the World Health Organization as a limitation that lasts in time and causes a disability in activity, always produced by a disease. To date, no study found improvement in daily living activities or functional disability after a cognitive rehabilitation program. One randomized controlled trial included the Parkinson's disease Questionnaire (PDQ-39) to assess the change in the quality of life of the PD patients that attended the cognitive rehabilitation program, but no significant changes were found (París et al., 2011). These authors attributed the absence of change in quality of life to the short duration of the treatment (1 month) (París et al., 2011).

Further research needs to be done towards the understanding of the cognitive improvements and the transfer effects to functional and clinical aspects after cognitive treatment in PD.

2.8.2 Brain changes after cognitive rehabilitation

Little is known about the neurobiological effects of cognitive rehabilitation programs on PD. To date, literature is scarce about the presence of cerebral changes associated with cognitive treatments assessed with structural and functional MRI techniques in PD (Cerasa et al., 2014; Nombela et al., 2011).

The first study in PD that assessed brain changes after training did not apply a traditional cognitive rehabilitation program, but PD patients trained individually with Sudoku exercises at home for 6 months (Nombela et al., 2011). Before and after training, PD patients performed a modified Stroop Task during the fMRI acquisition (Nombela et al., 2011). After the intervention, PD patients showed increased performance in the Stroop test that was accompanied by reduced brain activation during the Stroop task inside the scanner, compared with the PD patients who did not receive treatment. This reduced activation in PD patients at post-treatment was similar to the brain activation pattern of HC. Hence, the authors concluded that an over-activation was present in PD patients before treatment, which was reduced after Sudoku training (Nombela et al., 2011).

A second study assessed functional brain changes during a resting-state fMRI acquisition after an attention rehabilitation program in PD patients (Cerasa et al., 2014). The attention rehabilitation was group-based and consisted in computer-assisted tasks that trained attention and information processing during 6 weeks. This study found improvements in attention and processing speed tasks and increased brain activation in the left dorsolateral prefrontal cortex and the superior parietal cortex in PD patients after 6 weeks (Cerasa et al., 2014). Both brain areas have been associated with attention, executive functioning and working memory (Duncan et al., 2016; Hanna-Pladdy, 2007).

These studies are focused on one cognitive domain and only used one neuroimaging approach to study cerebral changes after rehabilitation. Further studies are needed to replicate and complement these findings.

2.8.3 Long-term effects of cognitive rehabilitation

Furthermore, the ultimate goal of cognitive treatments is to ensure that benefits are maintained over long periods of time, but little is known about the maintenance of cognitive improvements over time in PD patients (Walton et al., 2017). One study in PD showed the persistence of some cognitive improvements over 6 months after cognitive training (Sinforiani, Banchieri, Zucchella, Pacchetti, & Sandrini, 2004). On the contrary, another study in PD found that only cognitive training combined with transfer training and physical activity maintained cognitive improvements after 6 months' follow-up (Reuter, Mehnert, Sammer, Oechsner, & Engelhardt, 2012). A later study in PD assessed the long-term effects of cognitive rehabilitation for a longer period of time and found that cognitive improvements persisted after 12 months, concluding that cognitive treatment could prevent cognitive decline (Petrelli et al., 2015). Regarding the maintenance of neuroimaging changes, to date, no studies have been published assessing the longitudinal effects of cognitive rehabilitation. Literature is scarce about the longitudinal effects of cognitive rehabilitation in PD and more research needs to be done (Walton et al., 2017).

III. Approach to the present study and objectives

3. Approach to the present study and objectives

The present thesis consists of five studies examining the brain correlates of cognitive impairment in Parkinson's disease patients and evaluating the cognitive, functional and cerebral changes related to a cognitive rehabilitation program.

Paper I

"Neuroanatomical correlates of Theory of Mind deficit in Parkinson's disease: A multimodal imaging Study"

Background

PD patients show cognitive deficits in a wide range of cognitive domains. However, ToM deficit has been less studied in this pathology, and to date, no study has assessed the brain correlates of ToM deficit in PD.

Objectives

- The main objective was to assess GM and WM correlates of ToM deficit in PD.
- The second objective was to explore the relationship between ToM, working memory and executive functions, and to analyse the cerebral correlates of ToM, after controlling for these two cognitive functions.

Hypotheses

- ToM deficit in PD would correlate with GM volume and WM in the medial prefrontal cortex, temporo-parietal junction and superior temporal sulcus.
- ToM performance in PD patients would correlate with executive functions and working memory.
- The influence of executive functions and working memory on ToM would be reflected in the medial prefrontal cortex, reducing the association between the frontal areas and ToM.

Paper II

"Dynamic functional connectivity in Parkinson's disease patients with mild cognitive impairment and normal cognition"

Background

Previous static FC studies have helped to understand the cerebral correlates of cognitive impairment in PD. Recent studies have suggested that FC may actually vary during the acquisition time (i.e. dynamic FC), therefore, a dynamic FC approach may add relevant information as it represents more accurately the dynamic nature of the brain. To date, no study has been published assessing the dynamic FC characteristics in PD-MCI and PD-NC patients.

Objective

- The objective was to assess the dynamic FC and local/global connectivity in PD-MCI and PD-NC using the combination of dynamic FC and graph-theoretical approaches during rs-fMRI.

Hypotheses

- Based on previous FC studies in PD-MCI and the previous dynamic FC study in PD, PD-MCI patients from the present study will show dynamic FC alterations.
- Based on previous graph theoretical results in PD-MCI patients, PD-MCI patients from the present study will show graph parameter alterations compared to HC.

Paper III

"Improving functional disability and cognition in Parkinson disease: Randomized controlled trial"

Background

Some studies in PD have demonstrated efficacy on improving cognitive functions. However, research in this area is very limited, and to date, no cognitive rehabilitation study included social cognition in the rehabilitation program, and no study found transfer effects to functional or clinical symptoms in PD.

Objectives

- The main objective was to evaluate the efficacy of cognitive rehabilitation with the REHACOP program in patients with PD on improving processing speed, visual learning and memory, verbal learning and memory, executive functioning, and ToM.
- The secondary objective was to analyze whether this program would improve clinical symptoms and functional disability.

Hypothesis

- PD patients after attending cognitive rehabilitation would show increased cognitive performance compared to the control group.

Paper IV

"Increased brain connectivity and activation after cognitive rehabilitation in Parkinson's disease: a randomized controlled trial"

Background

Brain changes after cognitive rehabilitation have been demonstrated in other pathologies. However, to date, few studies have sought to elucidate cerebral changes associated with cognitive rehabilitation in PD.

Objectives

- The objective of the present study was to assess the structural and functional cerebral changes associated to cognitive rehabilitation in the same cohort of PD patients.
- Due to the relevance of memory deficits in PD, a memory fMRI paradigm was included in this study to assess whether a cognitive rehabilitation program could produce changes in brain activation during learning and recognition memory tasks.

Hypothesis

- PD patients would show functional but not structural cerebral changes after attending REHACOP program compared with the control group (CG).

Paper V

"Long-term effects of cognitive rehabilitation in brain, functional outcome and cognition in Parkinson's disease"

Background

Little is known about the maintenance of the cognitive improvements in PD patients over time. To the best of our knowledge, no cognitive rehabilitation studies in PD have been published using >12 months follow-up period. Moreover, to date no study has assessed the long-term effects of cognitive rehabilitation in PD using neuroimaging techniques.

Objectives

- This study aimed to investigate the longitudinal effects of a cognitive rehabilitation program evaluating the cognitive, behavioral and neuroimaging changes after an 18-month follow-up period.

Hypothesis

- PD patients at long-term follow-up would show maintenance of cognitive changes, but these cognitive improvements would be reduced compared to post-treatment.

IV. Methods

4. Methods

4.1. Study sample

PD patients were recruited from the Department of Neurology at the Hospital of Galdakao and from the PD Biscay Association (ASPARBI). HC were also recruited, matched by age-gender-education with PD patients. PD patients were enrolled in the study, if:

Inclusion Criteria:

- They fulfilled the UK PD Society Brain Bank diagnostic criteria.
- Age between 45-75.
- Hoehn and Yahr disease stage $\leq$ 3 (Hoehn & Yahr, 1967).
- Unified PD Rating Scale (UPDRS) evaluated by the neurologist (Martinez-Martin et al., 1994).

Exclusion criteria:

- The presence of dementia as defined by the DSM-IV-R (American Psychiatric Association, 2003) and the Movement Disorders Society clinical criteria for PD-dementia.
- Scores on the Mini-Mental State Examination (MMSE) < 24 (Lobo et al., 2001).
- The presence of other neurological illness/injury (traumatic brain injury).
- Unstable psychiatric disorders (e.g. schizophrenia).
- Visual hallucinations as assessed by the Neuropsychiatric Inventory Questionnaire (Kaufer et al., 2000).
- Patients with depression evaluated with the Geriatric Depression Scale (score of >5) (Yesavage & Sheikh, 1986).

- Other conditions incompatible with optimal pre-processing of MRI data and whole-group analysis such as cerebral haemorrhage, traumatic brain injury, dilated ventricles.

4.2 Procedure

PD and HC underwent a neuropsychological assessment and MRI acquisition at baseline. After first evaluation, PD patients were randomly divided into REHACOP group and CG. After three months attending cognitive rehabilitation or occupational therapy, both groups attended a second assessment. After 18 months from post-treatment, the REHACOP group attended a third assessment (Figure 3). This randomized controlled trial was registered in clinicaltrials.gov with number: NCT02118480.

Figure 3: Project Design

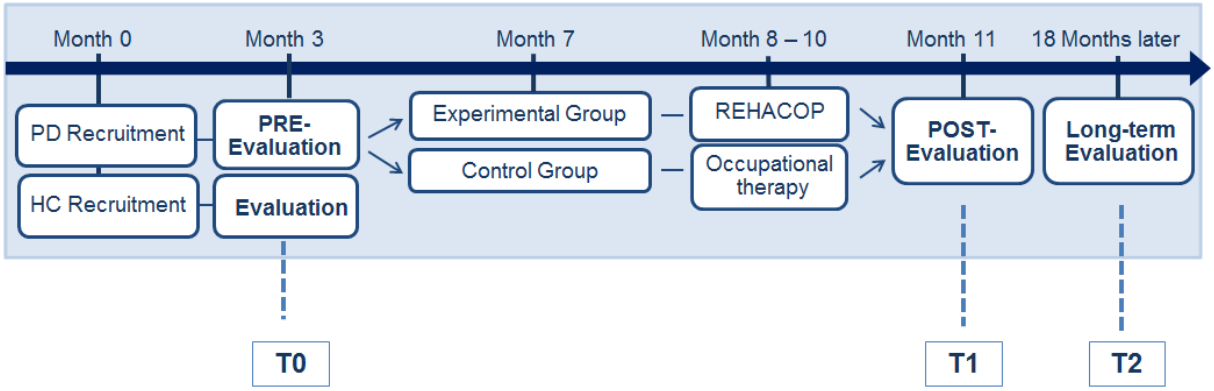


Figure 3 Legend: PD= Parkinson's disease; HC=Healthy Controls; REHACOP= Cognitive Rehabilitation Program.

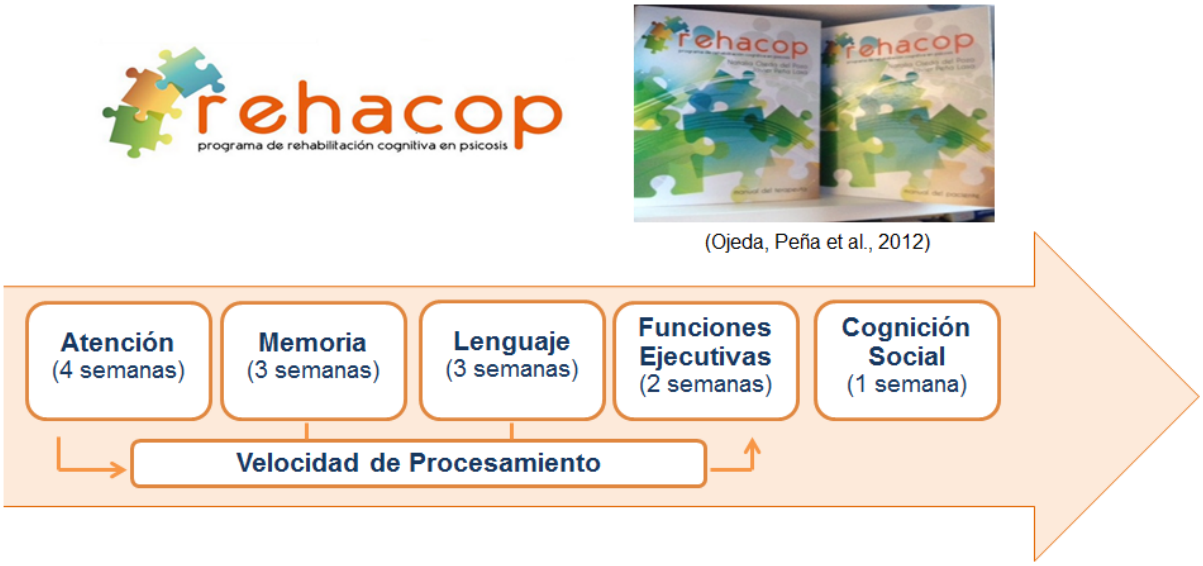
4.3 REHACOP: Integrative cognitive rehabilitation program

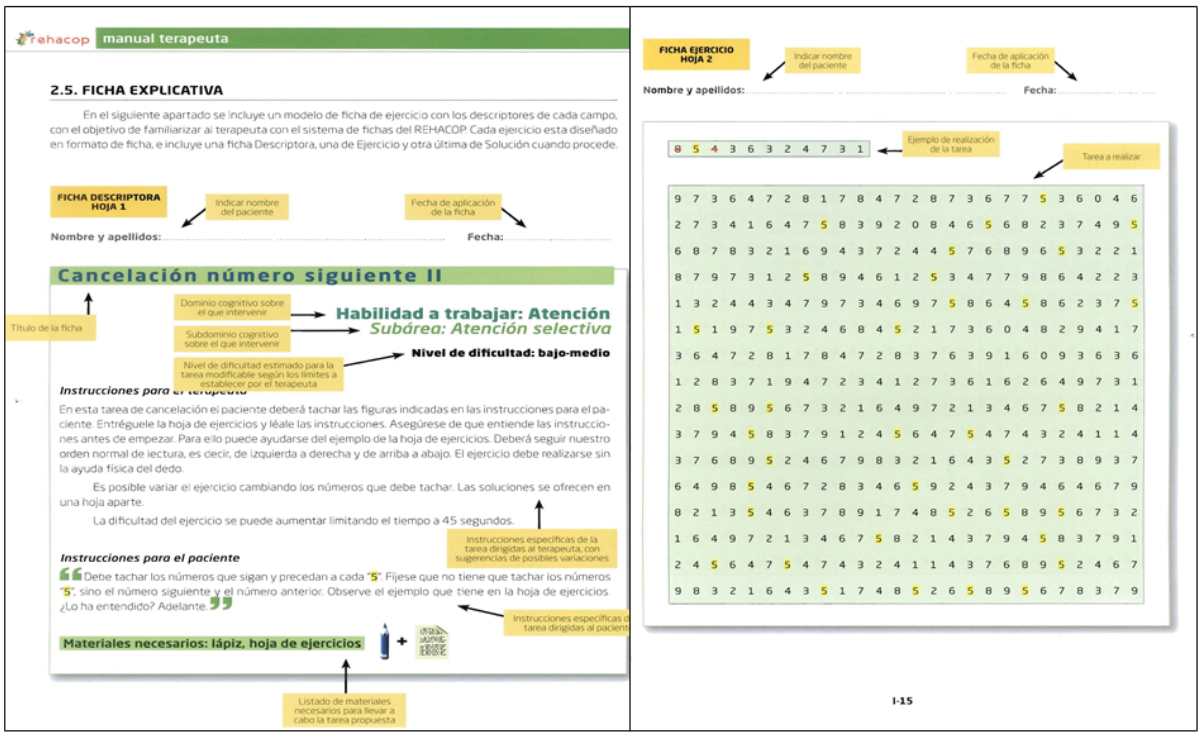
The cognitive rehabilitation program used in the present thesis is the REHACOP (www.rehacop.deusto.es). REHACOP is a structured program using paper-pencil tasks (based on restoration, compensation, and optimization strategies of rehabilitation) with a gradual level of cognitive effort and demand. REHACOP was initially designed for patients with psychosis and obtained successful results (Ojeda et al., 2012). Psychotic and neurodegenerative disorders share a common pattern of cognitive deficits, such as deficits in memory, executive functions, or processing speed; therefore, the REHACOP was used in the present project. REHACOP trains different cognitive domains, such as attention, memory, processing speed, language, executive functioning, and social cognition. Several tasks are timed, so processing speed is trained throughout various modules. The program format allows for either individual or group sessions (between 5 and 8 patients per group), although for the purpose of this study, group sessions were chosen.

In this study, PD patients attended 60-minute-long sessions 3 days per week, 1 hour per day. Specifically, PD patients trained the following cognitive domains: attention unit (4 weeks) and trained sustained, selective, alternant, and divided attention; memory unit (3 weeks) focused on visual and verbal learning, recall, and recognizing memory; language unit (3 weeks) and trained syntax, vocabulary, verbal fluency, verbal comprehension, and abstract language; executive functions unit (2 weeks) that trained cognitive planning, proverbs, and analogies; and social cognition unit (1 week) focused on ToM, social reasoning, and moral dilemmas (Figure 5).

The control group attended occupational activities. The activities included drawing, reading the daily news, and constructing using different materials (such as paper or wood). These activities were accomplished in a group format and with the same duration and frequency as the implementation of REHACOP in the experimental group.

Figure 4: Cognitive rehabilitation program (REHACOP) applied in PD





4.4 Clinical and neuropsychological assessment

All studies included a clinical and neuropsychological assessment to establish the sociodemographic, clinical and cognitive characteristics of the sample. PD patients underwent the same cognitive battery at the T_0, T_1 and T_2. To avoid learning effects, different versions of the memory tests were used at T_0 (form 2 of HVLT and form 1 of BVMT), T_1 (form 4 of HVLT and form 3 of BVMT) and at T_2 (form 3 of HVLT and form 5 of BVMT).

- The clinical assessment included:

PD Rating scale	Unified PD Rating Scale (UPDRS)	(Martinez-Martin et al., 1994)
	Hoehn and Yahr Scale (H&Y)	(Hoehn & Yahr, 1967)
Medication	Levodopa Equivalent Daily Dose (LEDD)	(Tomlinson et al., 2010)

- The cognitive assessment included:

Premorbid Intelligence	National Adult Reading Test	(Moltó, Igual, & Pastor, 1997)
Cognitive Reserve	Cognitive Reserve Questionnaire	(Rami et al., 2011)
Global Cognition screening test	Mini-Mental State Examination (MMSE)	(Lobo et al., 2001)
Attention	Brief Test of Attention (BTA)	(Schretlen, 1989)
Attention, Working Memory	Digit Span Forward and Backward	(Pena-Casanova et al., 2009)
Attention, Executive Functions	Stroop Test	(Golden, 1994)
Attention, Working Memory	Trail Making Test (A+B)	(Pena-Casanova et al., 2009)
Processing Speed	Salthouse Letter Comparison Test	(Salthouse & Babcock, 1991)
Verbal Fluency	Phonetic and Semantic Fluency	(Pena-Casanova et al., 2009)
Verbal Memory	Hopkins Verbal Learning Test (HVLT)	(Brandt, 1991)
Visual Memory	Brief Visual Memory Test (BVMT)	(Benedict, Schretlen, Groninger, Dobraski, & Shpritz, 1996)

Language	Boston Naming Test	(Borod, Goodglass, & Kaplan, 1980)
Visuo-perceptive Visuo-spatial	Visual Object and Space Perception (VOSP)	(Warrington & James, 1991)
Visuo-constructive	Clock Drawing Test (order + copy)	(Mainland & Shulman, 2013)
Theory of Mind	Strange Stories Task (Happe Test)	(Happé, 1994)

- The behavioral assessment included:

Depression	Geriatric Depression Scale (GDS)	(Yesavage & Sheikh, 1986)
Apathy	Lille Apathy Rating Scale (LARS)	(Sockeel et al., 2006)
Functional Disability	World Health Organization Disability Assessment Schedule II (WHO-DAS II)	(Vázquez-Barquero et al., 2000)
Neuropsychiatry symptoms	Neuropsychiatric Inventory Questionnaire (NPI-Q)	(Kaufer et al., 2000)

4.5 Neuroimaging acquisition

Structural and functional imaging data were acquired on a 3T MRI (Philips Achieva TX) at OSATEK, Hospital of Galdakao. All sequences were acquired during a single session, and the same acquisition protocol was used at T_0, T_1 and T_2.

- T1-weighted images were obtained in a sagittal orientation (TR= 7.4 ms, TE= 3.4 ms, matrix size= 228x218 mm; flip angle= 9º, FOV= 250x250 mm, slice thickness= 1.1 mm, 300 slices, voxel size= 0.98x0.98x0.60 mm, acquisition time= 4’55’’).

- Diffusion-weighted images were obtained in an axial orientation in an anterior-posterior phase direction, using a single-shot EPI sequence (TR= 7540 ms, TE= 76 ms, matrix size = 120x117 mm; flip angle= 90º, FOV= 240x240 mm, slice thickness= 2 mm, no gap, 66 slices, voxel size= 1.67x1.67x2.0 mm, acquisition time= 9’31’’)

with two identical repetitions (32 uniformly distributed directions b= 1,000 s/mm2 and 1 b= 0 s/mm2).

- The resting-state fMRI was obtained in an axial orientation in an anterior-posterior phase direction, using a sequence sensitive to blood oxygen level dependent (BOLD) contrast and multi-slice gradient echo EPI sequence (TR= 2100 ms, TE= 16 ms, matrix size= 80x78 mm, flip angle= 80º, FOV= 240x240 mm, slice thickness= 3 mm, 214 volumes, 40 slices, voxel size= 3.00x3.00x3.00 mm, acquisition time= 7'40'').

- The Memory fMRI paradigm (learning and recognition tasks) were acquired using a multi-slice gradient echo (EPI) sequence [TR= 2000 ms, TE= 29 ms, matrix size= 100x100 mm, flip angle= 90º, FOV= 240x240 mm, slice thickness= 3 mm; 280 volumes (140 volumes, 36 slices, each learning and recognition task), voxel size= 1.67x1.67x3.00 mm, acquisition time= 9'36'' (4'48'' each learning and recognition task)].

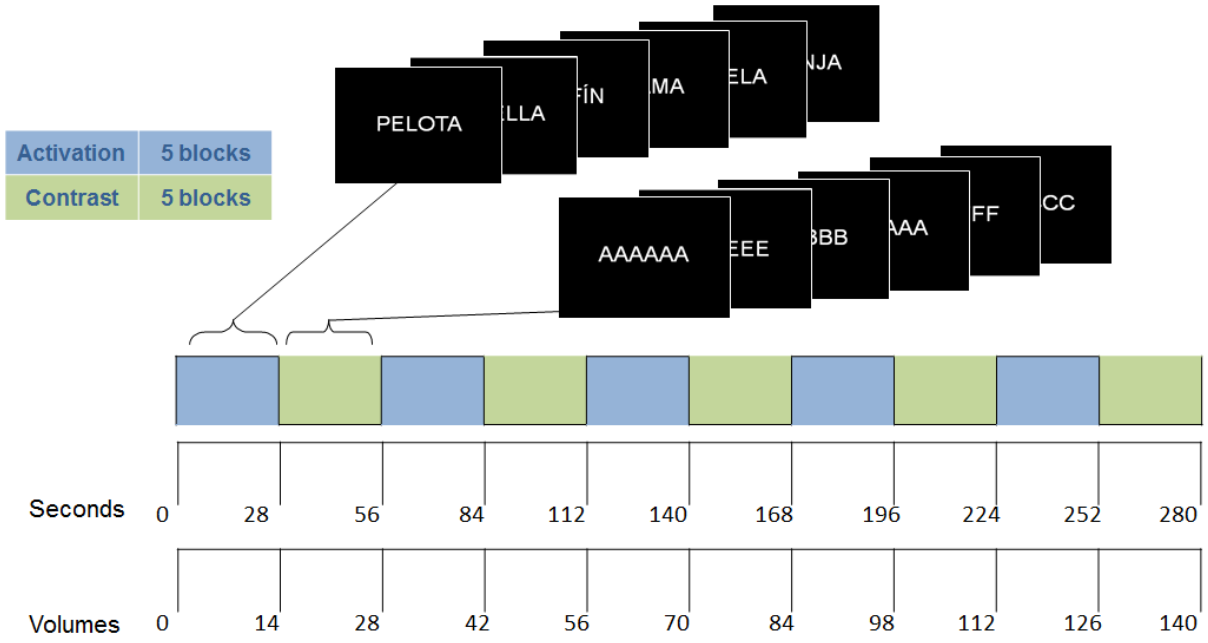
The memory fMRI paradigm consisted of words presented inside a 3T magnet with Visual Digital MRI Compatible High Resolution Stereo 3D glasses and Presentation® version 10.1 (Neurobehavioral Systems), running on Windows XP. They were also given two controls (one in each hand) connected to a MR-compatible response box to record/register their responses. The entire experiment consisted of a 10-block paradigm (learning and recognition tasks) that alternated activation and control conditions (5 blocks each) and lasted a total of 280 s (28 s per block) (see Figure 6).

In the learning memory fMRI task, participants viewed 30 words (with a duration of 2 s per word and inter-word intervals of 2 s) and were asked to press the right button (with their

right hand) if they liked the word or the left button (with their left hand) if they did not like the word; this was done to make sure they were reading the words (activation condition). Moreover, six concatenations of letters were projected (simulating the length of a word) of which three were the letters "AAAAAA" and the other three were random letters (control condition). A review of 4 experiments confirms that this paradigm is effective as a control condition for posterior recognition (Marsolek, Kosslyn, & Squire, 1992).

After 20 minutes, the recognition memory fMRI task is presented inside the scanner. During the recognition memory fMRI task, subjects were asked to recognize these 15 words during the fMRI scanning from a list of 30 words (15 previously presented words and 15 new words). They viewed six words in each block, of which three had been previously presented. They were tasked to press the button using their right hand to if they remembered having read the word in the list before scanning. However, if they thought that the word in the screen was new, they were asked to press the left button. They were encouraged to respond while the word was on the screen (2 s). Responses given outside this interval were excluded from the analysis. In the control condition of the recognition memory fMRI task, participants were asked to press the right button on the response box to indicate that the item was "AAAAAA" and press the left button when other concatenations of letters appeared (Ibarretxe-Bilbao et al., 2011). Responses given with two controls connected to the MR response box, during verbal memory fMRI paradigm, were coded as behavioral data. Hits were recorded when they answered yes when it was yes, correct rejections, when they answered no when it was not, false negatives, when they answered no when it was yes, and false positives, when they answered yes when it was not. This paradigm was presented at baseline, post-treatment and long-term evaluations. To avoid learning effects, the long-term version of the paradigm was created including different words but with phonetic similarities and with the same number of syllables as the baseline and post-treatment versions.

Figure 6: Schematic representation of activation and contrast blocks in the learning and recognition tasks of the memory fMRI paradigm



4.6 Neuroimaging preprocessing

Voxel-based morphometry (VBM)

(Used in Paper I, Paper IV, paper V)

Voxel-based morphometry (VBM) (Douaud et al., 2007) analyses were carried out using the FMRIB Software Library (FSL) tools (Smith et al., 2004). First, a study-specific template was created so that all of the images could be registered in the same stereotactic space (spatial normalization). Then, the GM images were affine registered to the GM MNI-152 template and averaged to create an affine GM template. Next, the GM images were re-registered to this affine GM template using a non-linear registration and averaged to create a study-specific, non-linear GM template in standard space. Second, individual GM images were registered non-linearly to the study-specific template. After normalization, the resulting

GM images were modulated by multiplying by Jacobian determinants to correct for volume change induced by the nonlinear spatial normalization. Then, the images were smoothed with a sigma of 3.5 mm (8 mm FWHM).

Cortical thickness

(Used in Paper IV, paper V)

Cortical Thickness changes were analyzed with Freesurfer (Fischl, 2012) (version 5.3; available at http://surfer.nmr.mgh.harvard.edu). The processing of T1 high-resolution images for the cortical surface reconstruction followed the Freesurfer analysis pipeline (Dale, Fischl, & Sereno, 1999; Fischl, Sereno, & Dale, 1999): Automated Talairach transformation, intensity normalization, skull stripping, WM segmentation, tessellation of the GM/WM boundary, automated topology correction, and surface deformation following intensity gradients to optimally place the fluid borders (GM/WM and GM/cerebrospinal fluid) at the location. All surface models were visually inspected for accuracy. No model was excluded due to misclassification of tissue types. Cortical thickness was calculated as the closest distance from the GM/WM boundary to the GM/cerebrospinal fluid boundary at each vertex on the tessellated surface. The bilateral mean cortical thickness values were extracted based on the parcellation of (Destrieux, Fischl, Dale, & Halgren, 2010) and were introduced in SPSS for statistical analysis.

Tract-Based Spatial Statistics (TBSS)

(Used in Paper I, Paper IV, paper V)

Diffusion data were preprocessed and analyzed using FSL. First, each subject's images were concatenated and radiologically oriented. Then, the data were corrected for motion and eddy currents, performed brain-extraction BET, and the diffusion gradients

(bvecs) were rotated to be corrected accordingly, providing a more accurate estimate of tensor orientations (Jones & Cercignani, 2010). Then, all fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD) and axial diffusivity (AD) images were obtained by fitting a tensor model to the raw diffusion data using FDT (DTIFIT). After, TBSS was used for group comparisons (Smith et al., 2006). Using TBSS, the data were prepared to apply a nonlinear registration of all FA images into standard space. The mean FA image was created using a threshold of 0.2 and thinned to create a "mean FA skeleton" which represents the centres of all tracts common to the group. MD data were analyzed using "tbss non FA" script from TBSS, which applies the original non lineal registration to the MD data, merges all subjects warped MD data into a 4D file, then project this onto the original mean FA skeleton, and creates the 4D projected data. The same process was repeated for RD and AD.

Data-driven approach for Resting-state fMRI

(Used in Paper, II, Paper IV and V)

Rs-fMRI data were acquired during a so-called resting-state block. Subjects were instructed to neither engage in any particular cognitive or motor activity, to keep their eyes closed without thinking about anything in particular and they were told they could not fall asleep. Once the resting-state fMRI acquisition finished, the neuroradiologist talked with the patients and asked them whether they fell asleep or not. No patient reported to fall asleep. Foam padding and headphones were used to limit head movement and reduce scanner noise for the subject.

Rs-fMRI data were preprocessed using CONN Functional Connectivity Toolbox 14.p (Whitfield-Gabrieli & Nieto-Castanon, 2012). First, each subject' 214 functional images were realigned and unwarped, slice-timing corrected, coregistered with structural data, spatially normalized into the standard MNI space (Montreal Neurological Institute), then, outliers were

detected (ART-based scrubbing) and finally images were smoothed using a Gaussian kernel of 8 mm FWMH. All preprocessing steps were conducted using default preprocessing pipeline for volume-based analysis (to MNI-space). Structural data were segmented in GM, WM and cerebrospinal fluid and normalized in the same default preprocessing pipeline. Moreover, noise was reduced via the anatomical CompCor approach, which extracts principal components from WM and cerebrospinal fluid time series. These components were added as confounds in the denoising step of the CONN toolbox. The six head motion parameters derived from spatial motion correction were also added as cofounds. As recommended band-pass filtering was performed with a frequency window of 0.008 to 0.09 Hz (Weissenbacher et al., 2009). Linear detrending was additionally performed.

Specifically in Paper II:

After preprocessing the data with CONN toolbox as previously described, Group ICA of fMRI Toolbox (GIFT) was used to decompose the data into functional networks using group spatial independent component analysis (ICA) (Calhoun et al., 2001). 29 independent components (ICs) were finally selected. The 29 ICs were divided in: 2 ICs in the subcortical network, 2 ICs in the auditory network, 5 ICs in the somatomotor network, 5 ICs in the visual network, 6 ICs in the cognitive control (which included the salience network and language network), 7 ICs in the default-mode network and 2 ICs in the cerebellar network. After ICs selection, subject-specific spatial maps and times courses were postprocessed, following (Allen et al., 2014), and included a detrending, a filter cutoff of low frequency fluctuation set at 0.15, and despiking. Head movement effect was regressed out to obtain more accurate results.

Dynamic FC analysis was performed with the GIFT toolbox. A sliding time window of 22 TR method for each subject was applied (Allen et al., 2014), with a Gaussian window

alpha value of 3, and a step between windows of 1 TR, resulting in the analysis of 192 windows. Due to the short time segments that could have insufficient information, the regularized inverse covariance matrix was used (Varoquaux, Gramfort, Poline, & Thirion, 2010). All the dynamic functional networks connectivity windows across all subjects were used to estimate the FC states. To do so, k-means clustering analysis was repeated 100 times to obtain the unbiased initial cluster, and was used to cluster the dynamic FC windows. K-means clustering applies Euclidean distance to regroup similar FC matrices of the different windows. The number of clusters (*k*) can be calculated in several ways. In this study we used the elbow criterion following previous dynamic FC studies (Allen et al., 2014; Damaraju et al., 2014) and the cluster number was set to 2. We used the Pearson correlation coefficient for clustering analysis, which is also the most widely used FC measure in rs-fMRI studies (Chang & Glover, 2010; Damaraju et al., 2014; Handwerker, Roopchansingh, Gonzalez-Castillo, & Bandettini, 2012; Hutchison et al., 2013; Sakoğlu et al., 2010).

Indexes from dynamic FC were used: 1) *Mean dwell time* defined as the number of consecutive windows in a specific state, or time that the subjects remain in the one FC state (Allen et al., 2014); 2) *Number of transitions between states or state transition* was calculated counting the total number of changes between states for each subject.

In addition, FC characteristics in each dynamic state were analyzed with the network-based statistic (NBS) approach (Zalesky, Fornito, & Bullmore, 2010). Moreover, the Brain Connectivity Toolbox (BCT) (https:// sites.google.com/site/bctnet/) was used to analyze the graph characteristics (both global and local aspects) of the networks obtained based on the ICs resulting from the ICA analysis. We selected sparsity of 0.34 to maximise global and local efficiency (Achard & Bullmore, 2007). Global and local parameters were assessed (Bullmore & Sporns, 2009; Wang et al., 2011).

Specifically in Paper IV and V:

After preprocessing the data with CONN toolbox as previously described, whole-brain analysis was performed using Region of Interest (ROI-to-ROI) approach according to CONN toolbox options, and previously used in a recent study (Demirakca, Cardinale, Dehn, Ruf, & Ende, 2015). In order to get a complete picture of possible cerebral changes, we used all existing areas as ROIs, based on the pre-defined ROIs loaded automatically in CONN toolbox, including default network connectivity (FOX) and a complete list of Brodmann areas obtained from the Talairach Daemon atlas (Lancaster et al., 2000). Following recommendations, *p*-FDR threshold was used in the connection-level analysis to correct for multiple comparisons (Whitfield-Gabrieli & Nieto-Castanon, 2012).

Model-driven approach for Memory fMRI Paradigm

(Used in Paper IV and V)

FMRI data were analyzed using Statistical Parametric Mapping (SPM) (Ashburner et al., 2012). The functional data of each participant were motion-corrected, realigned to the first acquired volume in the session, and a mean realigned volume was created for each participant. Then, all realigned volumes were spatially normalized into the standard MNI space and smoothed using a Gaussian kernel of 8 mm FWMH. Statistical parametric maps were calculated at first-level analysis for each subject with a general linear model, and parameters for the memory fMRI paradigm model specification were introduced. Then, after model estimation, a matrix was obtained for each subject showing higher brain activation while the activation condition compared to the control condition (activation>control).

4.7 Neuroimaging analyses

Paper I

Whole-brain VBM differences between PD and HC and the relationship between GM volume and ToM were analyzed with randomize tool (Winkler, Ridgway, Webster, Smith, & Nichols, 2014) (5000 permutations) and with threshold-free cluster enhancement (TFCE). Total intracranial volume was calculated, transformed to a Z score and introduced as a covariate in between-group analysis. The significant regions were located and labelled anatomically with the Harvard- Oxford Cortical Structures Atlas. Statistical threshold for VBM analysis was set at $p < .05$ corrected for multiple comparisons using family wise error (FWE-corrected). Exploratory analyses were also performed at $p < .001$ (FWE-uncorrected) level, with minimum extended cluster K > 20 voxels to be considered as a significant result.

To examine the differences between PD and healthy controls in WM FA, RD, MD and AD and to assess the relationships between WM indexes and ToM, randomize tool (5000 permutations) and a regression analysis with TFCE correction was used. The significant regions were located and labelled anatomically with the JHU-ICBM-DTI-81WM Labels and JHU White-Matter tractography Atlas. Statistical threshold was set at $p < .05$ (FWE-corrected), and exploratory analyses using $p < .001$ (FWE-uncorrected, K >20 voxels) were also reported.

Paper II

Dynamic FC differences between PD-MCI, PD-NC and HC were performed including age as covariate, following previous recommendations (Allen et al., 2011). In addition, differences between groups regarding the FC characteristics in each dynamic FC state and the graph theoretical parameters were also performed. LEDD was also included as covariate when assessing the differences between PD-MCI and PD-NC, due to its influence in fMRI signal

(Mattay et al., 2002). Statistical differences between groups were performed using two sample t-tests.

Paper IV

Whole-brain analysis was performed to study structural and functional cerebral changes. Baseline differences between REHACOP group and CG were tested with two sample t-test analysis. Longitudinal analysis to test differences between pre-treatment and post-treatment for REHACOP group and CG data were assessed with repeated-measures ANOVA 2 × 2 analysis for group x time interaction analysis. The between-subjects factor was group (REHACOP group or CG) and the within-subjects factor was time (pre-treatment and post-treatment). Paired-t-test analysis was also performed to explore intragroup changes.

VBM and cortical thickness analyses used total intracranial volume as a covariate. For the fMRI analyses, LEDD was used as a covariate because of the influence of dopaminergic treatment on brain activation (Mattay et al., 2002).

Moreover, because the REHACOP group showed lower scores on UPDRS III and higher scores on MMSE at baseline, both variables were included as covariates in longitudinal analyses. For both structural and functional analyses the statistical threshold was set at $p < .05$ corrected for multiple comparisons and $p < .001$ uncorrected analysis was also performed for exploratory results.

Paper V

To evaluate the evolution of the 15 PD patients after attending cognitive rehabilitation, non-parametric paired t-tests were performed in neuroimaging data between T_0 and T_2 assessments and between T_1 and T_2 assessments. All neuroimaging analyses were performed at $p < .05$ corrected for multiple comparisons and fMRI data used LEDD as covariate

(Mattay et al., 2002). FMRI analyses were performed with whole-brain. Region-of-interest (ROI) analyses were also performed to test the maintenance at T_2 of the increased FC from T_0 to T_1 found in PD patients after attending cognitive rehabilitation. FC values between these ROIs were extracted from PD patients at the three time points and entered into SPSS.

4.8 Statistical analyses for neuropsychological and clinical data

The sociodemographic, clinical and neuropsychological data were analyzed in SPSS 22.0.

Paper I

First, all variables were tested for normality. Differences between PD and HC were assessed with t-test, chi-squared (X^2) test and ANOVA for neuropsychological differences. Correlation analysis was performed with r-Pearson. Raw scores were transformed into Z scores. Executive functions were measured using a composite score, calculated from phonetic and semantic Verbal Fluency Test and the Clock Drawing Test (order) (alpha = .747). In addition, test-retest reliability for Fazekas Scale was performed and correlation analysis calculated (Spearman´s Rho = .835; $p < .001$). Age and gender were introduced as nuisance variables in neuropsychological and neuroimaging analyses. Effect sizes for each cluster of the group comparisons and correlations were calculated according to Cohen´s d formula or r formula respectively.

Paper II

Demographic, clinical and behavioral variables were tested for normality using the Shapiro-Wilk test. Sociodemographic differences between PD-MCI, PD-NC and HC were tested with the Analysis of Variance (ANOVA) or Kruskal-Wallis test for 3-group

comparisons and 2-tailed t-test or U-Mann Whitney for 2-group comparisons and chi-squared test for qualitative variables. Finally, effect size was calculated with Cohen's *d*, considering 0.2, 0.5 and 0.8, small, medium and large effect sizes respectively (Hojat and Xu, 2004).

Paper III

Normality of data was tested using the Kolmogorov-Smirnov test. All variables appeared as normal distributions, with the exception of the Geriatric Depression Scale, which was log-transformed for further analyses. Categorical data were analyzed with the X^2 test or Fisher exact test, as indicated. Sociodemographic variables, clinical variables, cognition, and functional disability at baseline were compared between the REHACOP and CG using 2-tailed t tests.

Change scores (post-treatment to baseline) were compared between REHACOP and CG on each of the cognitive, clinical, and functional disability variables with ANOVA. To obtain adjusted mean differences in change scores, we used bootstrapping, a resampling technique in which random subsamples are generated from the observed sample. We generated 1,000 subsamples from within each group (with replacement). Effect size (Cohen' *d* and 95% confidence interval [CI]) was calculated based on change score differences between groups. The X^2 test was used to compare the percentage of patients in both groups who disclosed a score improvement after the training.

Paper IV

Longitudinal analysis to test differences between pre-treatment and post-treatment for REHACOP group and CG were assessed with repeated-measures ANOVA 2x2 analysis data for group x time interaction analysis. The between-subjects factor was group (REHACOP group or CG) and the within-subjects factor was time (pre-treatment and post-treatment).

Paired-t-test analysis was also performed to explore intragroup changes. Moreover, UPDRS III and MMSE at baseline were included as covariates in longitudinal analyses. Effect sizes for each cluster were calculated according to Cohen's d formula (Thalheimer & Cook, 2002). Finally, Rho-Spearman test was used to determine the relationships between MRI data at post-treatment and the performance in cognitive domains after rehabilitation, including executive functions, processing speed, verbal and visual memory and theory of mind. Bootstrapping was used in correlations to obtain more adjusted results (Efron & Tibshirani, 1994).

Paper V

Normality of data was tested using the Shapiro-Wilk test. To evaluate the evolution of the 15 PD patients after attending cognitive rehabilitation, non-parametric paired t-tests were performed in cognitive and behavioral data between T_0 and T_2 assessments and between T_1 and T_2 assessments.

4.9 Ethics Statement

The study protocol was approved by the Ethics Committee at the Health Department of the Basque Mental Health System in Spain and the Ethics Committee from University of Deusto (Psi-09/11-12). All patients were volunteers who provided written informed consent to participate in the study. This study was registered at clinicaltrials.gov (registration number NCT02118480).

V. Results

5. Results

Paper I

"Neuroanatomical correlates of Theory of Mind deficit in Parkinson's disease: A multimodal imaging Study"

Paper II

"Dynamic functional connectivity in Parkinson's disease patients with mild cognitive impairment and normal cognition"

Paper III

"Improving functional disability and cognition in Parkinson disease: Randomized controlled trial"

Paper IV

"Increased brain connectivity and activation after cognitive rehabilitation in Parkinson's disease: a randomized controlled trial"

Paper V

"Long-term effects of cognitive rehabilitation in brain, functional outcome and cognition in Parkinson's disease"

Paper I

PLOS ONE

RESEARCH ARTICLE

Neuroanatomical Correlates of Theory of Mind Deficit in Parkinson's Disease: A Multimodal Imaging Study

María Díez-Cirarda[1], Natalia Ojeda[1], Javier Peña[1], Alberto Cabrera-Zubizarreta[2], María Ángeles Gómez-Beldarrain[3], Juan Carlos Gómez-Esteban[4], Naroa Ibarretxe-Bilbao[1]*

1 Department of Methods and Experimental Psychology, Faculty of Psychology and Education, University of Deusto, Bilbao, Basque Country, Spain, **2** OSATEK, MR Unit, Hospital of Galdakao, Galdakao, Basque Country, Spain, **3** Neurology Service, Hospital of Galdakao, Galdakao, Basque Country, Spain, **4** Neurodegenerative Unit, Biocruces Research Institute; Neurology Service, Cruces University Hospital, Baracaldo, Biscay, Spain

* naroa.ibarretxe@deusto.es

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Abstract

Background

Parkinson's disease (PD) patients show theory of mind (ToM) deficit since the early stages of the disease, and this deficit has been associated with working memory, executive functions and quality of life impairment. To date, neuroanatomical correlates of ToM have not been assessed with magnetic resonance imaging in PD. The main objective of this study was to assess cerebral correlates of ToM deficit in PD. The second objective was to explore the relationships between ToM, working memory and executive functions, and to analyse the neural correlates of ToM, controlling for both working memory and executive functions.

Methods

Thirty-seven PD patients (Hoehn and Yahr median = 2.0) and 15 healthy controls underwent a neuropsychological assessment and magnetic resonance images in a 3T-scanner were acquired. T1-weighted images were analysed with voxel-based morphometry, and white matter integrity and diffusivity measures were obtained from diffusion weighted images and analysed using tract-based spatial statistics.

Results

PD patients showed impairments in ToM, working memory and executive functions; grey matter loss and white matter reduction compared to healthy controls. Grey matter volume decrease in the precentral and postcentral gyrus, middle and inferior frontal gyrus correlated with ToM deficit in PD. White matter in the superior longitudinal fasciculus (adjacent to the parietal lobe) and white matter adjacent to the frontal lobe correlated with ToM impairment in PD. After controlling for executive functions, the relationship between ToM deficit and white matter remained significant for white matter areas adjacent to the precuneus and the parietal lobe.

Competing Interests: The authors have declared that no competing interests exist.

Conclusions

Findings reinforce the existence of ToM impairment from the early Hoehn and Yahr stages in PD, and the findings suggest associations with white matter and grey matter volume decrease. This study contributes to better understand ToM deficit and its neural correlates in PD, which is a basic skill for development of healthy social relationships.

Introduction

Parkinson's disease (PD) is a neurodegenerative disease comprising both motor symptoms and cognitive impairment [1]. Recent studies suggest that PD patients also suffer from deficits in social cognitive abilities, such as recognition of emotional prosody [2], facial emotion recognition [2–4], decision-making [4], irony comprehension [5] and specifically, Theory of Mind (ToM) deficit [3,5–7] from the early stages of the disease [3,7].

ToM was described as the ability to make inferences about others' mental states for the first time by Premark and Woodruff [8]. More recently, ToM has been characterised as the ability to understand and predict another's beliefs, intentions, emotions, behaviour and knowledge [6,7]. Scientific interest in ToM deficit and its cerebral correlates in PD is increasing. It has been suggested that social cognitive impairment may appear before motor symptoms in PD [3], and that ToM may play a relevant role in the dementing process [9,10]. Moreover, ToM deficit has been associated with impairment in PD patient's quality of life [6,7,10]. ToM performance has been related to working memory and executive functions in healthy subjects [11]. The few studies that have assessed this association in PD [5,12], have reported that executive functions and working memory are involved in ToM, enhancing its performance. However, contradicting results have also been reported, suggesting the need to further explore this relationship [10,13].

ToM is related to the mirror-neuron system, whose core regions are located in the rostral part of the inferior parietal lobe, the precentral gyrus and the inferior frontal gyrus [14]. Magnetic Resonance imaging (MRI) studies have described a core network for ToM that includes the medial prefrontal cortex, bilateral posterior temporo-parietal junction [15,16] and the superior temporal sulcus [15]. Other regions, such as the precuneus and the anterior cingulate cortex, are also associated with ToM performance [15]. These findings are supported by common findings in non-human primates [14–16], autism disorder [15,16], lesion studies [16], schizophrenia [16] and healthy adults [14–16]. These anatomical areas related to ToM are known to be progressively impaired in PD [17,18]. However, to date, as far as the authors are aware, there are no studies in PD assessing the neuroanatomical correlates of ToM deficit using MRI.

The main objective of this study was to assess grey matter (GM) and white matter (WM) correlates of ToM deficit in PD. The second objective was to explore the relationships between ToM, working memory and executive functions, and to analyse the cerebral correlates of ToM, after controlling for these two cognitive functions. Voxel-based morphometry (VBM) and tract-based spatial statistics (TBSS) were used to analyse the neural correlates of ToM deficit in PD. Among diffusion tensor imaging (DTI) indexes, fractional anisotropy (FA) is the most frequently evaluated and has been related to fibres integrity, mean diffusivity (MD) has been related inversely to membrane density, radial diffusivity (RD) has shown associations with demyelination and axial diffusivity (AD) has shown increment with brain maturation but also decrement in axonal injury [19].

We hypothesised that ToM deficit in PD would correlate with GM volume and WM in the medial prefrontal cortex, temporo-parietal junction and superior temporal sulcus, all core

regions related to ToM. Finally, we hypothesised that ToM performance in PD patients would correlate with executive functions and working memory. Working memory and executive functions are related to the frontal lobes [13,20,21] hence, we hypothesised that the influence of executive functions and working memory on ToM would be reflected in the medial prefrontal cortex, reducing the association between the frontal areas and ToM.

Materials and Methods

Subjects

The sample included 44 PD patients recruited from the Department of Neurology at the Galdakao Hospital and from the PD Biscay Association (ASPARBI). The main purpose of the study was to analyze the neuroanatomical correlates of ToM deficit in PD; however, we also recruited 15 healthy controls, who were matched with the patients by age, gender and years of education, to explore differences between groups.

PD patients were enrolled in the study if they fulfilled the UK PD Society Brain Bank diagnostic criteria. Other inclusion criteria were as follows: i) age between 45–75; ii) Hoehn and Yahr disease stage < 3 [22]; iii) Unified PD Rating Scale (UPDRS) [23] evaluated by the neurologist. The exclusion criteria were as follows: i) the presence of dementia as defined by the DSM-IV-R [24] and the Movement Disorders Society clinical criteria for PD-dementia; ii) scores on the Mini Mental State Examination < 24; iii) the presence of other neurological illness/injury (e.g. traumatic brain injury); iv) unstable psychiatric disorders (e.g. schizophrenia); v) PD patients with visual hallucinations as assessed by the Neuropsychiatric Inventory Questionnaire [25]; and vi) Diagnosis of depression or depression evaluated with the Geriatric Depression Scale >5 [26]. WM hyperintensity ratings were calculated twice by the same neuroradiologist using the Fazekas Scale [27] based on T1-weighted images. Considering that some degree of WM hyperintensity is typical in the elderly, these criteria did not exclude any of the participants. Five patients were excluded due to exclusion criteria and 2 patients refused to participate, therefore the final PD sample consisted of 37 PD patients.

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 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, dopamine agonist and MAO-B (n = 9), combination of dopamine agonist and MAO-B (n = 4), combination of dopamine agonist and anticholinergics (n = 2), combination of glutamate agonists in combination with others (n = 4), catechol-O-methyltransferase (COMT) inhibitors in combination with others (n = 2). Participants were symptomatically stable and tested while on their medication. Their L-dopa equivalent daily dose was registered [28].

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, in accordance with the Declaration of Helsinki.

Neuropsychological assessment

Participants underwent a neuropsychological battery including the Spanish version of the Mini-Mental State Examination [29] as a screening cognitive measure. Digit Span Backward [30] was used to assess working memory, and the Clock Drawing Test (order) [31] and Verbal

fluency Test (phonetic and semantic) [32] to evaluate executive functions. Executive functions and working memory tests were chosen following the recommendations by the Movement Disorders Society Task Force for diagnosis of mild cognitive impairment in PD [33]. ToM was assessed with the Spanish version of the Happe Test "Strange Stories Task" [34], developed by Pousa [34,35] (an Advanced Test of Theory of Mind), and the global score was selected for correlation with diffusion weighted images and T1 derived measures. Happe test is composed of 8 stories concerning double bluff, mistakes, persuasion and white lies, and has been previously used for the assessment of the neuroanatomical correlates of ToM [34,36]. This study is part of a more extensive longitudinal study; therefore, to avoid test-retest learning effect at longitudinal evaluation, we evaluated ToM with 4 stories at first time (included in this study) and 4 at second time. Participants had to read aloud each story and then, answer a question requiring an inference about the character's thoughts, which required an inference about the speaker's/actor's intentions. The participant was asked to answer the required questions, explaining his/her point of view, after demonstrating that he/she understood the task with an example story. Responses were scored between 0 and 2, strictly following the instructions of the manual, where explicit answers were scored with 2 points and implicit answers with 1 point and no response or non-related responses with 0 points. A trained neuropsychologist gave the score of the Happe Task to each participant, guided by the definition and examples showed in the manual to score explicit and implicit answers. Results of ToM performance in this PD sample have been previously published in a longitudinal study [37], and results showed that PD patients, who received cognitive rehabilitation therapy, improved their ToM performance.

Image acquisition and analysis

Diffusion-weighted images were obtained on a Phillips 3T Achieva, in an axial orientation in an anterior-posterior phase direction using a single-shot EPI sequence (TR = 7540 and TE = 76, matrix size = 120mm x 117mm; flip angle = 90°, FOV = 240x240x132, slice thickness = 2 mm, no gap, 66 slices, acquisition time = 9'31", voxel size = 1.67x1.67x2.0) with diffusion weighting in 32 uniformly distributed directions (b = 1,000 s/mm^2) and 1 b = 0 s/mm^2. A T1-weighted scan was also acquired in sagittal orientation (TR = 7.4 and TE = 3.4, matrix size = 228mm x 218mm; flip angle = 9°, FOV = 250x250x180, slice thickness = 1.1 mm, 300 slices, acquisition time = 4'55", voxel size = 0.98x0.98x0.6).

VBM analysis in GM. VBM analyses were carried out using the FMRIB Software Library (FSL) [38] tools (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLVBM) [39]. First, a study-specific template was created so that all images could be registered in the same stereotactic space (spatial normalisation). To do this, brain-extracted structural images were segmented into GM, WM, and cerebrospinal fluid. Then, GM images were affine registered to the GM ICBM-152 template and averaged to create an affine GM template. Next, GM images were re-registered to this affine GM template using a non-linear registration and averaged to create the study-specific non-linear GM template in standard space. Second, individual GM images were registered non-linearly to the study-specific template. After the normalisation, the resulting GM images were modulated by multiplying with Jacobian determinants to correct for the volume change induced by the nonlinear spatial normalisation. Finally, the images were smoothed with sigma of 3.5 mm (8 mm FWHM).

TBSS analysis in WM. Diffusion data were preprocessed and analysed using tools from FSL [38]. First, each subject's images were concatenated and radiologically oriented. Then, the data were corrected for motion and eddy currents, performed brain-extraction BET, and the diffusion gradients (bvecs) were rotated to be corrected accordingly, providing a more accurate estimate of tensor orientations [40]. Then, all FA, MD, RD and AD images were

obtained by fitting a tensor model to the raw diffusion data using FDT (DTIFIT). After, TBSS [41] was used for group comparisons and correlations analyses. Using TBSS, the data were prepared to apply a nonlinear registration of all FA images into standard space, the mean FA image was created using a threshold of 0.2 and thinned to create a "mean FA skeleton" which represents the centres of all tracts common to the group. MD data were analysed using "tbss non FA" script from TBSS, which applies the original non lineal registration to the MD data, merges all subjects warped MD data into a 4D file, then project this onto the original mean FA skeleton, and creates the 4D projected data. The same process was repeated for RD and AD.

Statistical analysis

All variables were tested for normality. Differences between groups were assessed with t-test, chi-squared (X^2) test and ANOVA for neuropsychological differences. Correlation analysis was performed with r-Pearson. Raw scores were transformed into Z scores. Executive functions were measured using a composite score, calculated from phonetic and semantic Verbal Fluency Test and the Clock Drawing Test (order) (alpha = .747). In addition, test-retest reliability for Fazekas Scale was performed and correlation analysis calculated (Spearman´s Rho = .835; $p <$ .001). Age and gender were introduced as nuisance variables in neuropsychological and neuroimaging analyses.

Whole-brain VBM differences between groups and the relationships between GM volume and ToM were analysed with randomise tool [42] (5000 permutations) and with threshold-free cluster enhancement (TFCE). Total intracranial volume was calculated, transformed to a Z score and introduced as a covariate in between-group analysis, following previous GM studies [43–45]. The significant regions were located and labelled anatomically with the Harvard-Oxford Cortical Structures Atlas. Statistical threshold for VBM analysis was set at $p < .05$ corrected for multiple comparisons using family wise error (FWE). Exploratory analyses were also performed at $p < .001$ (uncorrected) level, with minimum extended cluster K>20 voxels to be considered as a significant result. To examine the differences between groups in WM FA, RD, MD and AD and to assess the relationships between WM indexes and ToM, randomise tool [42] (5000 permutations) and a regression analysis with TFCE correction was used. The significant regions were located and labelled anatomically with the JHU-ICBM-DTI-81 WM Labels and JHU White-Matter tractography Atlas. Statistical threshold was set at $p < .05$ (FWE-corrected), and exploratory analyses using $p < .001$ (uncorrected, K>20 voxels) were also reported. Effect sizes for each cluster of the group comparisons and correlations were calculated according to Cohen´s *d* formula or *r* formula respectively, in line with previous investigations [46–48]. Cohen´s *d* of 0.20, 0.50 and 0.80 were considered small, medium and large, respectively [49]. Interpretation of *r* score was considered small, medium and large when scores were 0.10, 0.30 and 0.50, respectively [49].

Results

Neuropsychological results

The clinical and sociodemographic characteristics of the sample are shown in Table 1.

PD participants obtained significantly lower scores on ToM, working memory and executive functions compared to healthy controls (Table 1). Moreover, a significant positive correlation was found between ToM and executive functions (r = .45; $p = < .01$), but not with working memory (r = .30; $p = .06$) in PD.

Table 1. Sociodemographic, clinical and neuropsychological characteristics of the sample.

		PD (n = 37)	HC (n = 15)	Statistic	*p*
Sociodemographic and clinical characteristics					
Age		67.97 (6.17)	65.07 (7.01)	t = 1.47	.15
Gender (Male)		22 (59.5%)	11 (73.3%)	X^2 = .88	.52
Years of education		10.24 (4.81)	12.27 (4.30)	t = -1.41	.16
Handedness	Right handed	33 (89.2%)	15 (100%)	X^2 = 1.75	.31
	Ambidextrous*	4 (10.8%)	0%		
Fazekas Scale		.51 (.69)	.67 (.90)	X^2 = 2.89	.23
		0 = 22	0 = 9		
		1 = 11	1 = 2		
		2 = 4	2 = 4		
Geriatric Depression Scale		2.57 (2.80)	1.20 (1.37)	t = 1.79	.08
Neuropsychiatric Inventory		3.46 (4.07)	-	-	-
Side of disease onset	Right side of the body	14 (37.8%)	-	X^2 = 1.40	.24
	Left side of the body	21 (56.8%)	-		
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)	-	-	-
Hoehn & Yahr		1.89 (.45)	-	-	-
		1 = 5	-	-	-
		1.5 = 3	-	-	-
		2 = 26	-	-	-
		2.5 = 1	-	-	-
		3 = 2	-	-	-
Neuropsychological assessment					
ToM (Z score)		-.23 (1.05)	.57 (.54)	F = 5.854	.019
Working Memory (Z score)		-.30 (.79)	.63 (.77)	F = 8.911	.004
Executive Functions (Z score)		-.26 (.74)	.56 (.59)	F = 12.57	.001
Cognitive Reserve (Z score)		-.14 (1.03)	.35 (.83)	F = 1.929	.137

Values are expressed as mean (S.D) unless otherwise noted. PD = Parkinson's disease; HC = Healthy controls; UPDRS = Unified Parkinson Disease Rating Scale; LEDD = Levodopa Equivalent Daily dose; ToM = Theory of Mind.

*Ambidextrous understood as people who were originally left handed and who learned to be right handed during childhood.

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VBM analysis in GM

Group Comparison. PD patients showed reduced GM volume in the left temporal, parietal and occipital lobes ($p < .001$ uncorrected). More specifically, GM regions that showed potential reductions in PD patients compared to healthy controls were mostly located in the left inferior temporal gyrus (anterior and posterior division) and the temporal fusiform cortex (Fig 1; Table 2). Other regions that also showed potential reductions were the superior and inferior parietal lobe, left supramarginal gyrus, and the lateral occipital cortex (Table 2). The healthy control group did not show any areas with reduced GM volume compared to PD patients.

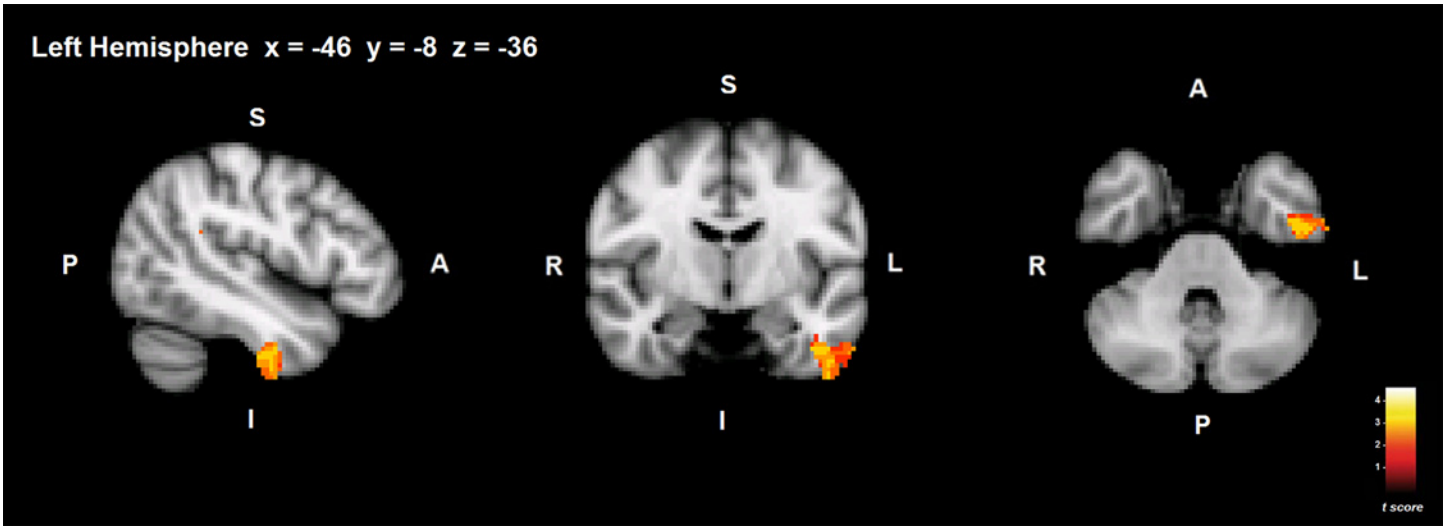

Fig 1. Group differences in GM volume. GM areas showing volume decrease in PD compared to healthy controls are shown in red-yellow. S = superior; I = inferior; A = anterior; P = posterior. Coordinates are shown in MNI space (Montreal Neurological Institute).

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Correlations between ToM and GM volume in PD. No significant correlations were observed at $p < .05$ (FWE-corrected) statistical threshold, but the exploratory analysis showed possible associations between ToM and GM volume, in the left precentral and postcentral gyrus, anterior cingulate gyrus, middle frontal gyrus and the inferior frontal gyrus in PD (Table 2) ($p < .001$ uncorrected). Healthy controls' performance in ToM test showed no significant correlation with GM volume.

Correlations between ToM and GM volume in PD, controlling for executive functions. Because executive functions showed a positive association with ToM, we also included

Table 2. VBM results: Group comparison and correlation analysis with ToM in PDBrain Area.

	Cluster size (voxels)	MNI coordinate			t value	*p* value	Effect size (Cohen´s *d* / *r*) *df* = 36
		x	y	z			
Group Comparison							
L Inferior temporal gyrus	1973	-48	-10	-48	3.77	.001*	1.15
	267	52	-18	-40	3.05	.003*	.84
L Lateral Occipital Cortex, L Superior Parietal Lobe	745	-18	-76	56	3.33	.001*	.93
L Inferior Parietal Lobe	582	-44	-44	22	2.99	.001*	.91
R Temporal Lobe	158	44	26	-26	3.73	.003*	1.14
Correlation with ToM in PD							
L Precentral gyrus, L Postcentral gyrus	830	-32	-24	64	3.59	< .001*	.51
L Anterior Cingulate gyrus	147	-4	-12	28	2.24	< .001*	.34
	109	0	32	2	2.91	< .001*	.43
L Middle frontal gyrus, L Inferior frontal gyrus	84	-30	18	32	2.17	< .001*	.34

Cluster size denotes the extent of the cluster of significant voxels. MNI coordinates refer to the location of the most statistically significant voxel in the cluster.

*Differences are significant at $p < .001$ uncorrected.

PD = Parkinson's disease; ToM = Theory of Mind; L = Left; R = Right; MNI = Montreal Neurological Institute. *df* = Degrees of Freedom.

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this variable as a covariate in the regression analysis. No significant clusters were obtained in the regression analysis between GM volume decrease and ToM after controlling for executive functions in PD.

TBSS analysis in WM

Group Comparison. PD patients showed FA reduction in the right uncinate fasciculus adjacent to the insular cortex and slight WM FA reduction was observed in the frontal lobe compared to healthy control group ($p < .001$ uncorrected). Results showed no significant differences between PD and healthy control groups in MD, RD or AD indexes.

Correlations between ToM and WM in PD. ToM deficit in PD patients correlated positively with FA reduction and negatively with MD and RD indexes of WM tracts. Most significant correlations were found between WM and ToM deficit in the bilateral superior longitudinal fasciculus in PD (Fig 2; Table 3).

WM FA reduction in the right superior longitudinal fasciculus and corticospinal tract adjacent to the primary somatosensory cortex correlated with ToM deficit in PD (Brodmann Area 3a) ($p < .05$ FWE-corrected) (Fig 2; Table 3).

In addition, MD index correlated negatively with ToM deficit in PD, and significant clusters were found in the left superior longitudinal fasciculus located longitudinally in the superior frontal gyrus and premotor cortex (Brodmann Area 6), continuing through the primary somatosensory cortex in the parietal lobe, the precuneus and finishing in the occipital cortex. Furthermore, MD in the left inferior longitudinal fasciculus, the right inferior fronto-occipital fasciculus and the left uncinate fasciculus, adjacent to middle temporal gyrus, to the orbitofrontal cortex, and frontal lobe respectively also correlated with ToM deficit in PD. Finally, MD in the callosal body also correlated with ToM impairment in PD patients (Fig 2; Table 3).

Moreover, RD in the left superior longitudinal fasciculus and corticospinal tract adjacent to the secondary somatosensory cortex, in the external capsule, and in the left anterior thalamic radiation and inferior fronto-occipital fasciculus in the frontal lobe, correlated negatively with ToM deficit in PD (Fig 2; Table 3).

AD index showed no significant relationship with ToM deficit in PD. No significant correlations were found between ToM performance in healthy controls and FA, RD, MD or AD.

Correlations between ToM and WM in PD, controlling for executive functions. After controlling for executive functions, MD in the left superior longitudinal fasciculus adjacent to anterior intra-parietal sulcus, superior parietal lobe and precuneus showed significant associations with ToM deficit in PD (Fig 3; Table 3) ($p < .05$ FWE-corrected). Exploratory analyses showed potential associations between ToM impairment in PD and FA and RD in the right superior longitudinal fasciculus adjacent to somatosensory cortex (Table 3) ($p < .001$ uncorrected).

Discussion

The main objective of the study was to assess the neuroanatomical correlates of ToM deficit in PD. The results suggest that ToM deficit is associated with WM in PD and possible associations with GM volume decrease. More specifically, performance on ToM task in PD was related to GM volume decrease in the left medial frontal cortex, inferior frontal gyrus, anterior cingulate gyrus and precentral gyrus, all regions known to be involved in ToM performance [14–16]. Indeed, similar results have been obtained in other neurodegenerative disorders such as progressive supranuclear palsy [43], and the anterior cingulate has also been related to ToM in Alzheimer´s disease [46]. GM volume loss in the postcentral gyrus also showed possible correlations with ToM deficit. In previous studies, the somatosensory cortex has been related to

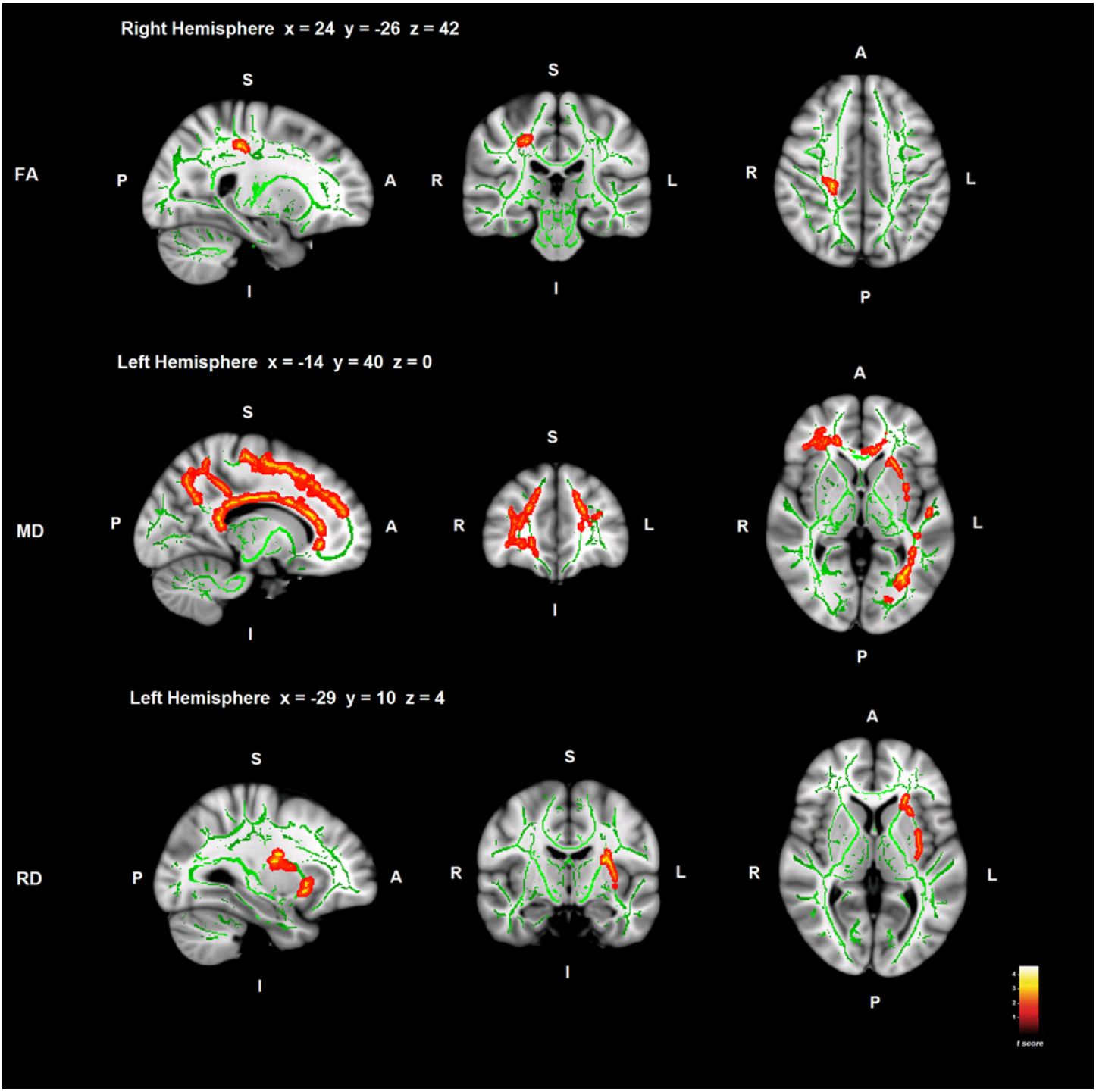

Fig 2. Correlations between ToM deficit and WM in PD. Significant WM regions are shown in red-yellow; the WM skeleton is shown in green. S = superior; I = inferior; A = anterior; P = posterior. Coordinates are shown in MNI space (Montreal Neurological Institute).

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ToM deficit in autism spectrum disorder and schizophrenia [50]. Moreover, FA, MD and RD in the superior longitudinal fasciculus showed significant correlations with ToM deficit in PD. This tract connects the dorsolateral prefrontal cortex with the parieto-temporal association

Table 3. DTI results: Group comparison and correlation analysis with ToM in PD.

Brain Area	Cluster size (voxels)	MNI coordinate			t value	*p* value	Effect size (Cohen´s *d* / *r*) *df* = 36
		x	y	z			
Group Comparison							
FA							
R Uncinate Fasciculus	42	34	15	-13	2.95	.001*	.81
Correlation with ToM in PD							
FA							
R Superior Longitudinal Fasciculus	97	23	-29	42	5.18	.032**	.65
MD							
L Superior longitudinal Fasciculus	13046	-40	-55	36	5.86	.031**	.69
	259	-31	14	28	5.20	.040**	.65
L External Capsule	483	-33	3	4	4.14	.039**	.56
RD							
L Superior Longitudinal Fasciculus	650	-30	-10	14	3.8	.040**	.53
Correlation with ToM in PD controlling for Executive Functions							
FA							
R Superior Longitudinal Fasciculus	227	28	-26	43	2.61	.002*	.39
MD							
L Superior Longitudinal Fasciculus	1322	-40	-55	35	5.33	.049**	.66
	878	-19	-45	43	3.93	.043**	.54
L Inferior Longitudinal Fasciculus	165	-31	-69	-1	4.04	.049**	.55
RD							
R Corticoespinal Tract	296	14	-13	66	1.24	.002*	.20
	124	-27	-20	63	0.86	.001*	.14
L Inferior Longitudinal Fasciculus	169	-27	-63	47	1.69	.001*	.27
	115	-28	-8	-16	1.23	.001*	.20
L Superior Longitudinal Fasciculus	109	-58	-26	6	1.31	.002*	.21

Cluster size denotes the extent of the cluster of significant voxels. MNI coordinates refer to the location of the most statistically significant voxel in the cluster.

*Differences are significant at $p < .001$ uncorrected.

**Differences are significant at $p < .05$ corrected for family-wise error (FWE).

PD = Parkinson's disease; ToM = Theory of Mind; R = Right; L = Left; FA = Fractional Anisotropy; MD = Mean Diffusivity; RD = Radial Diffusivity; MNI = Montreal Neurological Institute; *df* = Degrees of Freedom.

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areas [51], involving all cortical areas related to ToM performance [16]. In addition, MD and RD in WM tracts located in the frontal lobe and specifically in the uncinate fasciculus and inferior fronto-occipital fasciculus adjacent to the orbitofrontal cortex showed significant associations with ToM deficit in PD. These findings add evidence to previous studies that related the ability to process social and emotional information to the frontal lobes in PD [4,5,13–18], and to the uncinate fasciculus and inferior fronto-occipital fasciculus in other pathologies [52,53].

However, previous studies assessing the neuroanatomical correlates of ToM in healthy controls [14–16,18], in progressive supranuclear palsy [43], autism and schizophrenia [50] did not evaluate the potential influence of working memory and executive functions in the MRI analysis. Because of contradicting results on the influence of these cognitive functions on ToM performance in PD, the second objective of the present study was to assess this relationship and to

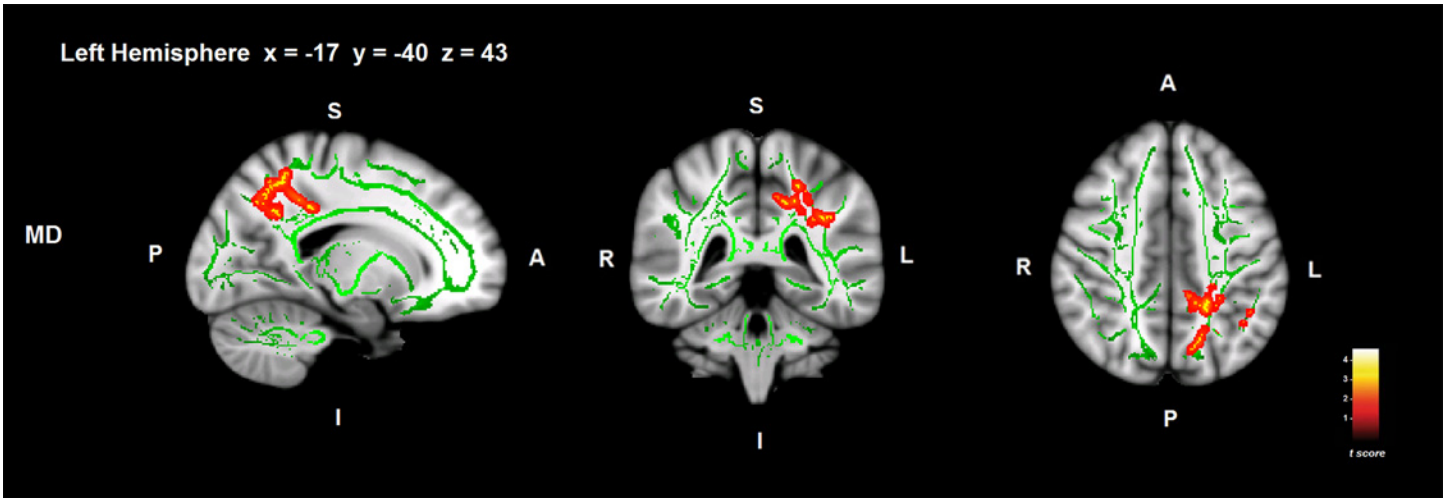

Fig 3. Correlations between ToM deficit and WM MD controlling for executive functions in PD. Significant WM regions are shown in red-yellow; the WM skeleton is shown in green. S = superior; I = inferior; A = anterior; P = posterior. Coordinates are shown in MNI space (Montreal Neurological Institute).

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evaluate the neuroanatomical correlates of ToM deficit after controlling for both cognitive functions. In support of previous literature [5,12,13,21], a correlation between ToM and executive functions was observed in PD, but not with working memory. After controlling for the influence of executive functions, WM MD in the frontal regions that initially appeared significantly associated to ToM deficit in PD, was no longer so. The bilateral frontal cortices are also defined as neural correlates of executive functions [12,20,21]. As we hypothesised, the prefrontal and medial frontal clusters may mostly represent the influence of executive functions on ToM. The strength of the correlation between ToM deficit and WM in PD remained significant mainly in WM tracts adjacent to the parietal lobe and precuneus. The most significant cluster region in the correlation between ToM impairment and the MD of WM in PD even when controlling for executive functions, was found in the right superior longitudinal fasciculus. Studies in autism disorder concluded that WM alterations in the right superior longitudinal fasciculus [54] could be related to ToM impairment [52,54]. Despite the relationship between ToM and executive functions, both cognitive functions showed different cerebral correlates, therefore, ToM should be considered as an independent cognitive function, and ToM deficits cannot be only understood as a consequence of executive dysfunction.

One possible interpretation for the effects that are lost when executive functions are controlled may also be due to the executive functions per se, rather than to their influence on ToM. Executive functions may be part of ToM but may also be acting as a confounding variable. Furthermore, studies have demonstrated different patterns of brain volume decrease among PD patients with normal cognition, PD patients with mild cognitive impairment and demented PD patients [55,56]. Despite PD group in this study showed cognitive impairment in some cognitive functions, there may be variability in the cognitive profile among PD patients in the sample and a more extensive neuropsychological battery is needed to better characterise the cognitive status of each PD patient and the associated cerebral characteristics. Future studies should assess the different neuroanatomical correlates of ToM comparing PD patients with and without mild cognitive impairment and demented PD patients.

PD patients in this study were at relatively early Hoehn and Yahr stages of the disease, so results also reinforce the prompt appearance of ToM deficit in the disease [3,7,17]. Focusing on cerebral differences between patients and healthy controls, reduced GM volume mainly in the

temporal lobe but also in the parietal and occipital lobes was found in PD patients, as reported before [44,57]. On the other hand, exploratory analysis showed slight WM differences between groups. PD patients in this study showed FA reduction in the uncinate tract, which has been related to less WM integrity [19]. In addition, PD patients showed no significant differences with healthy controls group in MD (membrane density) as suggested in previous studies [58], and neither in RD (axonal demyelination) nor AD (axonal injury) indexes. The literature suggests that WM impairment in PD occur with the progression of the disease [9,55], and that this deterioration can be detected in PD patients at moderate stages of the disease [9,55,59]. A strong correlation between ToM deficit and WM in PD was obtained. Hence, with the progression of the disease, WM differences between groups would very likely be accentuated, and the association between ToM impairment and WM disruption might be stronger. Further studies are needed to assess WM integrity and diffusivity in PD patients at both primary and later stages of the disease.

No significant correlations were found between ToM and GM or WM in heathy control group. We relate the absence of correlation between ToM performance and brain characteristics in healthy adults to the small sample size, the ceiling effect of Happe test found in our sample and consequently, the reduced variability of the data. Firstly, the small sample size makes more difficult to reach the significant level in statistical analysis. Secondly, answers in Happe test are scored between 0 and 2, and most of the healthy participants of the sample scored 7 points (maximum punctuation of 8), producing a ceiling effect. These two facts bring a reduced variability of the data. The reduced variability of the data, added to the preservation of the cerebral characteristics in healthy control group, may be the reasons for not findings significant relationships between ToM performance and GM and WM.

An important issue to consider is that GM correlates of ToM in PD and WM differences between groups were reported with uncorrected results. However, we calculated the effect sizes (Cohen's *d* and r) of the results to support these findings. Uncorrected results reflected medium-large effect sizes which brings a useful indicator of the clinical importance of these results [49]. Moreover, the study included a minimum extended cluster K>20 voxels in neuroimaging analyses to consider results as significant findings, reducing the probability of reporting false positives in the results. Another limitation of the study is that executive functions were assessed with Verbal Fluency Test and Clock Drawing Test (order), two cognitive tests that measure executive functions in different ways, however, another test would be more representative for assessing this cognitive function, such as the Wisconsin card sorting Test (WCST) or the Tower of London Test. Despite this limitation, both tests showed a high internal consistency (Cronbach´s alpha = .747). Finally, ToM has also been related to clinical symptoms such as depression and quality of life in PD patients, future studies should also assess this relationship and test the possible moderation effects of depression in the relationship between ToM and cerebral correlates.

The lack of differences between groups in WM lesions, assessed with the Fazekas scale [27], allows us to attribute WM dysfunction in PD to the neurodegenerative process and not to vascular risk. Other studies [9,57] emphasise the use of WM hyperintensities as a covariate if differences existed between groups, to report more accurate results. However, we measured WM lesions using a T1-weighted sequence.

To summarise, the present study reinforces the presence of ToM impairment from the early Hoehn and Yahr stages of PD, and the findings suggest associations with WM integrity and with GM volume. Specifically, GM volumes in the prefrontal cortex, precentral gyrus and somatosensory cortex showed potential relationships with ToM deficit in PD. In addition, the WM in the right superior longitudinal fasciculus and corticospinal tract (adjacent to the parietal lobe), and WM tracts adjacent to the orbitofrontal cortex were related to ToM deficit in PD.

However, after controlling for executive functions in the regression analysis, the associations of prefrontal regions with ToM deficit were no longer significant. This may suggest that the frontal component of ToM is due to the influence of executive functions and that "pure ToM" is related to the precuneus and parietal lobe.

Preserved ToM performance is essential for developing healthy social relationships and it is thought to have an impact on a patient´s quality of life. The study of ToM deficit in PD and its cerebral correlates increases our knowledge and may help in identifying more effective treatments to rehabilitate this function. Future studies with larger samples are needed to deeply explore the neuroanatomical correlates of ToM deficit in PD and the mediating effects of executive functions and working memory on ToM performance.

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Author Contributions

Conceived and designed the experiments: NIB NO JP. Performed the experiments: MDC NIB NO JP ACZ MAGB JCGE. Analyzed the data: MDC JP ACZ. Wrote the paper: MDC NIB NO JP ACZ MAGB JCGE. Preparation of the first draft: MDC.

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Dynamic functional connectivity in Parkinson's disease patients with mild cognitive impairment and normal cognition

María Díez-Cirarda[a], Antonio P. Strafella[b,c], Jinhee Kim[b,c], Javier Peña[a], Natalia Ojeda[a], Alberto Cabrera-Zubizarreta[d], Naroa Ibarretxe-Bilbao[a,*]

[a] Department of Methods and Experimental Psychology, Faculty of Psychology and Education, University of Deusto, Bilbao, Basque Country, Spain
[b] Research Imaging Centre, Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health, University of Toronto, Toronto, Ontario, Canada
[c] Division of Brain, Imaging and Behaviour – Systems Neuroscience, Krembil Research Institute, UHN, University of Toronto, Ontario, Canada
[d] OSATEK, MR Unit, Hospital of Galdakao, Galdakao, Basque Country, Spain

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ABSTRACT

The objective was to assess dynamic functional connectivity (FC) and local/global connectivity in Parkinson's disease (PD) patients with mild cognitive impairment (PD-MCI) and with normal cognition (PD-NC).

The sample included 35 PD patients and 26 healthy controls (HC). Cognitive assessment followed an extensive neuropsychological battery. For resting-state functional MRI (rs-fMRI) analysis, independent component analysis (ICA) was performed and components were located in 7 networks: Subcortical (SC), Auditory (AUD), Somatomotor (SM), visual (VI), cognitive-control (CC), default-mode (DMN), and cerebellar (CB). Dynamic FC analysis was performed using the GIFT toolbox. FC differences between groups in each FC state were analysed with the network-based statistic (NBS) approach. Finally, a graph-theoretical analysis for local/global parameters was performed.

The whole sample showed 2 dynamic FC states during the rs-fMRI. PD-MCI patients showed decreased mean dwell time in the hypo-connectivity state ($p = 0.030$) and showed increased number of state transitions ($p = 0.007$) compared with the HC. In addition, in the hypo-connectivity state, PD-MCI patients showed reduced inter-network FC between the SM-CC, SM-VI, SM-AUD, CC-VI and SC-DMN compared with the HC ($p < 0.05$-FDR). These FC alterations in PD-MCI were accompanied by graph-topological alterations in nodes located in the SM network ($p < 0.001$). In contrast, no differences were found between the PD-NC and HC.

Findings suggest the presence of dynamic functional brain deteriorations in PD-MCI that are not present in PD-NC, showing the PD-MCI group dynamic FC dysfunctions, reduced FC mostly between SM-CC networks and graph-topological deteriorations in the SM network. A dynamic FC approach could be helpful to understand cognitive deterioration in PD.

1. Introduction

Cognitive deficits in Parkinson's disease (PD) patients are common from early to moderate stages (Aarsland et al., 2009; Elgh et al., 2009) and up to 80% of the patients may develop dementia in the course of the disease (Hely et al., 2008). Moreover, the presence of cognitive impairment is related to a reduction in quality of life and functional disability in PD (Leroi et al., 2012; Rosenthal et al., 2010).

Magnetic resonance imaging (MRI) studies have shown that cognitive deficits in PD patients are correlated with structural (Duncan et al., 2016) and functional brain dysfunctions (Christopher and Strafella, 2013; Gao and Wu, 2016). More specifically, resting-state functional MRI (rs-fMRI) is a non-invasive method that shows reliability and high reproducibility to easily explore the functional activity of the different brain networks (Biswal et al., 2010; Van Den Heuvel et al., 2010). To date, most rs-fMRI studies in PD have investigated functional connectivity (FC) patterns as a static phenomenon. While these studies have shown a general impairment in PD patients compared with healthy controls (HC), [for a review see: (Gao and Wu, 2016)], others have focused on assessing differences between PD patients with mild cognitive impairment (PD-MCI) and with normal cognition (PD-NC). PD-MCI patients seemed to present FC alterations within (Amboni et al., 2015; Baggio et al., 2015; Gorges et al., 2015) and between networks (Baggio et al., 2015) compared with HC, and also compared with PD-

* Corresponding author at: University of Deusto, C/ Universidades 24, 48007 Bilbao, Spain.
E-mail addresses: maria.dcirarda@deusto.es (M. Díez-Cirarda), Antonio.Strafella@camh.ca (A.P. Strafella), jin-hee.kim@camhpet.ca (J. Kim), javier.pena@deusto.es (J. Peña), nojeda@deusto.es (N. Ojeda), acabrera@osatek.net (A. Cabrera-Zubizarreta), naroa.ibarretxe@deusto.es (N. Ibarretxe-Bilbao).

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NC (Baggio et al., 2015; Gorges et al., 2015). Less pronounced FC differences between PD-NC and HC have also been reported (Amboni et al., 2015; Baggio et al., 2015; Gorges et al., 2015).

However, more recently, rs-fMRI studies have shown that FC may actually vary during the acquisition time (i.e. dynamic FC) (Allen et al., 2014; Calhoun et al., 2014; Hutchison et al., 2013). A widely applied method for temporal dynamic FC analysis is the sliding time window method (Allen et al., 2014; Damaraju et al., 2014; Du et al., 2016; Hutchison et al., 2013). This method divides acquired rs-fMRI into windows and calculates the variation of FC across those windows. The results represent the dynamic characteristic of FC. Given that static FC has helped to understand the cerebral correlates of cognitive impairment in PD, a dynamic FC approach may add relevant information as it represents more accurately the dynamic nature of the brain (Calhoun et al., 2014; Hutchison et al., 2013).Therefore, a dynamic approach to study FC may help clarify the neurobiological substrates of presence of MCI in PD. To date, only one dynamic FC study has been recently published in PD, and showed dynamic FC alterations in PD patients compared to HC (Kim et al., 2017).

Furthermore, the characteristics of the brain networks can be investigated with graph-theory, which divides the networks in *nodes* (the brain regions) and in *edges*, representing the connections between the nodes (Bullmore and Sporns, 2009; Van Den Heuvel et al., 2010). Most graph-theoretical studies in PD showed significant reductions in both global and local parameters compared with HC (Göttlich et al., 2013; Koshimori et al., 2016; Luo et al., 2015; Skidmore et al., 2011; Tinaz et al., 2016) but increased graph parameters have also been found in PD compared with HC (Göttlich et al., 2013; Zhang et al., 2015). A graph theory approach may contribute to understanding of cognitive impairment in PD. To date, only one study has assessed the differences in graph parameters between PD-MCI and PD-NC, and found that PD-MCI patients showed decreased graph characteristics compared with PD-NC and HC (Baggio et al., 2014), but also increased graph parameters that correlated negatively with cognitive performance, suggesting the presence of compensatory mechanisms (Baggio et al., 2014).

Despite the fact that some steps have been taken towards understanding the FC differences between PD-MCI and PD-NC, the literature is still scarce and more specific studies are needed in this field. Dynamic FC is a novel FC approach that could add relevant information about the presence of MCI in PD, and the combination with other neuroimaging methods of analysis could help to better understand the neurodegenerative process that underlies cognitive impairment in PD. Therefore, the objective of this study was to assess the dynamic FC and local/global connectivity in PD-MCI and PD-NC using the combination of dynamic FC and graph-theoretical approaches during rs-fMRI.

2. Materials and methods

2.1. Subjects

The sample included 37 PD patients and 26 HC, matched with PD patients by age, gender and years of education. PD patients were recruited from the Department of Neurology at the Hospital of Galdakao and from the PD Biscay Association (ASPARBI). PD patients were enrolled in the study if they fulfilled the UK PD Society Brain Bank diagnostic criteria. Other inclusion criteria were: i) age between 45 and 75; ii) Hoehn and Yahr (H&Y) disease stage (Hoehn and Yahr, 1998) ≤ 3; iii) Unified PD Rating Scale (UPDRS) (Martinez-Martin et al., 1994) evaluated by the neurologist. Exclusion criteria were: i) presence of dementia as defined by the DSM-IV-TR and the Movement Disorders Society clinical criteria; ii) presence of other neurological illness/injury; iii) unstable psychiatric disorders; iv) visual hallucinations as assessed by the Neuropsychiatric Inventory Questionnaire (Kaufer et al., 2000); v) depression evaluated with the Geriatric Depression Scale (GDS) (score > 5) (Yesavage and Sheikh, 1986).

All patients were symptomatically stable, and tested while on their medication. Their Levodopa equivalent daily dose (LEDD) was recorded (Tomlinson et al., 2010).

2.2. Neuropsychological assessment

PD and HC underwent a neuropsychological battery that included the Mini-Mental State Examination (MMSE) as a screening measure (Lobo et al., 2001). Five cognitive domains were assessed: 1) *Attention and working memory* measured with the Digit Span Backward (Pena-Casanova et al., 2009), the Brief Test of Attention (BTA) (Schretlen, 1989), the Trail Making Test (A) (Pena-Casanova et al., 2009) and the Stroop Test (Words and Color) (Golden, 1994); 2) *Executive functions* measured with the Trail Making Test (B) and the Clock Drawing Test (order) (Mainland and Shulman, 2013); 3) *Language* evaluated with the Boston Naming Test (abbreviated version) and the Verbal Fluency Test (semantic); 4) *Memory* assessed with the Hopkins Verbal Learning Test (HVLT) (Brandt, 1991) and the Brief Visual Memory Test (BVMT) (Benedict et al., 1996); 5) *Visuospatial ability* measured with the subtest Incomplete letters from the Visual Object and Space Perception (VOSP) (Rapport et al., 1998) and the subtest cube analysis from the VOSP.

Classification for PD-MCI followed Level II of Movement Disorders Society Task Force criteria corresponding to a comprehensive assessment (Litvan et al., 2012). PD patients that showed impairment in two tests within a single cognitive domain or impairment in at least two tests in different cognitive domains were classified as PD-MCI. PD scores were considered impaired when the score was 1.5 standard deviations (SD) below the mean of the matched HC group. PD patients who failed to meet these specific criteria were classified as PD-NC.

2.3. Neuroimaging acquisition

Imaging data were acquired in a 3 T MRI scanner (Philips Achieva TX) at OSATEK, Hospital of Galdakao. All sequences were acquired during a single session. T1-weighted images acquisition were obtained in a sagittal orientation (TR = 7.4 ms, TE = 3.4 ms, matrix size = 228 × 218; flip angle = 9°, FOV = 250x250mm, slice thickness = 1.1 mm, 300 slices, voxel size = 0.98 × 0.98 × 0.60 mm, acquisition time = 4′55″).

The rs-fMRI was obtained in an axial orientation in an anterior-posterior phase direction using sequence sensitive to blood oxygen level dependent (BOLD) contrast and multi-slice gradient echo EPI sequence (TR = 2100 ms, TE = 16 ms, matrix size = 80 × 78, flip angle = 80°, FOV = 240x240mm, slice thickness = 3 mm, slice gap = 0.25 mm, 214 volumes, 40 slices, voxel size = 3.00 × 3.00 × 3.00 mm, acquisition time = 7′40″).

Rs-fMRI data were acquired during a so-called resting-state block. Subjects were instructed to neither engage in any particular cognitive nor motor activity, to keep their eyes closed without thinking about anything in particular and they were told they could not fall asleep. Once the rs-fMRI acquisition terminated, the participant was asked whether they had fallen asleep or not. No patient reported having fallen asleep. Foam padding and headphones were used to limit head movement and reduce scanner noise for the subject.

2.4. Neuroimaging preprocessing

Preprocessing for rs-fMRI data was performed using the Conn Functional Connectivity Toolbox 14.p (Whitfield-Gabrieli and Nieto-Castanon, 2012). All preprocessing steps were conducted using the default preprocessing pipeline for volume-based analysis (to MNI-space). Three volumes were acquired previous to the 214 volumes of the rs-fMRI acquisition and were then discarded prior to the analysis. First, each subject's 214 functional images were realigned to the first volume and unwarped (which implements the removal of dynamic EPI distortions, movement-by-susceptibility interactions as described in http://www.fil.ion.ucl.ac.uk/spm/toolbox/unwarp/), slice-timing

corrected (interleaved botton-up), co-registered with structural data, spatially normalized into the standard MNI space (Montreal Neurological Institute) and finally images were smoothed using a Gaussian kernel of 6 mm FWMH. Moreover, noise was reduced via the anatomical CompCor approach, which extracts principal components from white matter and cerebrospinal fluid time series. These components were added as confounds in the denoising step of the CONN toolbox. The six head motion parameters derived from spatial motion correction were also added as cofounds. As recommended band-pass filtering was performed with a frequency window of 0.008 to 0.09 Hz (Weissenbacher et al., 2009). Linear detrending was additionally performed.

2.5. Group ICA

After preprocessing the data, Group ICA of fMRI Toolbox (GIFT) was used to decompose the data into functional networks using group spatial independent component analysis (ICA) (Calhoun et al., 2001). First, subject-specific data was reduced to 120 independent components (ICs) with the principal component reduction as previously done (Allen et al., 2014; Damaraju et al., 2014). In a second step group-data was reduced to 100 ICs with the expectation maximization algorithm (Roweis, 1998). To ensure stability and validity we repeated 20 times the Infomax ICA algorithm in ICASSO (Himberg et al., 2004). Aggregated spatial maps were estimated. The back reconstruction approach (GICA) was used to obtain subject-specific maps and time courses as implemented in GIFT software (Calhoun et al., 2001). Visual inspection and the spatial correlation values between ICs and the template were used for ICs selection (Shirer et al., 2012), based on the FC atlas networks of mialab (http://mialab.mrn.org/data/index.html), according to these 7 categories: Subcortical (SC), Auditory (AUD), Somatomotor (SM), visual (VI), cognitive-control (CC), default-mode (DMN), and cerebellar (CB) networks (Allen et al., 2014). Components were classified as intrinsic connectivity networks (ICNs) if they exhibited peak activations in grey matter, high correlation values with resting-state networks, and had time courses dominated by low-frequency fluctuations (Cordes et al., 2000). This process resulted in 29 ICs out of the 100 ICs obtained, divided in: 2 ICs in the SC network, 2 ICs in the AUD network, 5 ICs in the SM network, 5 ICs in the VI network, 6 ICs in the CC (which included the salience network and language network), 7 ICs in the DMN and 2 ICs in the CB network (see Fig. 1; Supplementary Table 1).

After ICs selection, subject-specific spatial maps and time courses were post-processed, following (Allen et al., 2014), and included a

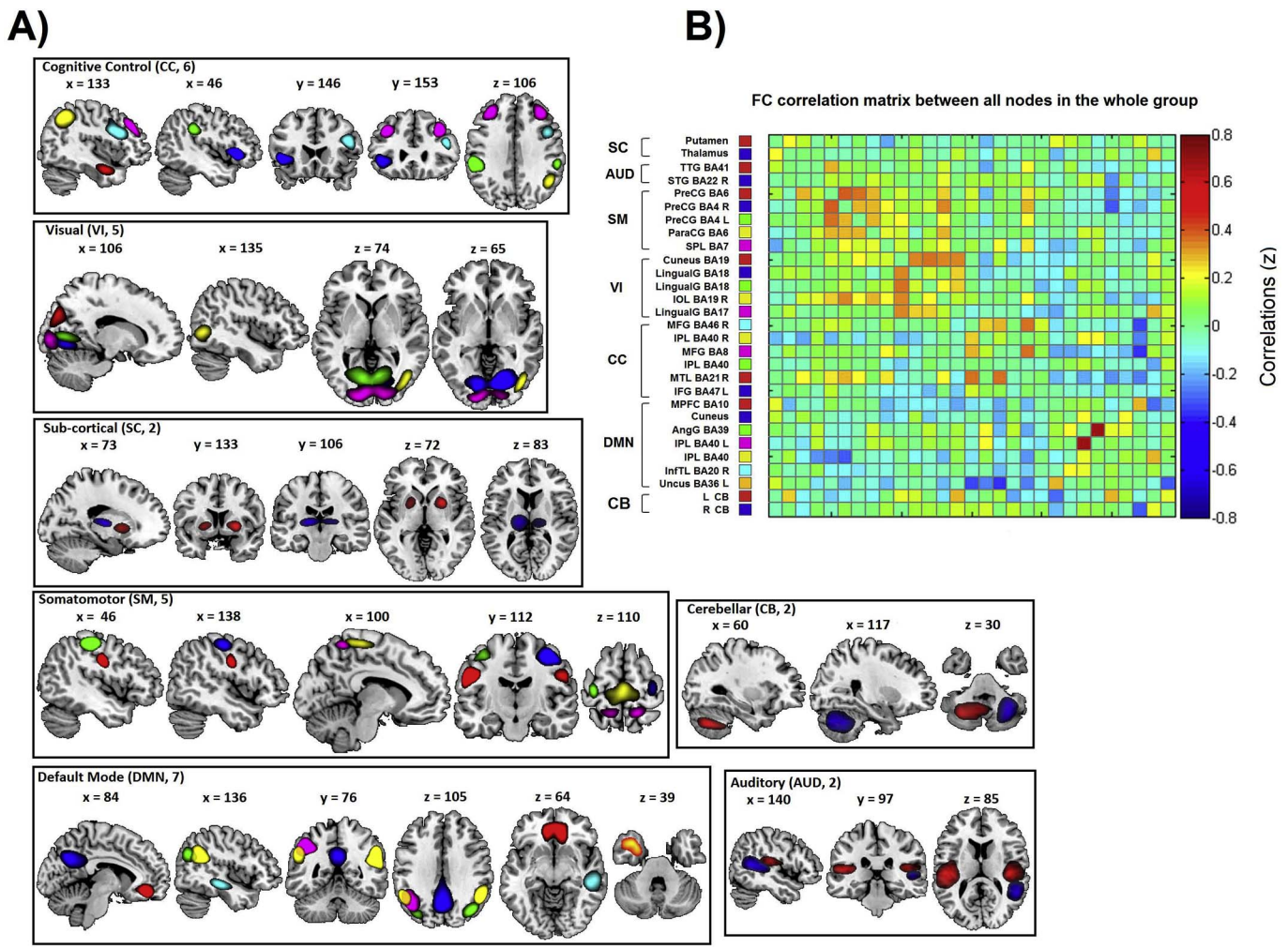

Fig. 1. Spatial Maps from the ICs (A) and the static FC between them in the whole sample (B)
A) Spatial Maps from the 29 Independent Components (ICs) and B) the static FC between them in the whole sample. 29 ICs are divided in 7 networks. Each IC has a specific color in A) which corresponds to the color in B). Each ICs in B) have a specific label, which represents bilateral activations unless it is specified Left (L) or Right (R). The colorbar represents the value of the correlations; Red color represents positive correlations, Blue color represents negative correlations. BA = Brodmann Area; TTG = transverse temporal lobe; STG = superior temporal gyrus; PreCG = precentral gyrus; SPL = superior parietal lobe; LingualG = lingual gyrus; IOL = inferior occipital lobe; MFG = middle frontal gyrus; IPL = inferior parietal lobe; MTG = middle temporal lobe; IFG = inferior frontal gyrus; MPFC = medial prefrontal Cortex; AngG = angular gyrus; InfTL = Inferior temporal lobe; CB = Cerebellum. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 1
Sociodemographic and clinical characteristics of the sample.

	HC $n = 26$	PD-NC $N = 12$	PD-MCI $N = 23$	Statistic	p
Age	68.31 (7.52)	65.17 (8.31)	69.17 (4.48)	F = 1.44	0.243
Gender (male)	69%	50%	56%	$\chi^2 = 1.42$	0.489
Education (years)	11.31 (4.73)	12.50 (4.33)	9.22 (4.64)	H = 3.68	0.159
MMSE	28.85 (1.31)	28.67 (1.30)	26.86 (2.10)	H = 18.87	< 0.001
FD	0.18 (0.07)	0.18 (0.06)	0.19 (0.08)	H = 0.463	0.793
UPDRS III	–	18.45 (6.91)	22.65 (11.08)	$t = 1.31$	0.259
H&Y	–	1.79 (0.39)	1.93 (0.50)	$\chi^2 = 1.79$	0.782
Disease duration (years)	–	5.93 (5.88)	7.11 (5.67)	U = 108.00	0.294
LEDD	–	548.85 (459.64)	904.52 (518.54)	$t = -2.05$	0.054

All values are expressed in mean (SD).
HC = healthy controls; PD-NC = PD patients with normal cognition; PD-MCI = PD patients with mild cognitive impairment; MMSE = Mini-Mental State Examination; FD = Framewise displacement; UPDRS-III = Unified Parkinson's Disease Rating scale, Motor Score; H&Y = Hoehn and Yahr stages; LEDD = Levodopa Equivalent Daily Dose.

detrending, a filter cutoff of low frequency fluctuation set at 0.15, and despiking. Head movement effect was regressed out to obtain more accurate results.

2.6. Motion correction

To minimize the impact of head motion in the connectivity results, maximum displacement and mean frame displacement (FD) were calculated. Subjects were excluded if the maximum displacement (absolute value) in translation indexes x, y, or z was higher than 3.0 mm and in rotation indexes was higher than 3.0° (Chen et al., 2016). No subject was excluded due to this criterion. Moreover, mean frame displacement (FD) was calculated for each subject using the published formula (Power et al., 2012). Subjects with a mean FD of > 0.5 mm were excluded from the analysis. Two PD subjects were excluded from the analysis due to this criterion. Therefore, the analyses were carried out with 35 PD patients and 26 HC. Mean FD values for each group are included in Table 1.

2.7. Dynamic FC analysis

Dynamic FC analysis was performed with the GIFT toolbox. A sliding time window of 22 TR method for each subject was applied (Allen et al., 2014), with a Gaussian window alpha value of 3, and a step between windows of 1 TR, resulting in the analysis of 192 windows. Due to the short time segments that could have insufficient information, the regularized inverse covariance matrix was used (Varoquaux et al., 2010). All the dynamic functional networks connectivity windows across all subjects were used to estimate the FC states. To do so, k-means clustering analysis was repeated 100 times to obtain the unbiased initial cluster, and was used to cluster the dynamic FC windows. K-means clustering applies Euclidean distance to regroup similar FC matrices of the different windows. The number of clusters (k) can be calculated in several ways. In this study we used the elbow criterion following previous dynamic FC studies (Allen et al., 2014; Damaraju et al., 2014) and the cluster number was set to 2. We used the Pearson correlation coefficient for clustering analysis, which is also the most widely used FC measure in rs-fMRI studies (Chang and Glover, 2010; Damaraju et al., 2014; Handwerker et al., 2012; Hutchison et al., 2013; Sakoğlu et al., 2010).

Indexes from dynamic FC were used to test differences between groups: 1) *Mean dwell time* defined as the number of consecutive windows in a specific state, or time that the subjects remain in the one FC state (Allen et al., 2014); 2) *Number of transitions between states or state transition* was calculated counting the total number of changes between states for each subject, and the differences between groups were assessed with two-sample t-test in the Statistical Package for Social Science (SPSS) (IBM SPSS Statistics 22).

In addition, FC differences between groups in each FC state were analysed with the network-based statistic (NBS) approach (Zalesky et al., 2010). The nodes were specified with the peak coordinates of each IC and the edges were represented with the correlation values in Z-scores. A nonparametric permutation approach (15,000 permutations) is applied. In each permutation, the group to which each subject belongs was randomly exchanged, and the statistical test is recalculated in each permutation in order to test the null-hypothesis. Then, p value was calculated FDR corrected for multiple comparisons.

2.8. Graph-theory parameter analysis

The Brain Connectivity Toolbox (BCT) (https://sites.google.com/site/bctnet/) was used to analyse the graph characteristics (both global and local aspects) of the networks obtained based on the ICs resulting from the ICA analysis. To ensure the same number of edges in the graphs from the different groups, a sparsity threshold needs to be fixed (Achard and Bullmore, 2007; Stam, 2014). Sparsity value was defined as the number of connections between nodes in a network divided by the total possible connections in that network. We selected sparsity of 0.34 to maximise global and local efficiency (Achard and Bullmore, 2007).

The global parameters (Bullmore and Sporns, 2009; Wang et al., 2011) assessed were: 1) *Global efficiency* defined as the efficiency of the network to transmit the information through the network; 2) *Clustering coefficient* of a network defined as the mean of clustering coefficients of each node in the network.

The local parameters assessed (Bullmore and Sporns, 2009; Wang et al., 2011) were: 1) *Local efficiency* defined as the efficiency of transmission of information from one node to other close nodes; 2) *Clustering coefficient* defined as the number of existing connections divided by the maximum number of possible connections; 3) *Betweenness centrality* reflected the relevance of a node in a network, and was defined as the number of shortest connections between two other nodes that should go through that node.

Graph-theoretical parameter analyses were adjusted with Bonferroni correction considering the number of intergroup comparisons.

2.9. Ethics statement

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

2.10. Statistical analyses

The SPSS 22.0 was used to perform statistical analyses. Demographic, clinical and behavioral variables were tested for normality using the Shapiro-Wilk test. Sociodemographic differences between groups were tested with the Analysis of Variance (ANOVA) or Kruskal-Wallis test for 3-group comparisons and 2-tailed t-test or U-Mann Whitney for 2-group comparisons and chi-squared test for qualitative variables.

Regarding neuroimaging analysis, differences between groups were performed including age as covariate, following previous

Table 2
Group differences in cognitive domains.

	HC $n = 26$	PD-NC $n = 12$	PD-MCI $n = 23$	F	p^*
Attention and working memory	0.32 (0.71)	0.27 (0.44)	− 0.56 (0.82)	4.24	0.019
Memory	0.42 (0.63)	0.24 (0.33)	− 0.87 (0.49)	17.59	< 0.001
Executive functions	0.34 (0.34)	0.40 (0.33)	− 0.83 (0.96)	10.54	< 0.001
Language	0.43 (0.84)	0.24 (0.73)	− 0.76 (0.69)	4.78	0.012
Visuospatial	0.39 (0.26)	0.16 (0.34)	− 0.57 (0.83)	7.94	0.001

Values are expressed in Z scores, mean (standard deviation).
HC = healthy controls; PD-NC = PD patients with normal cognition; PD-MCI = PD patients with mild cognitive impairment.
* Significant differences were found between PD-MCI < HC and PD-MCI < PD-NC.

recommendations (Allen et al., 2011). LEDD was also included as covariate when assessing the differences between PD-MCI and PD-NC, due to its influence in fMRI signal (Mattay et al., 2002). Statistical differences between groups were performed using two sample *t*-tests. Finally, effect size was calculated with Cohen's *d*, considering 0.2, 0.5 and 0.8, small, medium and large effect sizes respectively (Hojat and Xu, 2004).

3. Results

3.1. Sociodemographic and cognitive characteristics of the sample

Twenty-three PD patients were classified as PD-MCI and 12 PD patients as PD-NC. Sociodemographic, clinical and disease characteristics of the sample are shown in Table 1. In addition, mean values of each cognitive domain and statistical differences between groups are shown in Table 2. Post-hoc analyses revealed significant impairment in all the cognitive domains assessed in the PD-MCI group compared with the PD-NC and HC (see Table 2).

3.2. Dynamic FC differences

Following the elbow criterion, the whole sample showed 2 different states during the rs-fMRI acquisition (see Fig. 2). State 1 (22% of the windows) was characterized by the presence of stronger connectivity, with positive correlation between SM and VI networks, and anti-correlations between CC, DMN and CB; State 2 (78% of the windows) was characterized by weaker connectivity within and between networks, showing some modularity in SM, VI and DMN (see Fig. 2). PD-MCI patients showed significantly reduced mean dwell time in state 2, characterized by weaker connectivity, compared with the HC ($t = 2.14$; $p = 0.030$; Cohen'$d = 0.61$) (see Fig. 3). As well, PD-MCI patients showed significantly increased state transition compared with the HC ($t = 2.82$; $p = 0.007$; Cohen'$d = 0.80$) (see Fig. 3). PD-NC patients showed no significant differences in mean dwell time or the number of transitions between states compared with the HC or PD-MCI groups (see Fig. 3).

Additionally, FC differences were calculated between groups in each dynamic FC state. In state 2, significant FC differences between groups were found in PD-MCI patients compared with HC. PD-MCI patients showed reduced inter-network connectivity compared with the HC group (see Table 3, Fig. 4). Connectivity reductions were found mostly between the SM and CC networks, but SM-VI, SM-AUD, CC-VI and SC-DMN reductions were also found in PD-MCI compared with the HC (see Table 3, Fig. 4). We found no significant differences in state 1 between PD-MCI and HC and no significant differences were found between any other groups.

3.3. Graph topological parameters

Results revealed that PD-MCI patients showed a reduced *clustering coefficient* in the right precentral gyrus (BA4; SM) compared with the HC ($t = 3.54$; $p < 0.001$; Cohen'$d = 1.03$). As well, PD-MCI patients also showed reduced *betweenness centrality* in the left paracentral gyrus (BA6; SM) compared with PD-NC patients ($t = 3.57$; $p < 0.001$; Cohen'$d = 1.03$). We found no significant differences in graph parameters between PD-NC and the HC.

4. Discussion

The aim of this study was to evaluate dynamic FC and local/global connectivity in PD-MCI and PD-NC using the combination of dynamic FC and graph-theoretical approaches during rs-fMRI. Findings suggest dynamic FC alternations in PD-MCI patients during rs-fMRI that were accompanied by graph topological dysfunctions in the SM network and

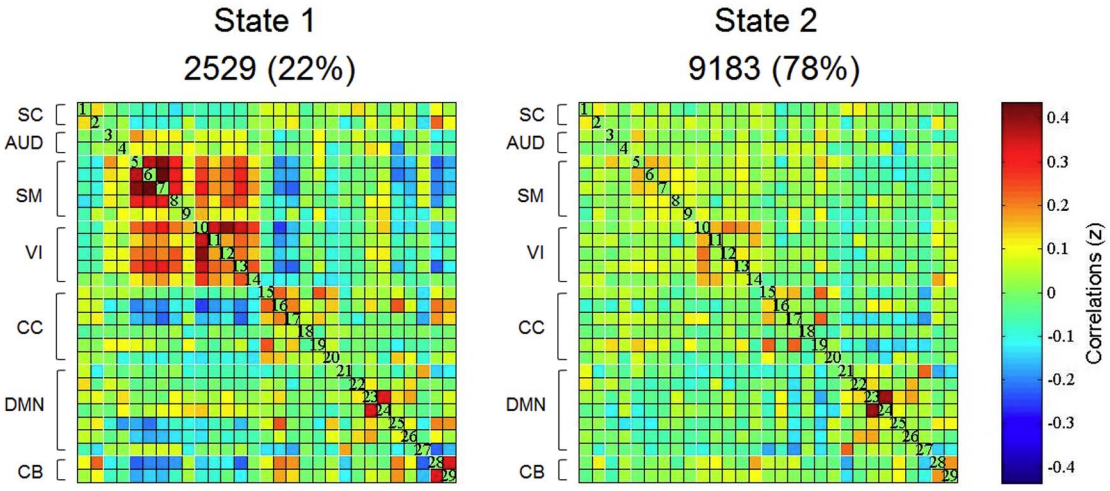

Fig. 2. Dynamic FC states in the whole sample ($k = 2$).
Cluster centroids are shown for each state. The total number of occurrences and the percentage of total occurrences are shown for each state. The color bar represents the value of the correlations: Red color represents positive correlations, Blue color represents negative correlations. SC = Subcortical Network; AUD = Auditory Network; SM = Somatomotor Network; VI = Visual Network; CC = Cognitive Control Network; DMN = Default Mode Network; CB = Cerebellar Network. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

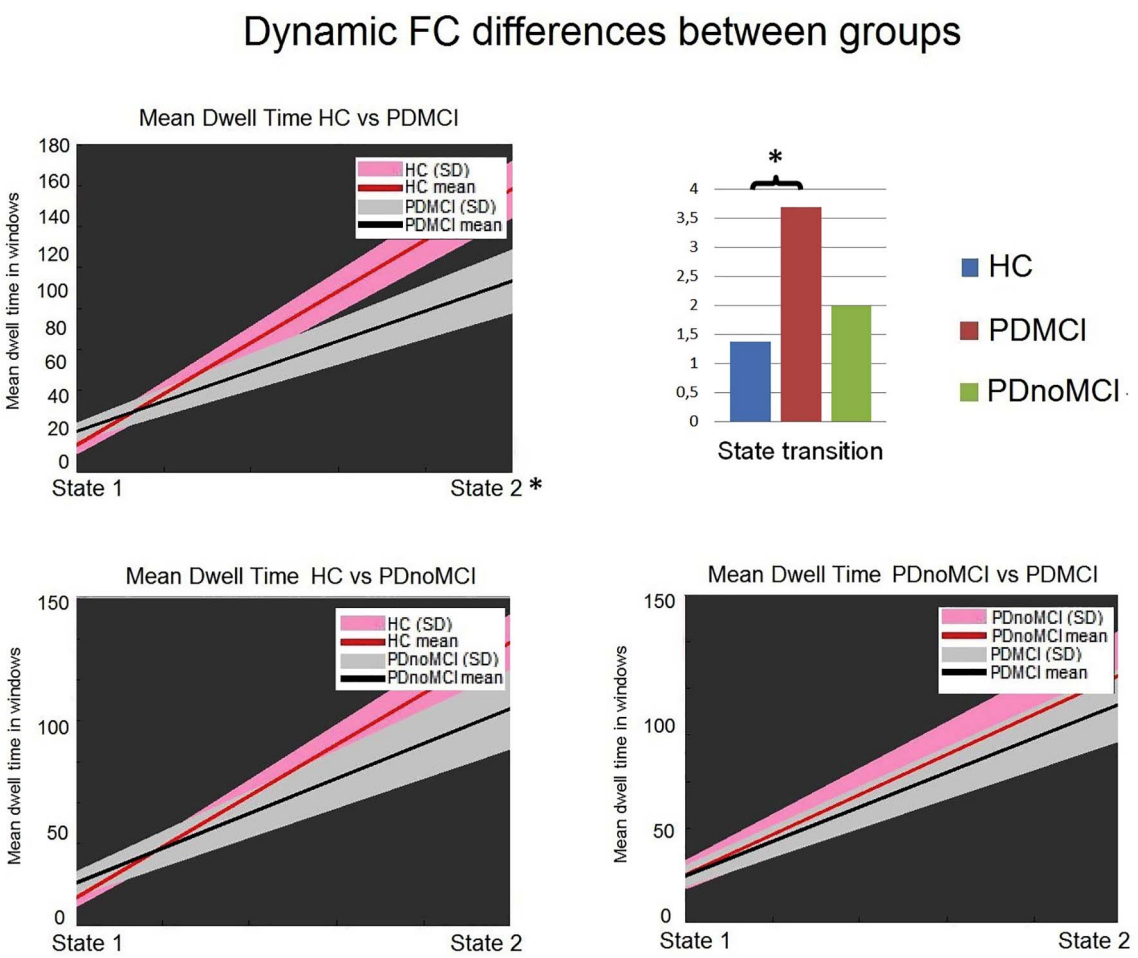

Fig. 3. Dynamic FC differences between groups.
*Significant differences between groups. HC = healthy controls; PD-NC = PD patients with normal cognition; PD-MCI = PD patients with mild cognitive impairment; FC = functional connectivity; SD = Standard deviation.

Table 3
FC reductions in state 2 in PD-MCI compared with HC.

Inter-network connectivity reduction		t*	Cohen'*d*
SM-CC			
BA4R- Precentral gyrus	BA8R- Middle frontal gyrus	3.91	1.11
BA4L- Precentral gyrus	BA8R- Middle frontal gyrus	3.20	0.91
	BA47L- Inferior frontal gyrus	3.29	0.94
BA6L- Paracentral lobe	BA40R- Inferior parietal lobe	3.51	1.00
SM-VI			
BA4R- Precentral gyrus	BA19R- Inferior Occipital Lobe	3.51	1.00
BA6L- Paracentral lobe	BA19R- Cuneus (Occipital Lobe)	3.78	1.08
SM-AUD			
BA6L- Paracentral lobe	BA22R- Superior temporal gyrus	4.38	1.25
CC-VI			
BA8R- Middle frontal gyrus	BA19R- Inferior Occipital Lobe	5.31	1.52
SC-DMN			
Thalamus L	BA36- Uncus (Limbic Lobe)	3.10	0.88

FC = Functional Connectivity; PD-MCI = PD patients with mild cognitive impairment; HC = healthy controls; SM = Somatomotor Network; CC = Cognitive Control Network; VI = Visual Network; AUD = Auditory Network; SC = Subcortical Network; DMN = Default Mode Network; BA = Brodmann area. R = Right; L = Left.
* Results at $p < 0.05$ FDR-corrected.

reduced FC between networks, whereas PD-NC patients showed similar patterns of FC compared with HC.

The whole sample presented two different connectivity states, a hyper-connected state and a hypo-connected state. The sparsely connected state was present 78% of the time. Results showed that PD-MCI patients exhibited dynamic FC alterations compared with the HC. In a recent dynamic FC study in PD, the sample also showed two dynamic FC states, and PD patients significantly spent less time in the hypo-connected state compared to HC group (Kim et al., 2017). Similarly, previous dynamic FC studies have also been performed with schizophrenia patients, and also showed alterations in mean dwell time compared with the HC (Damaraju et al., 2014; Du et al., 2016; Lottman et al., 2017). Specifically, the present study analysed the dynamic FC pattern in PD patients with MCI and with normal cognition. Results showed that PD-MCI patients spent significantly less time in the state characterized by hypo-connectivity compared with the HC. These differences were not found in PD-NC patients. Therefore, findings suggest that the dynamic FC pattern could be associated with the presence of MCI in PD patients. Previous static FC studies in PD also showed a relationship between FC pattern during rs-fMRI and MCI (Amboni et al., 2015; Baggio et al., 2015; Gorges et al., 2015), and the present study suggest that temporal properties of FC in PD could also be related to cognitive performance.

Moreover, PD-MCI patients showed increased number of changes between states compared with the HC. Contrary to PD-MCI patients, there were no dynamic FC significant differences between PD-NC and the HC group, neither in mean dwell time nor state transitions. However, despite not finding significant differences, PD-NC patients showed slight increased state transitions compared to the HC. The previous dynamic FC study in PD subjects without MCI diagnosis showed no significant differences in state transitions compared to HC,

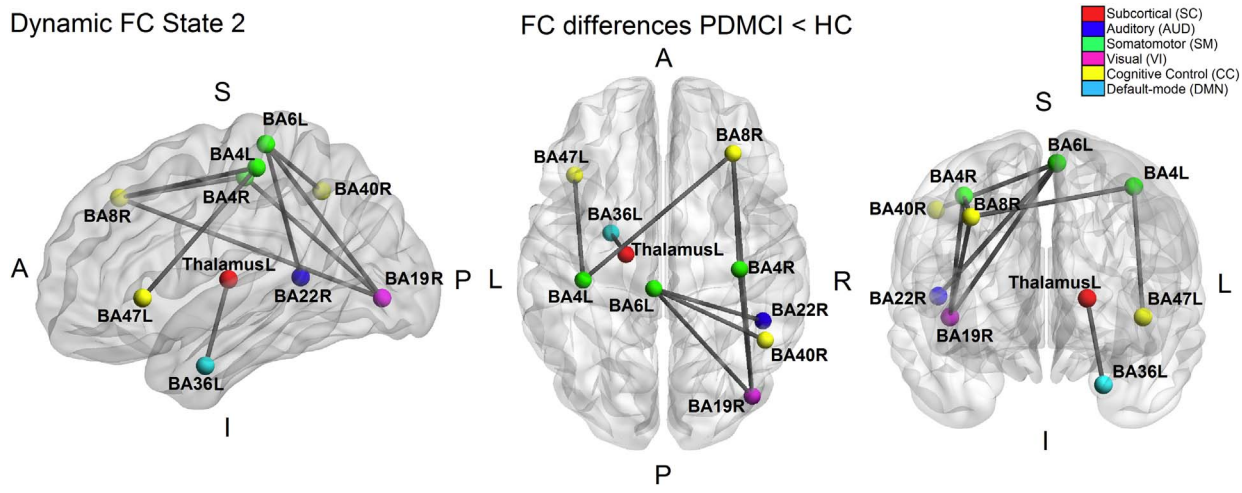

Fig. 4. FC reductions in state 2 in PD-MCI compared with HC.
FC = Functional Connectivity; PD-MCI = PD patients with mild cognitive impairment; HC = healthy controls; BA = Brodmann area. R = Right; L = Left; S = Superior; I = Inferior; P = Posterior.
Results at $p < 0.05$ FDR-corrected.

but the number of transitions was also slightly elevated compared to HC (Kim et al., 2017). Results in both studies might represent a gradual dysfunctional pattern in PD patients that increases with more severe cognitive deterioration. Dynamic FC analysis could add relevant information about the neural substrates of PD-MCI deterioration, and its differences with PD-NC patients.

Furthermore, FC differences between groups in each dynamic FC state were also investigated. PD-MCI patients in this study showed reduced FC in the hypo-connected state compared with the HC, showing reduced inter-network connectivity mostly between the SM and CC networks, but also between the SM-VI, SM-AUD, CC-VI and SC-DMN networks. Previous studies in PD-MCI patients also found reduced FC compared with the HC. Interestingly, reduced FC in PD-MCI has also been found between the precentral gyrus and middle frontal gyrus (in this study: SM-CC) (Baggio et al., 2015), reduced FC between Rolandic operculum and cuneus (in this study: SM-VI) (Göttlich et al., 2013), reduced connectivity between medial frontal lobe and cuneus in PD (in this study: CC-VI) (Göttlich et al., 2013) and reduced connectivity between the medial frontal and occipital lobes in PD-MCI (in this study: CC-VI) (Baggio et al., 2015). The disconnection between networks has only been found in the PD-MCI group, while PD-NC patients showed no significant differences compared with the HC. These results, added to previous results in PD patients with MCI (Amboni et al., 2015; Baggio et al., 2015; Gorges et al., 2015; Lucas-Jiménez et al., 2016), suggest that reduced connectivity is linked to the presence of cognitive deficits in PD patients.

Dynamic FC alterations in PD-MCI patients were accompanied by impairment in graph topological parameters in two nodes located in the SM network (right BA4 and left BA6). Nodes with high level of betweenness centrality are important in a network, due to its crucial role in transferring the information (Bullmore and Sporns, 2009). The reduced betweenness centrality in the node BA6 (left hemisphere) in PD-MCI group suggests a poorer communication between the adjacent nodes in the network. Moreover, the clustering coefficient of a specific node is related with an efficient communication; therefore, PD-MCI patients might show a loss of efficiency when transferring the information in the node BA4 (right hemisphere). Both nodes were located in the SM network and remarkably, most of the reduced FC found in the PD-MCI group, was located between these two nodes and other brain regions. This may suggest that the reduced efficiency when transferring the information in the SM network could have influenced the poorer FC between SM network and other networks in PD-MCI patient.

Graph theoretical analyses could add information to the FC results in order to better understand the neurobiological process of cognitive deterioration in PD. Previous graph theoretical studies in PD also found reduced clustering coefficient (Tinaz et al., 2016) and reduced betweenness centrality (Koshimori et al., 2016) in different nodes of the SM network in PD patients compared with the HC. In the present study, the dysfunctional graph parameters were found in PD-MCI patients and not in PD-NC. A previous study that analysed graph differences between PD-MCI and PD-NC, found graph alterations in PD-MCI patients compared with the HC but not in PD-NC patients (Baggio et al., 2014). Both studies suggest a relationship between cognitive impairment and graph theoretical dysfunctions in PD that are not present in PD-NC. Contrary to results in this study, previous PD studies also found increased graph parameters compared to the HC (Baggio et al., 2014; Göttlich et al., 2013; Zhang et al., 2016). Specifically Baggio et al. (2014) reported that PD-MCI patients showed increased graph characteristics in nodes that normally have lower network relevance, as a compensatory mechanism for the reduced graph parameters found in more important nodes. PD-MCI patients in the present study were older, showed longer disease duration, higher scores on UPDRS III (motor complications) and lower scores on MMSE compared to the PD-MCI patients from the study of Baggio et al. (2014). We hypothesized that all these characteristic differences could be related to the absence of brain compensatory mechanisms found in the PD-MCI sample from this study.

Some limitations of the study must be considered. First, the length of the rs-fMRI acquisition is 7′39″. A recent study suggested that dynamic FC analysis should be performed with rs-fMRI acquisitions of > 10 mins (Hindriks et al., 2016). Also, the TE of the resting-state fMRI acquisition in this study is quite low. In addition, independent monitoring of wakefulness is a more accurate technique to control if any patients fell asleep during the rs-fMRI acquisition. Moreover, all patients from this study were on medication. It would be interesting to analyse dynamic FC in drug-naïve PD patients because of the relevance of PD medication in fMRI signal (Mattay et al., 2002). Moreover, PD-MCI patients were not distinguished between single domain MCI and multiple domain MCI. Future studies should assess the dynamic FC and graph theoretical characteristic differences between PD-MCI subtypes. Finally, longitudinal follow-up assessment would give us information about the dynamic FC progression of PD-MCI and PD-NC patients.

5. Conclusions

This is the first study to assess the dynamic FC characteristics in PD-MCI and PD-NC. Findings suggest that the temporal connectivity

alterations found in PD-MCI such as reduced mean dwell time in the hypo-connected state and reduced state transitions, could be related to the presence of cognitive impairment in PD. Dynamic FC has proven to be a useful approach in the study of PD brain dysfunction, and more research on the disease needs to be done with this technique. Future studies should evaluate the use of dynamic FC to monitor and predict MCI in PD. Moreover, the loss of graph properties in nodes of the SM network could be related to the reduced FC between the SM and other networks in PD-MCI group compared to HC. The combination of neuroimaging approaches such as graph theory and FC analyses could help in the understanding of neurobiological substrates of MCI in PD.

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Conflict of interest

The authors declare no conflict of interest.

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Paper III

Improving functional disability and cognition in Parkinson disease

Randomized controlled trial

OPEN

Javier Peña, PhD
Naroa Ibarretxe-Bilbao, PhD
Inés García-Gorostiaga, MD
Maria Angeles Gomez-Beldarrain, PhD
María Díez-Cirarda, MSc
Natalia Ojeda, PhD

Correspondence to Dr. Ibarretxe-Bilbao: naroa.ibarretxe@deusto.es

ABSTRACT

Objectives: To examine the efficacy of an integrative cognitive training program (REHACOP) to improve cognition, clinical symptoms, and functional disability of patients with Parkinson disease (PD).

Methods: Forty-two patients diagnosed with PD in Hoehn & Yahr stages 1 to 3 were randomly assigned to either the cognitive training group (REHACOP) or the control group (occupational activities) for 3 months (3 sessions, 60 min/wk). Primary outcomes were change on processing speed, verbal memory, visual memory, executive functioning, and theory of mind. Secondary outcomes included changes on neuropsychiatric symptoms, depression, apathy, and functional disability. The trial was registered with clinicaltrials.gov (NCT02118480).

Results: No baseline group differences were found. Bootstrapped analysis of variance results showed significant differences in the mean change scores between the REHACOP group and control group in processing speed (0.13 [SE = 0.07] vs −0.15 [SE = 0.09], $p = 0.025$), visual memory (0.10 [SE = 0.10] vs −0.24 [SE = 0.09], $p = 0.011$), theory of mind (1.00 [SE = 0.37] vs −0.27 [SE = 0.29], $p = 0.013$), and functional disability (−5.15 [SE = 1.35] vs 0.53 [SE = 1.49], $p = 0.012$).

Conclusions: Patients with PD receiving cognitive training with REHACOP demonstrated statistically significant and clinically meaningful changes in processing speed, visual memory, theory of mind, and functional disability. Future studies should consider the long-term effect of this type of intervention. These findings support the integration of cognitive training into the standard of care for patients with PD.

Classification of evidence: This study provides Class II evidence that for patients with PD, an integrative cognitive training program improves processing speed, visual memory, theory of mind, and functional disability. *Neurology*® 2014;83:2167–2174

GLOSSARY

ARR = absolute risk reduction; **CI** = confidence interval; ***DSM-IV-TR*** = *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition, Text Revision); **GDS** = Geriatric Depression Scale; **NNT** = number needed to treat; **NPI-Q** = Neuropsychiatric Inventory–Questionnaire; **PD** = Parkinson disease; **REHACOP** = cognitive rehabilitation program in psychosis; **TOM** = theory of mind; **WHO-DAS II** = World Health Organization Disability Assessment Schedule, version II.

The presence of cognitive impairment, including processing speed, visual and verbal memory, and executive function in Parkinson disease (PD)[1] is currently widely known. Moreover, these deficits have been associated with impairments on the activities of daily living.[2] Because of this association, there have been an increasing number of studies supporting nonpharmacologic interventions for PD. A recent systematic review[3] concluded that the research in this area is very limited and urged for additional controlled studies. Social cognition has been less studied in PD than other cognitive domains. Previous studies nonetheless indicate that patients with PD exhibit impaired theory of mind (TOM).[4]

The efficacy of cognitive training has been previously demonstrated in other pathologies, including traumatic brain injury,[5] dementia,[6] and schizophrenia.[7] The REHACOP was developed in this context, incorporating recent suggestions regarding the strategy of learning and

Supplemental data at Neurology.org

From the Department of Methods and Experimental Psychology (J.P., N.I.-B., M.D.-C., N.O.), Faculty of Psychology and Education, University of Deusto, Bilbao, Basque Country; and Department of Neurology (I.G.-G., M.A.G.-B.), Galdakao Hospital, Basque Country, Spain.

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transfer techniques.[8] Originally created for schizophrenia and after having demonstrated its efficacy in improving core symptoms refractory to pharmacologic treatment[9] and functional disability, the authors adapted it for the elderly population.

The primary aim was to evaluate the efficacy of cognitive training (REHACOP) in patients with PD for improving processing speed, visual learning and memory, verbal learning and memory, executive functioning, and TOM. The secondary aim was to analyze whether this program would improve clinical symptoms (depression, apathy, and neuropsychiatric symptoms) and functional disability, as previously noted for patients with schizophrenia.[9]

METHODS

Participants. Forty-two outpatients with PD were recruited from the Department of Neurology at Galdakao Hospital and the Parkinson's Disease Association (ASPARBI), both in Biscay, for a collaborative study coordinated by the Department of Methods and Experimental Psychology at the University of Deusto.

A neurologist specialized in movement disorders reached the diagnosis of PD based on the UK PD Society Brain Bank diagnostic criteria for PD.[10] Other inclusion criteria were as follows: (1) age 45 to 75 years; (2) either male or female; and (3) Hoehn & Yahr disease stage 1 to 3 as evaluated by the neurologist. Exclusion criteria were as follows: (1) the presence of dementia as defined by the *DSM-IV-TR*[11] and the Movement Disorders Society specific clinical criteria for PD dementia[12,13]; (2) the presence of other neurologic illness or injury (traumatic brain injury, multiple sclerosis); (3) unstable psychiatric disorders such as schizophrenia or major depression; and (4) the presence of visual hallucinations as assessed by the Neuropsychiatric Inventory–Questionnaire (NPI-Q).[14] All patients were symptomatically stable at the time of recruitment. All patients were provided with pharmacologic treatment and were tested while on their medication.

Standard protocol approvals, registrations, and patient consents. The study protocol was approved by the Ethics Committee at the Health Department of the Basque Mental Health System in Spain. This study was registered at clinicaltrials.gov (registration number NCT02118480). All patients were volunteers who provided written informed consent to participate in the study.

Measures. ***Cognitive evaluation.*** The cognitive battery included assessments to evaluate processing speed, verbal learning and memory, visual learning and memory, and executive functioning. All cognitive measures were converted into *z* scores based on the pooled PD group, and the sign of some measures was adjusted so that higher scores indicated better cognitive performance. All composite cognitive domains maintained satisfactory internal consistency. Processing speed (Cronbach $\alpha = 0.85$) was quantified based on the Trail Making Test–A[15] and Salthouse Letter Comparison Test.[16] For verbal learning and memory ($\alpha = 0.88$), learning and long-term recall performance on the Hopkins Verbal Learning Test[17] (version 2 at baseline and 4 at posttreatment) were utilized. For visual learning and memory ($\alpha = 0.96$), learning and long-term recall performance on the Brief Visual Memory Test[18] (version 1 at baseline and 3 at posttreatment) were used ($\alpha = 0.96$). Executive functioning ($\alpha = 0.78$) was determined based on the Stroop test,[19] using the word-color and interference scores.

Theory of mind. The Happé test[20] was administered to evaluate TOM. Four different stories (concerning double bluff, mistakes, persuasion, and white lies) were administered at baseline and follow-up, and they were summed into a total TOM score with a possible range of 0 to 8. Higher scores indicate better TOM.

Premorbid IQ and cognitive reserve. The Accentuation Reading Test (TAP),[21] the Spanish version of the National Adult Reading Test, was included to estimate patients' premorbid IQ. The scale ranged from 0 to 30. Cognitive reserve was estimated using the Cognitive Reserve Questionnaire.[22] This 15-item multiple-choice questionnaire includes questions about education/culture, working activity, leisure and hobbies, physical activities, and social activities. Higher scores indicate a better cognitive reserve, and the scale ranged from 0 to 26.

Global cognitive status. The Mini-Mental State Examination[23] was administered to obtain a general mental status score.

Medication use. Medications, dosages, and dose frequencies were used to calculate the levodopa equivalent daily dose (mg/d).[24]

PD assessment. The Unified Parkinson's Disease Rating Scale[25] and the Hoehn & Yahr scale were used for the assessment of the course and stage of the disease.

Depressive symptoms. Geriatric Depression Scale (GDS)[26] includes 15 items. Higher scores represent a higher degree of depression (range from 0 to 15).

Neuropsychiatric symptoms. The NPI-Q[14] was administered to evaluate neuropsychiatric symptoms. The test includes 10 items (delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, euphoria, apathy, disinhibition, irritability, and aberrant motor behavior). These subscales were summed into a total score with a possible range of 0 to 120. Higher scores indicate more frequent and severe neuropsychiatric symptoms.

Apathy. The Lille Apathy Rating Scale[27] consists of 33 items, including 9 subscales (everyday productivity, interests, taking initiative, novelty seeking/motivation, emotional responses, concern, social life, and self-awareness). These subscales were summed into a total apathy score with a possible range of −36 to 36. Lower scores indicate less apathy.

Functional disability. Functional disability was self-administered using the World Health Organization Disability Assessment Schedule II (WHO-DAS II), short version (12 items).[28]

Study outcome measures. The primary outcome measures were the change in mean processing speed, verbal memory, visual memory, executive functioning, and TOM total scores from baseline to the end of treatment.

The secondary outcome measures included change in mean NPI-Q, GDS, apathy, and WHO-DAS II scores from baseline to the end of treatment.

Procedure. A priori power analyses were conducted to determine the sample size based on a previous study that used REHACOP.[9] A sample size of 44 subjects, 22 in each group, was sufficient to attain an effect size of 0.88 to detect a difference in neurocognitive deficits between groups, with 80% power and a 5% level of significance. The study design was a parallel-group randomized trial with equal randomization. Recruitment and enrollment were conducted between June 2012 and January 2013. Patients were offered participation in the study via the neurologist and ASPARBI. Afterward, the participants were randomly allocated to either the REHACOP group or the control group (see figure 1). Assignment to the program was conducted on the basis of a computer-generated randomization of the list of participants. Posttreatment assessment (finished by June 2013) was performed within the first week after

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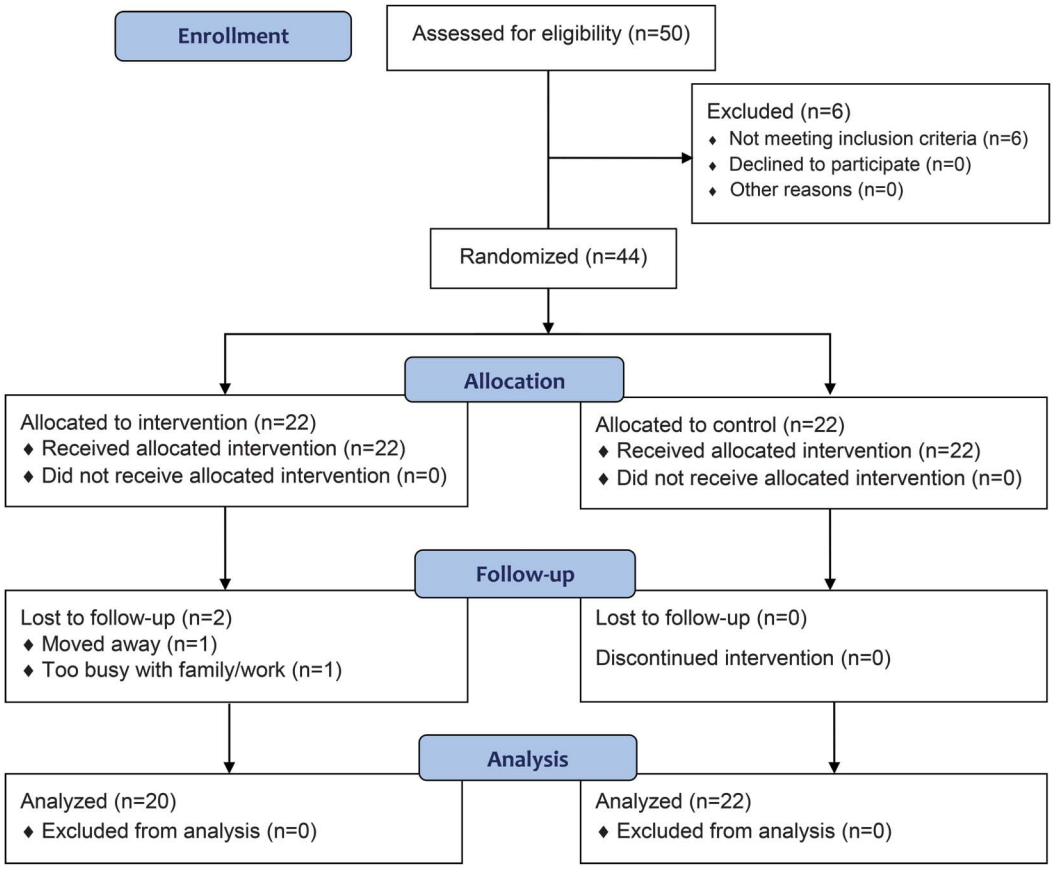
Figure 1 CONSORT flow diagram



CONSORT = Consolidated Standards of Reporting Trials.

completing the intervention. All raters were blinded to treatment condition and had no other role in the project that would undermine the blinding. There was an absence of prior relationship between psychologists and participants. Following ethical aspects, the control group was offered participation in a remediation program when the posttreatment assessment was finished.

Intervention. REHACOP is a structured program using paper-pencil tasks[29] (based on restoration, compensation, and optimization strategies of rehabilitation) with a gradual level of cognitive effort and demand. REHACOP trains different cognitive domains, such as attention, memory, processing speed, language, executive functioning, and social cognition. The program also includes one module for functional outcome: activities of daily living.

REHACOP includes up to 300 different tasks hierarchically organized into at least 3 levels of complexity and subtypes of abilities. Several tasks are timed, so processing speed is trained throughout various modules. The therapist moves forward to the next level of difficulty after a basic cognitive strategy has been well acquired. The program format allows for either individual or group sessions (between 5 and 8 patients per group), although for the purpose of this study, group sessions were chosen.

In this study, 2 psychologists conducted the REHACOP group attending 60-minute-long sessions 3 days per week at ASPARBI (2 groups) or the Hospital of Galdakao (1 group). Both psychologists prepared the sessions together, used the same materials and instructions, and received the same training on REHACOP. Specifically, REHACOP group remediation with patients with PD consisted of the following: attention unit (4 weeks) training sustained, selective, alternant, and divided attention; memory unit (3 weeks) focusing on visual and verbal learning, recall, and recognizing memory; language unit (3 weeks) including grammar, syntax, vocabulary, verbal fluency, verbal comprehension, and abstract language; executive functions unit (2 weeks) training cognitive planning, proverbs, and analogies; and social cognition unit (1 week) exercising TOM, social reasoning, and moral dilemmas.

The control group consisted of occupational group activities conducted by a psychologist at ASPARBI. The activities included drawing, reading the daily news, and constructing using different materials (such as paper or wood). These activities were accomplished in a group format and with the same frequency as the implementation of REHACOP in the experimental group.

Analyses. Normality of data was tested using the Kolmogorov-Smirnov test. All variables appeared as normal distributions, with the exception of GDS, which was log-transformed for further analyses. Categorical data were analyzed with the χ^2 test or Fisher exact test, as indicated. Sociodemographic variables, clinical variables, cognition, and functional disability at baseline were compared using 2-tailed *t* tests.

Change scores (posttreatment − baseline) were compared between REHACOP and control group on each of the cognitive, clinical, and functional disability variables with an analysis of variance. To obtain adjusted mean differences in change scores, we used bootstrapping,[30] a resampling technique in which random subsamples are generated from the observed sample. We generated 1,000 subsamples from within each group (with replacement).

Effect size (Cohen *d* and 95% confidence interval [CI]) was calculated based on change score differences between groups. The

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χ^2 test was used to compare the percentage of patients in the 2 groups who disclosed a score improvement after the training.

Number needed to treat (NNT) was calculated on the basis of the number of patients who needed treatment in order to show improvement at various levels of change (10%–30%) compared with a patient who did not receive treatment. Absolute risk reduction (ARR) was calculated as the difference between the control group's and REHACOP group's rate of improvement at various levels of change (10%–30%). The significance level was set at 0.05. All tests were 2-tailed.

Classification of evidence. The primary research question was whether REHACOP could improve performance in processing speed, verbal memory, visual memory, executive functioning, and TOM among patients with early to moderate stages of PD. The secondary research question was whether REHACOP could also alleviate the patients' clinical symptoms and functional disabilities. This study provides Class II evidence that for patients with PD, an integrative cognitive training program improves processing speed, visual memory, social cognition, and functional disability.

RESULTS Forty-two patients completed the posttest assessment, which reflects an attrition rate of 4.54% (figure 1). The sociodemographic and clinical characteristics of the REHACOP and control groups are provided in table 1. Differences between the groups were analyzed to confirm the success of the randomization. There were no significant differences between the groups in age, sex distribution, years of education, Mini-Mental State Examination score, premorbid IQ, cognitive reserve, illness duration, levodopa equivalent daily dose, Unified Parkinson's Disease Rating Scale score, Hoehn & Yahr stage (see table 1). There were no significant differences at baseline in other clinical characteristics (such as apathy, GDS, or NPI-Q), or functional disability (see table 2) or cognitive performance (see table 3). Based on a matched healthy control group (not reported here), 27.3% of patients in REHACOP showed impairment in processing speed at baseline (vs 27.3% in control group, $p = 1$), 68.2% in verbal memory (vs 54.5% in control group, $p = 0.353$), 50% in visual memory (vs 31.8% in control group, $p = 0.220$), 45.5% in TOM (vs 31.8% in control group, $p = 0.354$), and 22.7% in executive functioning (vs 13.6% in control group, $p = 0.434$). Although not significant, the cognitive performance in the control group was consistently better than in the REHACOP group at baseline. Raw scores are shown in table e-1 on the *Neurology*® Web site at Neurology.org. However, 15.4% of patients in REHACOP and 16.4% of patients in the control group showed depressive symptoms.

Seven patients from the REHACOP group diminished medication (vs 8 from the control group) and 2 needed to increase the medication (vs 3 from the control group). These differences were not significant (Fisher exact test = 0.39, $p = 1$).

The bootstrapped F test between the REHACOP and control groups for mean change scores was

Table 1 Participant characteristics at baseline

	REHACOP group (n = 22)		Control group (n = 22)		
		SD		SD	p
Age, y	67.55 (65.25–69.84)	5.2	68.13 (64.93–71.32)	7.5	0.928
Years of education	10.55 (8.29–12.81)	5.1	10.25 (8.17–12.33)	4.9	0.828
Sex, males, n (%)	13 (59.1)		14 (63.6)		0.757
Disease duration, y	5.6 (3.61–7.69)	4.6	7.4 (5.03–9.91)	5.7	0.218
Hoehn & Yahr stage, n (%)					0.474[a]
Stage 1	4 (18.2)		5 (22.7)		
Stage 2	18 (81.8)		15 (68.2)		
Stage 3	0 (0)		2 (9.1)		
UPDRS motor score	21.1 (16.83–25.53)	9.8	22.4 (17.17–27.70)	12.2	0.748
UPDRS total score	33.6 (27.43–39.66)	13.8	39.0 (30.14–47.86)	20.4	0.258
LEDD	699.0 (519.5–878.6)	405.0	876.7 (613.8–1139.5)	607.8	0.336
MMSE	27.4 (26.58–28.14)	1.7	26.7 (25.17–28.16)	3.5	0.563
TAP	19.9 (16.76–23.06)	6.9	20.9 (17.52–24.32)	8.0	0.413
Cognitive Reserve Questionnaire	12.5 (10.46–14.45)	4.5	12.1 (10.31–13.94)	4.3	0.945
Hypertension, n (%)	7 (31.8)		8 (36.4)		0.750[a]

Abbreviations: LEDD = levodopa equivalent daily dose; MMSE = Mini-Mental State Examination; REHACOP = cognitive rehabilitation program in psychosis; TAP = Test de Acentuación de Palabras (Spanish version of the National Adult Reading Test); UPDRS = Unified Parkinson's Disease Rating Scale.
Data are mean (95% confidence interval), unless otherwise indicated.
[a] Fisher exact test.

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Table 2 Cognitive performance, clinical characteristics, and functional disability in the REHACOP and control groups at baseline and posttreatment

	REHACOP group		Control group	
	Mean (95% CI)	SD	Mean (95% CI)	SD
PS				
Pre	0.03 (−0.29 to 0.37)	0.2	0.37 (0.03-0.70)	0.2
Post	0.16 (−0.17 to 0.50)	0.2	0.17 (−0.12 to 0.55)	0.2
VM				
Pre	−0.05 (−0.47 to 0.38)	0.2	0.19 (−0.22 to 0.58)	0.2
Post	0.13 (−0.30 to 0.57)	0.2	−0.07 (−0.47 to 0.35)	0.2
VSM				
Pre	0.07 (−0.22 to 0.37)	0.1	0.40 (0.11-0.69)	0.2
Post	0.17 (−0.15 to 0.50)	0.1	0.16 (−0.17 to 0.49)	0.1
EF				
Pre	−0.07 (−0.50 to 0.36)	0.2	0.27 (−0.16 to 0.69)	0.2
Post	0.05 (−0.33 to 0.42)	0.2	0.05 (−0.32 to 0.44)	0.2
TOM				
Pre	5.20 (4.38-6.01)	0.4	5.72 (4.95-6.50)	0.4
Post	6.20 (5.47-6.93)	0.4	5.46 (4.75-6.15)	0.3
GDS				
Pre	2.05 (0.84-3.26)	0.6	2.54 (1.38-3.70)	0.7
Post	2.05 (0.56-3.54)	0.7	3.82 (2.40-5.24)	0.7
NPI-Q				
Pre	3.70 (1.94-5.45)	0.8	3.09 (1.41-4.76)	0.6
Post	1.90 (0.72-3.10)	0.6	2.55 (1.41-3.67)	0.6
Apathy				
Pre	−26.95 (−29.4 to −24.5)	1.2	−23.82 (−26.1 to −21.5)	1.1
Post	−27.50 (−29.8 to −25.2)	1.1	−26.95 (−26.8 to −22.5)	1.1
WHO-DAS II				
Pre	20.90 (18.48-23.32)	1.2	19.31 (16.30-22.31)	1.4
Post	15.75 (13.08-18.42)	1.7	19.85 (16.53-23.16)	1.7

Abbreviations: Apathy = Lille Apathy Rating Scale; CI = confidence interval; EF = executive functioning; GDS = Geriatric Depression Scale; NPI-Q = Neuropsychiatric Inventory-Questionnaire; post = posttreatment; pre = pretreatment; PS = processing speed; REHACOP = cognitive rehabilitation program in psychosis; TOM = theory of mind; VM = verbal memory; VSM = visual memory; WHO-DAS II = World Health Organization Disability Assessment Schedule, version II.

significant in processing speed, visual learning and memory, TOM, and functional disability, indicating that there is a reliable mean difference between these groups. These results, along with the effect size, are shown in table 3.

Figure e-1 shows the percentage of patients from each group who improved from baseline to posttreatment. There were significant differences in visual memory ($\chi^2 = 4.62$, $p = 0.032$), TOM ($\chi^2 = 6.04$, $p = 0.014$), GDS ($\chi^2 = 6.31$, $p = 0.012$), and WHO-DAS II ($\chi^2 = 7.08$, $p = 0.006$).

NNT (95% CI) and ARR (95% CI) were calculated with WHO-DAS II scores. The NNT was 2.89 (2–5) and ARR was 0.346 (2.2–4.6) for a treatment response of 10%, NNT = 4.48 (2–5) and ARR = 0.423 (0.304–0.526) for a treatment response of 20%, and NNT = 5.78 (−4 to 14) and ARR = 0.173 (0.071–0.273) for a treatment response of 30%.

DISCUSSION This study provides evidence supporting the efficacy of REHACOP in PD. Significant differences between REHACOP and control groups in change scores were found in processing speed, visual learning and memory, TOM, and functional disability. The effect sizes were large for visual memory, TOM, and functional disability ($d = 0.81$, 0.83, and 1.02, respectively) and moderate for processing speed ($d = 0.76$). The improvement cannot be attributed to the

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Table 3 Baseline comparisons and differences in change scores between the REHACOP and control groups

	Baseline comparison between groups		REHACOP group		Control group		ANOVA for change scores		
	t	*p*	Mean change score (95% CI)	SE	Mean change score (95% CI)	SE	*F*	*p*[a]	Effect size, *d* (95% CI)
PS	1.42	0.164	0.13 (−0.01 to 0.27)	0.07	−0.15 (−0.33 to 0.04)	0.09	5.29	0.025	0.76 (0.12-1.37)
VM	1.18	0.242	0.18 (−0.14 to 0.46)	0.15	−0.26 (−0.58 to 0.07)	0.17	3.51	0.067	0.60 (−0.03 to 1.20)
VSM	1.58	0.121	0.10 (−0.10 to 0.27)	0.10	−0.24 (−0.42 to −0.07)	0.09	6.04	0.011	0.81 (0.17-1.42)
EF	1.13	0.266	0.12 (−0.10 to 0.37)	0.12	−0.21 (−0.72 to 0.33)	0.27	1.11	0.311	0.32 (−0.29 to 0.93)
TOM	1.65	0.107	1.00 (0.33-1.67)	0.37	−0.27 (−0.80 to 0.27)	0.29	7.19	0.013	0.83 (0.18-1.44)
GDS	0.74	0.462	0.01 (−0.67 to 0.70)	0.35	1.27 (0.25-2.46)	0.50	4.13	0.054	0.62 (0.01-1.23)
NPI-Q	0.23	0.817	−1.80 (−3.69 to −0.22)	0.88	−0.54 (−1.76 to 0.60)	0.59	1.45	0.258	0.37 (−0.24 to 0.98)
Apathy	1.89	0.065	−0.55 (−2.16 to 0.91)	0.79	−0.81 (−2.95 to 1.13)	1.03	0.04	0.851	0.06 (−0.55 to 0.67)
WHO-DAS II	0.70	0.491	−5.15 (−7.91 to −2.48)	1.35	0.53 (−2.56 to 3.31)	1.49	8.05	0.012	1.02 (0.36-1.64)

Abbreviations: ANOVA = analysis of variance; Apathy = Lille Apathy Rating Scale; CI = confidence interval; EF = executive functioning; GDS = Geriatric Depression Scale; NPI-Q = Neuropsychiatric Inventory-Questionnaire; PS = processing speed; REHACOP = cognitive rehabilitation program in psychosis; SE = standard error; TOM = theory of mind; VM = verbal memory; VSM = visual memory; WHO-DAS II = World Health Organization Disability Assessment Schedule, version II.

Change score = posttreatment score − pretreatment score; *d* = Cohen *d*. CI and SE derived from the bootstrap analysis.

[a] Significance levels were determined using *F* tests based on the bootstrap SE estimate for that comparison, rather than using a pooled SE estimate.

effect of treatment duration (given that both groups received the same number of hours) nor to group vs individual interventions, because both formats were alike.

Findings in processing speed and visual memory were consistent with previous literature regarding PD.[31–33] A recent study[31] trained processing speed and reported significant improvements after cognitive training. In another more comprehensive cognitive training program, the authors[32] detected significant improvements in processing speed, memory, visual abilities, semantic fluency, and executive functioning. A recent study[33] also noted significant improvements in learning and memory. These general results, summed in a recent review,[3] indicate that cognitive training is a promising tool for dealing with cognitive impairment in PD.

However, the lack of significant improvement in executive functions is not consistent with previous studies.[34,35] One potential explanation for this discrepancy is that, for the purpose of this study, executive functioning was evaluated based only on the Stroop color-word and interference subtest. However, the intrinsic nature of executive functioning may be better captured by other neuropsychological tools, such as WCST (Wisconsin Card Sorting Test) or BADS (Behavioral Assessment of the Dysexecutive Syndrome).[34,36]

Our patients also significantly improved in TOM, measured using the Happé test. Previous literature has shown that patients with PD are impaired in social cognitive abilities.[4,37,38] According to a recent review of nonpharmacologic treatment of cognitive dysfunction in PD,[3] there are no previous studies that have attempted to address the treatment of TOM in PD using cognitive training. Therefore, direct comparisons with previous studies in PD are not possible. However, positive results in studies of other pathologies[39,40] along with our results may be helpful to propose that TOM impairment could be improved. Nevertheless, additional studies are needed to replicate and extend our results.

Results regarding depressive symptoms showed marginally significant differences among groups, although these results must be taken with caution. REHACOP group's results were nearly identical from baseline to posttreatment assessment, whereas the control group's results decreased.

Nevertheless, the major finding of the present study was the improvement in functional disability ($d = 1.02$). A few studies have previously examined changes in functional status after cognitive training in PD,[31,34] and none reported significant improvements. One possible explanation for the positive findings in this study may be related to the specific characteristics of REHACOP, which was developed considering factors that may boost the benefits of cognitive training.[7,8] Among others, these factors include strategic learning and emphasis on transfer techniques. This finding is strengthened by the detection of similar improvements from the use of REHACOP in other populations.[9]

The attrition rate in this study was 4.54%. After receiving feedback (recorded in a focus group not yet published) from the patients, their positive comments about the program may explain the high adherence and low attrition rates of the experimental group. Cultural characteristics, such as broad social

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support, may also explain our result of a lack of attrition in the control group.

However, this study has several limitations. A longitudinal follow-up would show whether the effects of the treatments are maintained in the long term. Because the patients included in this study were in the mild to moderate stages of PD, we cannot generalize the positive results to patients in later stages of PD. The study was single-blinded. At the recruitment, participants were informed that they would receive either cognitive training or treatment with occupational activities, and they were initially blinded to this decision. However, it is possible that some of them guessed they were receiving REHACOP because of the nature of the tasks during the sessions. Moreover, some of the patients from each group were located in the same building. Future studies should also consider analyzing biomarkers of these improvements, including cerebral changes associated with cognitive rehabilitation. Combining cognitive training with other types of treatments may result in deeper and larger changes, which could also be tested in future studies.

AUTHOR CONTRIBUTIONS

Dr. Naroa Ibarretxe-Bilbao and Dr. Natalia Ojeda contributed to the study design and conceptualization. Statistical analyses and interpretation were performed by Dr. Javier Peña and Dr. Naroa Ibarretxe-Bilbao. Dr. Maria Angeles Gomez-Beldarrain, Dr. García-Gorostiaga, and María Díez-Cirarda contributed to data collection and management. All authors contributed to the writing and revision of the manuscript.

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DISCLOSURE

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Improving functional disability and cognition in Parkinson disease: Randomized controlled trial

Javier Peña, Naroa Ibarretxe-Bilbao, Inés García-Gorostiaga, et al.

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Paper IV

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ORIGINAL RESEARCH

Increased brain connectivity and activation after cognitive rehabilitation in Parkinson's disease: a randomized controlled trial

María Díez-Cirarda[1] · Natalia Ojeda[1] · Javier Peña[1] · Alberto Cabrera-Zubizarreta[2] · Olaia Lucas-Jiménez[1] · Juan Carlos Gómez-Esteban[3] · Maria Ángeles Gómez-Beldarrain[4] · Naroa Ibarretxe-Bilbao[1]

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Abstract Cognitive rehabilitation programs have demonstrated efficacy in improving cognitive functions in Parkinson's disease (PD), but little is known about cerebral changes associated with an integrative cognitive rehabilitation in PD. To assess structural and functional cerebral changes in PD patients, after attending a three-month integrative cognitive rehabilitation program (REHACOP). Forty-four PD patients were randomly divided into REHACOP group (cognitive rehabilitation) and a control group (occupational therapy). T1-weighted, diffusion weighted and functional magnetic resonance images (fMRI) during resting-state and during a memory paradigm (with learning and recognition tasks) were acquired at pre-treatment and post-treatment. Cerebral changes were assessed with repeated measures ANOVA 2 × 2 for group x time interaction. During resting-state fMRI, the REHACOP group showed significantly increased brain connectivity between the left inferior temporal lobe and the bilateral dorsolateral prefrontal cortex compared to the control group. Moreover, during the recognition fMRI task, the REHACOP group showed significantly increased brain activation in the left middle temporal area compared to the control group. During the learning fMRI task, the REHACOP group showed increased brain activation in the left inferior frontal lobe at post-treatment compared to pre-treatment. No significant structural changes were found between pre- and post-treatment. Finally, the REHACOP group showed significant and positive correlations between the brain connectivity and activation and the cognitive performance at post-treatment. This randomized controlled trial suggests that an integrative cognitive rehabilitation program can produce significant functional cerebral changes in PD patients and adds evidence to the efficacy of cognitive rehabilitation programs in the therapeutic approach for PD.

Keywords Parkinson's disease · Plasticity · Cerebral changes · Brain activation · Brain connectivity · Randomized controlled trial

Background

Parkinson's disease (PD) patients experience cognitive impairment in a wide range of cognitive domains (Goldman and Litvan 2011). Traditionally, PD has been related to deficits in executive functions, attention and visuospatial abilities, but also memory deficits are present in PD (Chiaravalloti et al. 2014; Whittington et al. 2006). Indeed, some studies found that memory was the most frequently affected cognitive domain in PD (Aarsland et al. 2010; Yarnall et al. 2014). This cognitive decline has been identified as a predictor of PD dementia and magnetic resonance imaging (MRI) studies have demonstrated a relationship between cognitive impairment and patterns of neurodegeneration in PD (Biundo et al. 2013; Christopher and Strafella 2013; Ibarretxe-Bilbao et al. 2011a).

✉ Naroa Ibarretxe-Bilbao
naroa.ibarretxe@deusto.es

[1] Department of Methods and Experimental Psychology, Faculty of Psychology and Education, University of Deusto, Bilbao, Biskay, Spain

[2] OSATEK, MR Unit, Hospital of Galdakao, Galdakao, Basque Country, Spain

[3] Neurodegenerative Unit, Biocruces Research Institute; Neurology Service, Cruces University Hospital, Bilbao, Biskay, Spain

[4] Neurology Service, Hospital of Galdakao, Galdakao, Basque Country, Spain

Cognitive rehabilitation is a behavioral treatment for cognitive impairment based on the restoration, compensation and optimization of the cognitive functions that targets cognitive skills, but also improves daily functioning (Bahar-Fuchs et al. 2013; Wykes and Spaulding 2011). The efficacy of cognitive rehabilitation programs has been recently demonstrated in PD, showing improvements in cognitive functions (Hindle et al. 2013; Leung 2015; Pena et al. 2014) and functional disability (Pena et al. 2014).

Moreover, in the last few years, cognitive rehabilitation has been related to functional cerebral changes in other pathologies such as multiple sclerosis (Chiaravalloti et al. 2012; Filippi et al. 2012; Leavitt et al. 2014), mild cognitive impairment (Belleville et al. 2011), Alzheimer's disease (van Paasschen et al. 2013) and schizophrenia (Penadés et al. 2013). Literature about structural cerebral changes associated to cognitive rehabilitation programs in neurodegenerative disorders is scarce. One study in multiple sclerosis found no significant white matter (WM) changes after cognitive rehabilitation (Filippi et al. 2012) but in patients with schizophrenia, increased WM was found after a 4 month-cognitive rehabilitation program (Penadés et al. 2013). Another study found grey matter (GM) preservation in schizophrenia patients after a 2-year intensive cognitive rehabilitation (Eack et al. 2010). However, to date, few studies have sought to elucidate cerebral changes associated with cognitive rehabilitation in PD. One study (Cerasa et al. 2014) found increased resting-state functional cerebral activation after attention rehabilitation in the left dorsolateral prefrontal cortex and the superior parietal cortex. In contrast, Nombela et al. (2011) found reduced brain activation during Stroop task after Sudoku training in PD. These two studies in PD patients included a specific treatment focused on the rehabilitation of one cognitive function and little is known about the neurobiological effects of an integrative cognitive rehabilitation program in PD, assessed with MRI combining both structural and functional MRI (fMRI) techniques.

In a previous study we demonstrated the efficacy of an integrative cognitive rehabilitation program, the REHACOP, on improving cognition and functional disability in PD patients (Pena et al. 2014). The objective of the present study was to assess the structural and functional cerebral changes associated to cognitive rehabilitation in the same cohort of PD patients. Due to the relevance of memory deficits in PD, a memory fMRI paradigm was included in this study to assess whether a cognitive rehabilitation program could produce changes in brain activation during learning and recognition memory tasks. Based on the findings of previous neuroimaging studies in neurodegenerative diseases (Belleville et al. 2011; Cerasa et al. 2014; Chiaravalloti et al. 2012; Filippi et al. 2012; Leavitt et al. 2014; Nombela et al. 2011; van Paasschen et al. 2013), we hypothesized that PD patients would show functional but not structural cerebral changes after attending REHACOP program compared with the control group (CG).

Methods

Subjects

The sample included 44 PD patients recruited from the Department of Neurology at the Hospital of Galdakao and from the PD Biscay Association (ASPARBI). PD patients were enrolled in the study if they fulfilled the UK PD Society Brain Bank diagnostic criteria. Other inclusion criteria were: i) age between 45 and 75; ii) Hoehn and Yahr disease stage ≤3 (Hoehn and Yahr 1998); iii) Unified PD Rating Scale (UPDRS) (Martinez-Martin et al. 1994) evaluated by the neurologist. Exclusion criteria were: i) the presence of dementia as defined by the DSM-IV-R (American Psychiatric Association 2003) and the Movement Disorders Society clinical criteria for PD-dementia; ii) scores on the Mini Mental State Examination <24; iii) the presence of other neurological illness/injury (traumatic brain injury); iv) unstable psychiatric disorders (e.g. schizophrenia); v) visual hallucinations as assessed by the Neuropsychiatric Inventory Questionnaire (Kaufer et al. 2000); vi) patients with depression evaluated with the Geriatric Depression Scale (score of >5) (Yesavage and Sheikh 1986). For the MRI part of the study, further exclusion criteria were: vii) other conditions incompatible with optimal pre-processing of MRI data and whole-group analysis such as cerebral haemorrhage, traumatic brain injury, dilated ventricles.

From the initial sample of 44 PD patients, three patients refused to attend MRI acquisition, two were lost to follow-up, eight patients were excluded from the MRI analysis and one refused to post-treatment MRI assessment (see Fig. 1 for the flow diagram). Hence, MRI analyses were carried out on 15 patients in the REHACOP group (patients receiving cognitive rehabilitation) and 15 patients in the CG, which received occupational therapy with the same duration and frequency.

Participants were symptomatically stable and evaluated during the "ON" period. Their Levodopa equivalent daily dose (LEDD) was registered (Tomlinson et al. 2010). The clinical and sociodemographic characteristics of the sample are shown in Table 1.

Procedure

Participants underwent a neuropsychological assessment and MRI acquisitions at baseline and after treatment. After first evaluation, PD patients were randomly divided into REHACOP group and CG. Design details of this randomized controlled trial are as described in a previous report (Pena et al. 2014) which is registered in clinicaltrials.gov with number: NCT02118480.

Intervention

The REHACOP is an integrative program which trains both basic and social cognition, in addition to psychoeducation,

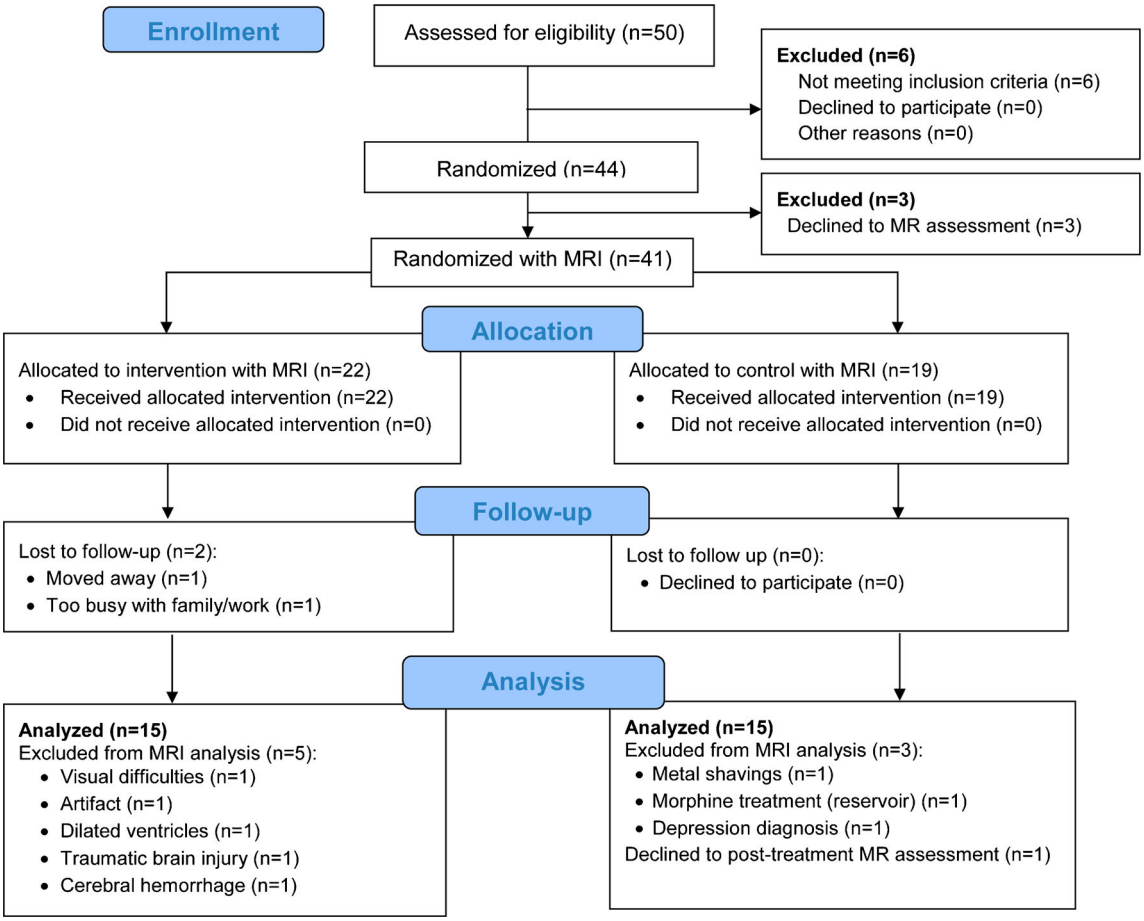

Fig. 1 CONSORT Flow Diagram. CONSORT = Consolidated Standards of Reporting Trials; MRI = Magnetic Resonance Imaging

with mainly although not exclusively, bottom-up tasks. The REHACOP program was administered over three months, three times per week and one hour per day. Participants attending REHACOP group trained: attention (4 weeks; sustained, selective, alternant and divided attention), memory (3 weeks; verbal and visual learning, recall, and recognition), language (2 weeks; verbal fluency, synonyms, antonyms, definition of words and extract the main idea from text), executive functions (2 weeks; cognitive planning, verbal reasoning) and social cognition (1 week; moral dilemmas, empathy, theory of mind). Groups were made of 6–8 patients maximum and were conducted by two neuropsychologists. More information about the REHACOP program can be found in previous publication in PD (Pena et al. 2014). CG attended occupational therapy during the same period and frequency, and the activities included drawing, reading the daily news, and constructing with different materials (such as paper or wood).

Neuroimage acquisition

Functional and structural imaging data were acquired on a 3 T MRI (Philips Achieva TX) at OSATEK, Hospital of Galdakao. All sequences were acquired during a single session.

T1-weighted images acquisition were obtained in a sagittal orientation (TR = 7.4 ms, TE = 3.4 ms, matrix size = 228 x218mm; flip angle = 9°, FOV = 250x250x180mm, slice thickness = 1.1 mm, 300 slices, voxel size = 0.98 × 0.98 × 0.60 mm, acquisition time = 4′55″).

Diffusion-weighted images were obtained, in an axial orientation in an anterior-posterior phase direction using a single-shot EPI sequence (TR = 7540 ms, TE = 76 ms, matrix size = 120x117mm; flip angle = 90°, FOV = 240x240x132mm, slice thickness = 2 mm, no gap, 66 slices, voxel size = 1.67 × 1.67 × 2.0 mm, acquisition time = 9′ 31″) with two identical repetitions (32 uniformly distributed directions b = 1000 s/mm^2 and 1 b = 0 s/mm^2).

The resting-state fMRI was obtained in an axial orientation in an anterior-posterior phase direction using sequence sensitive to blood oxygen level dependent (BOLD) contrast and multi-slice gradient echo EPI sequence (TR = 2100 ms, TE = 16 ms, matrix size = 80x78mm, flip angle = 80°, FOV = 240x240x130mm, slice thickness = 3 mm, 214 slices, voxel size = 3.00 × 3.00 × 3.00 mm, acquisition time = 7′40″).

Table 1 Sociodemographic, clinical characteristics and behavioral data at baseline

	REHACOP group (n = 15) Mean (SD)	CG (n = 15) Mean (SD)	U / X^2	p
Age	66.20 (4.99)	67.60 (7.39)	98.00	.545
Gender (Male)	8 (53.3 %)	10 (66.7 %)	.13	.709
Years of education	11.40 (4.56)	10.13 (5.12)	97.50	.530
Disease duration (years)	6.13 (5.23)	8.41 (6.57)	84.00	.234
Hoehn-Yahr stage	1.90 (.28)	2.03 (.51)	4.06	.398
Stage 1	1	1		
Stage 1.5	1	2		
Stage 2	13	9		
Stage 2.5	0	1		
Stage 3	0	2		
UPDRS Motor score	19.27 (7.95)	25.93 (11.38)	75.00	.119
LEDD	631.32 (415.43)	988.15 (613.11)	73.00	.101
NPI-Q	4.47 (5.20)	3.13 (3.11)	106.00	.784
MMSE	27.93 (1.10)	26.56 (3.46)	102.50	.671
Memory fMRI Paradigm: Behavioral data				
Hits	9.73 (4.46)	9.71 (3.58)	94.50	.643
Correct Rejections	12.00 (2.87)	11.71 (3.12)	98.50	.772
False Negatives	5.13 (4.38)	5.21 (3.59)	94.00	.627
False Positives	2.87 (2.99)	3.21 (2.94)	95.00	.657

REHACOP group group receiving cognitive rehabilitation program, *CG* control group, *SD* Standard deviation, *UPDRS motor score* Unified Parkinson's disease Rating Score, *LEDD* Levodopa Equivalent Daily Dose, *NPI-Q* Neuropsychiatric Inventory Questionnaire, *MMSE* Mini Mental State Examination

Finally, patients also performed a memory fMRI paradigm inside the scanner. The fMRI images were acquired using a multi-slice gradient echo EPI sequence [TR = 2000 ms, TE = 29 ms, matrix size = 100x100mm, flip angle = 90°, FOV = 240x240x136mm, slice thickness = 3 mm; 280 slices (140 slices each learning and recognition task), voxel size = 1.67 × 1.67 × 3.00 mm, acquisition time = 9′36″ (4′48″ each learning and recognition task)].

The memory fMRI paradigm was presented with visual digital MRI-compatible high resolution stereo 3D glasses and Presentation® version 10.1 (Neurobehavioral Systems) running on Windows XP. The entire experiment consisted of a 10-block paradigm (learning and recognition tasks) that alternated activation and control conditions (5 blocks each). Each paradigm had a total duration of 280 s (28 s/block). Participants were also given a response box that recorded their behavioral responses. During the learning memory fMRI task, participants viewed 30 words (duration of 2 s per word and an inter-word interval of 1 s) and were asked to press the right button if they liked the word or the left button if they did not like the word. This task was used to ensure that the participants fixed their attention on reading the words as suggested by (Marsolek et al. 1992). During the recognition memory fMRI task, participants were asked to recognize words from a list of 30 words, of which 15 words had been presented during the learning memory fMRI task and 15 words were new. Participants were asked to press the button using their right hand to indicate if they remembered having read the word in the list during the learning fMRI task or the left button if they had not seen it before. In the control blocks, participants were presented with six combinations of letters (simulating the length of a word) of which three were the letters "AAAAAA" and the other three were random letters. Again, participants were asked to press the right button on the response box to indicate that the item was "AAAAAA" and press the left button when other combinations of letters appeared. This paradigm has previously been used and has demonstrated to show cerebral activation related to recognition memory in PD (Ibarretxe-Bilbao et al. 2011b; Lucas-Jiménez et al. 2015). Behavioral data were coded as "Hits" when participants answered yes and the answer was yes; "Correct rejections" when participants answered no and the answer was no; "False positives" when participants answered yes and the answer was no; and "False negatives" when participants answered no and the answer was yes. Two equivalent versions of this memory fMRI paradigm were used at both time points (pre- and post-treatment) in order to avoid learning effects. In the pre-treatment version, the words were four to six letters in length and of moderate frequency of use and were obtained from the Lexesp-Corco database. The post-treatment version was created

including different words but with phonetic similarities and with the same number of syllables. Behavioral data from the recognition memory fMRI task were extracted and analyzed in SPSS.

Neuroimage pre-processing

GM

Voxel-based morphometry (VBM) (Douaud et al. 2007) analysis were carried out using the FMRIB Software Library (FSL) tools (Smith et al. 2004). First, a study-specific template was created so that all of the images could be registered in the same stereotactic space (spatial normalization Then, the GM images were affine registered to the GM MNI-152 template and averaged to create an affine GM template. Next, the GM images were re-registered to this affine GM template using a non-linear registration and averaged to create a study-specific, non-linear GM template in standard space. Second, individual GM images were registered non-linearly to the study-specific template. After normalization, the resulting GM images were modulated by multiplying by Jacobian determinants to correct for volume change induced by the nonlinear spatial normalization. Then, the images were smoothed with a sigma of 3.5 mm (8 mm FWHM). Finally, cluster-based analyses were performed.

Cortical Thickness changes were analyzed with Freesurfer (Fischl 2012) (version 5.3; available at http://surfer.nmr.mgh.harvard.edu). The processing of T1 high-resolution images for the cortical surface reconstruction followed the freesurfer analysis pipeline (Dale et al. 1999; Fischl et al. 1999): Automated Talairach transformation, intensity normalization, skull stripping, WM segmentation, tessellation of the GM/WM boundary, automated topology correction, and surface deformation following intensity gradients to optimally place the fluid borders (GM/WM and GM/cerebrospinal fluid) at the location. All surface models were visually inspected for accuracy. No model was excluded due to misclassification of tissue types. Cortical thickness was calculated as the closest distance from the GM/WM boundary to the GM/cerebrospinal fluid boundary at each vertex on the tessellated surface. The bilateral mean cortical thickness values were extracted based on the parcellation of (Destrieux et al. 2010) and were introduced in SPSS for statistical analysis.

WM

Diffusion data were also preprocessed and analysed using FSL. First, each subject's images were concatenated and radiologically oriented. Then, the data were corrected for motion and eddy currents, performed brain-extraction BET, and the diffusion gradients (bvecs) were rotated to be corrected accordingly, providing a more accurate estimate of tensor orientations (Jones and Cercignani 2010). Then, all fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD) and axial diffusivity (AD) images were obtained by fitting a tensor model to the raw diffusion data using FDT (DTIFIT). After, tract-based spatial statistic (TBSS) (Smith et al. 2006) was used for group comparisons. Using TBSS, the data were prepared to apply a nonlinear registration of all FA images into standard space, the mean FA image was created using a threshold of 0.2 and thinned to create a "mean FA skeleton" which represents the centres of all tracts common to the group. MD data were analysed using "tbss non FA" script from TBSS, which applies the original non lineal registration to the MD data, merges all subjects warped MD data into a 4D file, then project this onto the original mean FA skeleton, and creates the 4D projected data. The same process was repeated for RD and AD.

Resting-state fMRI

Resting-state fMRI data were acquired during a so-called resting-state block. Subjects were instructed to neither engage in any particular cognitive nor motor activity, to keep their eyes closed without thinking about anything in particular and they were told they could not fall asleep. Once the resting-state fMRI acquisition finished, the neuroradiologist talked with the patients and asked them whether they fell asleep or not. No patient reported to fall asleep. Foam padding and headphones were used to limit head movement and reduce scanner noise for the subject.

Functional connectivity analysis was performed using Conn Functional Connectivity Toolbox 14.p (Whitfield-Gabrieli and Nieto-Castanon 2012). First, each subject' 214 functional images were realigned and unwraped, slice-timing corrected, coregistered with structural data, spatially normalized into the standard MNI space (Montreal Neurological Institute), then, outliers were detected (ART-based scrubbing) and finally images were smoothed using a Gaussian kernel of 8 mm FWMH. All preprocessing steps were conducted using default preprocessing pipeline for volume-based analysis (to MNI-space). As recommended, band-pass filtering was performed with a frequency window of 0.008 to 0.09 Hz (Weissenbacher et al. 2009). Then, structural data were segmented in GM, WM and cerebrospinal fluid and normalized in the same default preprocessing pipeline. Whole-brain analysis was performed using Region of Interest (ROI-to-ROI) approach according to Conn toolbox options, and previously used in a recent study (Demirakca et al. 2015). In order to get a complete picture of possible cerebral changes, we used all existing areas as ROIs, based on the pre-defined ROIs loaded automatically in Conn toolbox, including default network connectivity (FOX) and a complete list of Brodmann areas obtained from the Talairach

Daemon atlas (Lancaster et al. 2000). Following recommendations, *p*-FDR threshold was used in the connection-level analysis to correct for multiple comparisons (Whitfield-Gabrieli and Nieto-Castanon 2012). Baseline differences in brain connectivity values between the REHACOP group and CG were introduced as covariates in the interaction analysis (group x time).

Memory fMRI paradigm

FMRI data were analyzed using SPM8 (Ashburner et al. 2012). The functional data of each participant were motion-corrected, realigned to the first acquired volume in the session, and a mean realigned volume was created for each participant. Then, all realigned volumes were spatially normalized into the standard MNI space and smoothed using a Gaussian kernel of 8 mm FWMH. Statistical parametric maps were calculated at first-level analysis for each subject with a general linear model, and parameters for the memory fMRI paradigm model specification were introduced. Then, after model estimation, a matrix was obtained for each subject showing higher brain activation while the activation condition compared to the control condition (activation > control).

Statistical analysis

Demographic, clinical and behavioral variables were analyzed with SPSS (IBM SPSS Statistics 22). Differences between groups were tested with Mann-Whitney U Test and chi-squared test for non-parametric variables. Longitudinal changes between groups in behavioral variables were tested with repeated measures ANOVA 2 × 2 for group x time interaction analysis.

For neuroimaging analysis, whole-brain analysis was performed to study structural and functional cerebral changes. Baseline differences between groups were tested with two-sample t-test analysis. Longitudinal analysis to test differences between pre-treatment and post-treatment for REHACOP group and CG were assessed with repeated-measures ANOVA 2 × 2 analysis data for group x time interaction analysis. The between-subjects factor was group (REHACOP group or CG) and the within-subjects factor was time (pre-treatment and post-treatment). Paired-t-test analysis was also performed to explore intragroup changes. VBM and cortical thickness analyses used total intracranial volume as a covariate. For the fMRI analyses, LEDD was used as a covariate because of the influence of dopaminergic treatment on brain activation (Mattay et al. 2002). Moreover, because the REHACOP group showed lower scores on UPDRS III and higher scores on MMSE at baseline, both variables were included as covariates in longitudinal analyses. For both structural and functional analyses the statistical threshold was set at $p < .05$ corrected for multiple comparisons and $p < .001$ uncorrected analysis was also performed for exploratory results. Effect sizes for each cluster were calculated according to Cohen's *d* formula (Thalheimer and Cook 2002). Cohen's *d* statistics of 0.20, 0.50 and 0.80 were considered small, medium and large, respectively (Hojat and Xu 2004). Finally, Rho-Spearman test was used to determine the relationships between MRI data at post-treatment and the performance in cognitive domains after rehabilitation, including executive functions, processing speed, verbal and visual memory and theory of mind; see previous publication (Pena et al. 2014). Bootstrapping was used in correlations to obtain more adjusted results (Efron and Tibshirani 1994).

Results

Sociodemographic, clinical characteristics and behavioral data

The sociodemographic characteristics of the sample are shown in Table 1. At baseline, no significant differences were found between groups in age, gender, years of education and clinical aspects of the disease (see Table 1). Regarding behavioral data from the memory fMRI paradigm, no baseline differences were found in hits, correct rejections, false positives or false negatives between groups (Table 1) and no significant changes were found after three months treatment between groups.

GM volume, cortical thickness and WM indexes

No baseline differences in GM volume, WM indexes or mean cortical thickness (left and right) were found between groups. Longitudinal analysis showed no significant structural changes within or between groups at post-treatment.

Resting-state fMRI

Baseline differences in brain activation in resting-state fMRI were found between groups, showing the CG more connectivity between the left dorsal posterior cingulate cortex Brodmann Area (BA31) and the left piriform cortex (BA27) compared to the REHACOP group ($t = 3.96$; $p = 0.04$ FDR-corrected). After controlling for baseline differences, resting-state fMRI data showed significant differences between groups (interaction effect group x time) in functional connectivity between the left inferior temporal lobe (BA20L; x = −51; y = −23; z = −29) and the left and right dorsolateral prefrontal cortex (BA9L; x = −29; y = 41; z = 25; F = 10.71; $p = .03$; $d = 1.17$) and (BA9R; x = 33; y = 42; z = 24; F = 10.01; $p = .03$; $d = 1.13$) respectively, showing the REHACOP group higher brain connectivity at post-treatment compared to the CG (see Fig. 2).

Memory fMRI paradigm

No baseline differences were found during the learning or the recognition memory fMRI tasks between groups. During the learning memory fMRI task, no significant results were found at the interaction level, but intragroup analysis showed that the REHACOP group increased brain activation in the left frontal lobe at post-treatment compared to pre-treatment ($p < .001$ uncorrected) (see Fig. 3; Table 2). On the contrary, CG showed no significant cerebral changes during the learning memory fMRI task.

During the recognition memory fMRI task, repeated measures analysis (interaction effect group x time) revealed significant brain activation changes at post-treatment in the left middle temporal lobe in the REHACOP group compared to the CG ($p < .05$ FWE-corrected). Only few voxels survived the corrected level, hence, results at $p < .001$ uncorrected are showed in Fig. 3 and Table 2.

Correlations between MRI data and neuropsychological scores in the REHACOP group at post-treatment

Results showed that the brain connectivity between the left inferior temporal lobe and the left dorsolateral prefrontal cortex during resting-state fMRI correlated with the performance on executive functions at post-treatment (Rho = .574; 95 % Confidence Interval [CI] = .083–.842; Standard Error [SE] = .178; $p = .032$). In addition, after cognitive rehabilitation, the REHACOP group showed a significant correlation between the brain activation during learning fMRI task and the scores on visual memory (Rho = .596; CI = .001–.950; SE = .263; $p = .025$). Finally, a marginally significant correlation was found between the brain activation during the recognition fMRI task and the performance on verbal memory at post-treatment (Rho = .512; CI = −.053–.824; SE = .224; $p = .060$).

Discussion

The objective of this study was to assess cerebral changes related to the integrative cognitive rehabilitation program REHACOP in patients with PD. These results show that patients with PD attending REHACOP program increased their brain connectivity between the temporal and bilateral frontal lobes during resting-state fMRI and increased brain activation in the frontal and temporal lobes during a memory fMRI paradigm. Moreover, the brain connectivity and activation in the REHACOP group at post-treatment correlated with the final performance in cognitive functions. Findings suggest the existence of brain plasticity in patients with this pathology, despite the neurodegenerative process, and support the efficacy of cognitive rehabilitation treatments on PD.

PD patients that received cognitive rehabilitation showed increased brain connectivity between the left inferior temporal lobe and the bilateral dorsolateral prefrontal cortex. Recently, reduced connectivity in the fronto-temporal network has also been found in PD and has been related to working memory encoding deficits in the disease (Wiesman et al. 2016). Impairment in the fronto-temporal network has also been found in schizophrenia patients, and are suggested to underlie encoding deficits (Wolf et al. 2007). In addition, the greater connectivity between temporal and dorsolateral prefrontal cortex has been related with the better performance in word recognition in healthy controls (Wolf et al. 2007). Moreover in this study, the cognitive function of attention was trained during 4 weeks and interestingly, a previous resting-state fMRI study in PD patients also found increased brain connectivity in the dorsolateral prefrontal cortex after attention rehabilitation (Cerasa et al. 2014). Furthermore, the fronto-temporal network connects the prefrontal with the temporal cortex, both areas related to other cognitive functions trained during the REHACOP program, such as executive functions (Nagano-Saito et al. 2005), language, verbal fluency (Pereira et al. 2009), memory (Cabeza and Nyberg 2000; van Paasschen et al. 2013) and theory of mind (Díez-Cirarda et al. 2015).

Results also showed that REHACOP group had increased brain activation after cognitive rehabilitation during the learning and recognition tasks of the memory fMRI paradigm. Specifically, during the recognition fMRI task, the REHACOP group showed increased brain activation in the left middle temporal lobe at post-treatment compared to the CG. These findings confirm previous studies that related the temporal lobe to the retrieval process (Cabeza and Nyberg 2000). Furthermore, during the learning fMRI task, PD patients from the REHACOP group had increased brain activation in the left inferior frontal area at post-treatment compared to pre-treatment. These results are coherent with previous literature because the frontal lobe is known to be involved in memory performance in PD in both encoding and retrieval processes (Cabeza and Nyberg 2000; Eichenbaum et al. 2007). However, the brain activation changes during memory fMRI paradigm should be taken with caution because they were found at an uncorrected level $p < .001$. Increased activation in the frontal and temporal areas after memory rehabilitation has also been found in multiple sclerosis (Chiaravalloti et al. 2012), mild cognitive impairment (Belleville et al. 2011) and healthy adults (Belleville et al. 2011). Compared to PD patients in this study, Alzheimer's disease patients showed activation changes in frontal but not temporal areas during a recognition fMRI task after memory rehabilitation (van Paasschen et al. 2013). Some authors suggested that Alzheimer's disease patients could compensate the more pronounced degeneration of the temporal lobe with an overactivation of the frontal lobe (Schwindt and Black 2009). Interestingly, the cerebral changes found

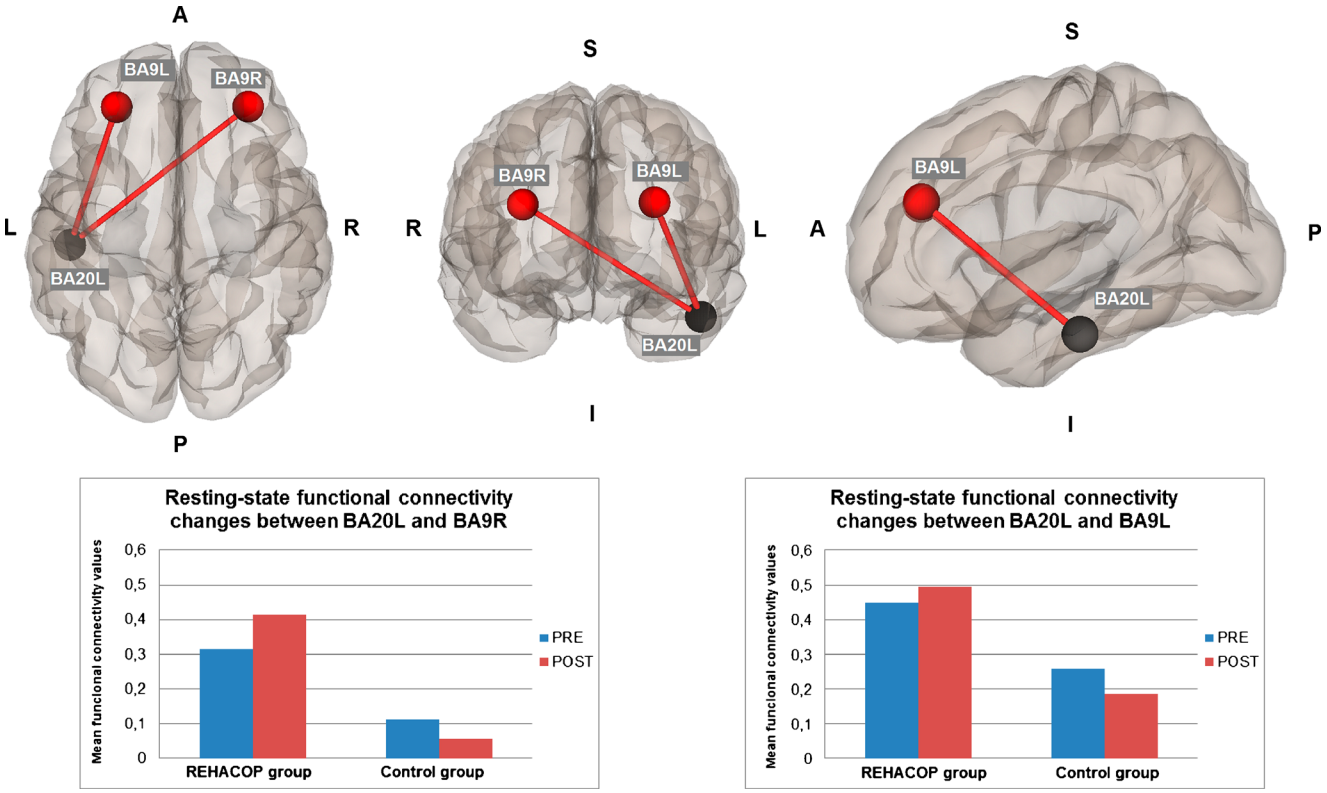

Fig. 2 Resting-state brain connectivity fMRI changes (interaction level group x time). Seed (black point) = the left inferior temporal lobe (BA20L; x = −51; y = −23; z = −29); Targets (red points) = left and right dorsolateral prefrontal cortex (BA9L; x = −29; y = 41; z = 25) and (BA9R; x = 33; y = 42; z = 24). Lines represent increased connectivity between the seed and target at the interaction level (group x time), showing the REHACOP group increased brain connectivity at post-treatment compared to the CG. Graphic shows mean connectivity values during resting-state at pre-treatment and post-treatment for REHACOP group and CG. Results are shown at $p < .05$ FDR-corrected. A = Anterior; P = Posterior; I = Inferior; S = Superior; CG = Control Group

during memory fMRI paradigm in this study were located in the left hemisphere, and verbal memory is known to be (in most cases) a cognitive function lateralized in the left hemisphere (Kelley et al. 1998).

Brain activation changes in the REHACOP group cannot be related to the treatment duration or to the format (group vs. individual) because the CG received occupational therapy with the same frequency, duration, and group format. Moreover, brain changes cannot be related to learning effects in the memory fMRI paradigm because different versions were used at pre-treatment and post-treatment.

With all, these findings suggest that integrative cognitive rehabilitation programs have an impact on cerebral activation and connectivity in PD patients. In addition, significant and positive relationships between the brain connectivity and activation and cognitive performance have been found in the REHACOP group after attending cognitive rehabilitation. These findings may suggest that the brain changes increased the activity which helped patients during cognitive performance. Findings of the present study go in line with previous research in other pathologies that also found improvements in cognitive functions and increased brain activation after cognitive rehabilitation (Belleville et al. 2011; Cerasa et al. 2014; Chiaravalloti et al. 2012; van Paasschen et al. 2013). However, decreased brain activation has also been related to better cognitive performance after training in PD (Nombela et al. 2011).

This study also assessed whether cognitive rehabilitation programs could be related to GM changes. As expected by the authors, no significant differences in GM volume after three months of cognitive rehabilitation were found. A previous study with multiple sclerosis patients who received cognitive treatment for the same period of time as in the present study, found the same negative findings (Filippi et al. 2012). Contrary to these results, schizophrenia patients showed neuroprotective effects against GM loss related to a two year intensive cognitive rehabilitation program (Eack et al. 2010) (60 h/week neurocognitive rehabilitation plus 45 weekly social/cognitive group sessions). Similarly, studies in healthy participants showed GM volume changes after three months of intensive cognitive activity (Draganski et al. 2006) and cortical thickness changes after memory training (Engvig et al. 2010). Furthermore, this study found no significant changes in WM integrity and diffusivity after REHACOP program. Filippi et al. (2012) found the same negative findings in multiple sclerosis patients in the assessment of WM

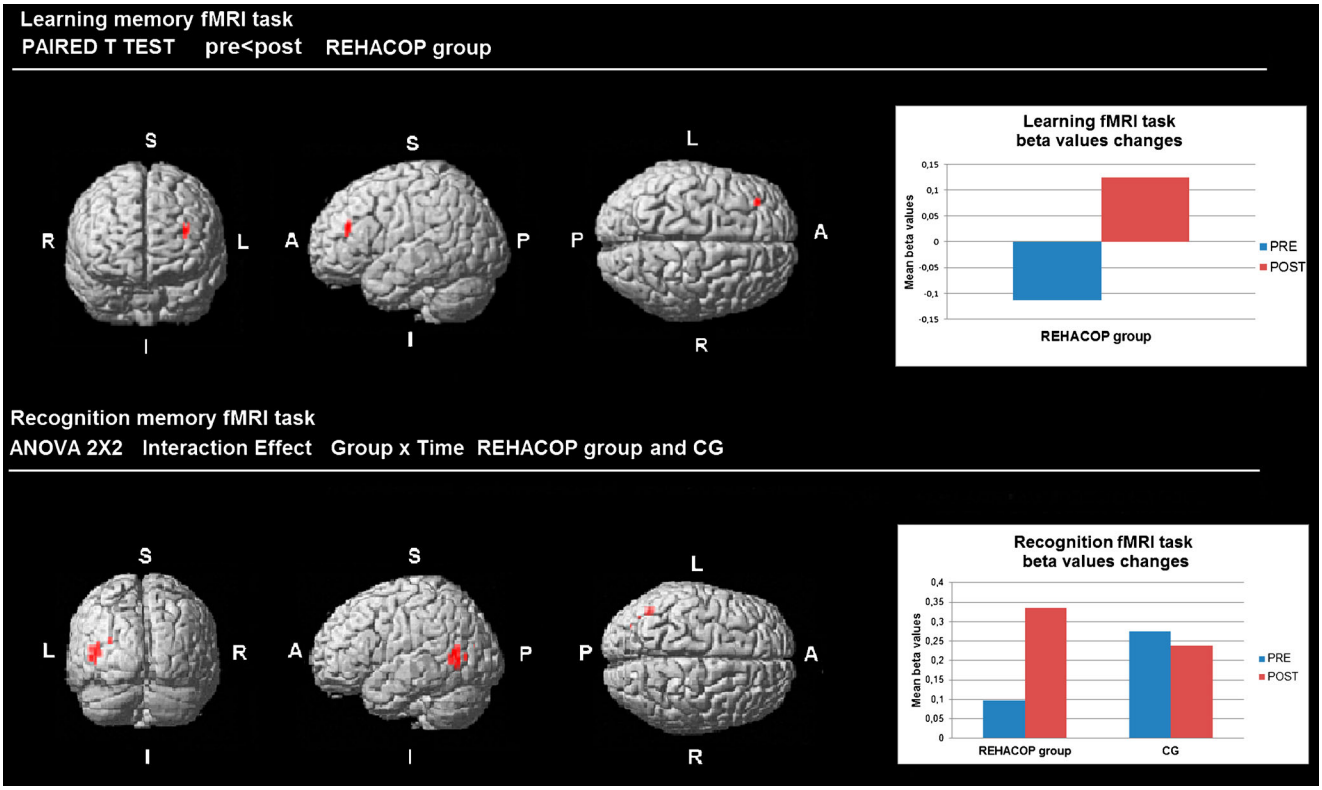

Fig. 3 fMRI activation changes during Memory fMRI Paradigm. Areas of brain activation change are shown in red. Graphics show mean beta values while the learning and the recognition memory fMRI tasks at pre-treatment and post-treatment. Results are shown at $p < .001$-uncorrected. A = Anterior; P = Posterior; I = Inferior; S = Superior; CG = Control Group

volume and diffusivity changes after cognitive rehabilitation. On the contrary, Penadés et al. (2013) found increased FA after four months of cognitive rehabilitation in schizophrenia patients. Therefore, the neurodegenerative process itself and the intensity of the cognitive program might be important variables to understand the absence of GM and WM changes in PD patients of this study. Findings of this study suggest that after three months of an integrative cognitive rehabilitation program, brain activation and connectivity changes could be found in PD, but these functional changes are not accompanied by structural changes.

Several limitations of this study must be taken into account. First, the sample size is small. However, despite the reduced sample size, both groups were equivalent in sociodemographic and clinical variables at baseline, and results showed consistent changes in brain activation values. All significant results showed large effect sizes, which support the clinical relevance of the findings

Table 2 Memory fMRI Paradigm activation changes

	Cluster size (voxels)	MNI coordinate			Statistical value	Effect size
		x	y	z		
Learning memory fMRI Task						
REHACOP group (pre < post)						
L Frontal Inferior (Pars triangularis)	12	-36	37	22	t = 6.07*	2.21
Recognition memory fMRI Task						
Interaction effect (group x time)						
L Middle Temporal Lobe	15	-41	-64	7	F = 30.40*	2.08

Cluster size denotes the extent of the cluster of significant voxels. MNI coordinates refer to the location of the most statistically significant voxel in the cluster. Effect sizes were calculated with Cohen's d.

L Left, *MNI* Montreal Neurological Institute

*Differences are significant at $p < .001$-uncorrected

(Hojat and Xu 2004). Future studies with larger samples are needed to replicate these findings in PD. Furthermore, longitudinal follow-up studies must be carried out to evaluate the course of brain changes after cognitive treatments. Moreover, it would be interesting to assess functional brain activation changes during other cognitive tasks, such as executive functions, processing speed or visuo-constructive abilities. Finally, PD patients were mainly at first Hoehn and Yahr stages of the disease. Therefore, further studies with PD patients at moderate and severe stages are needed to evaluate whether these findings can be replicated in more advanced stages of the disease.

Conclusions

In conclusion, this study reported increased brain activation and connectivity in PD patients after attending an integrative cognitive rehabilitation program. This study, together with results from previous research, adds evidence of the neurobiological effects of cognitive rehabilitation programs in patients with PD.

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Compliance with ethical standards

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Conflict of interest statement N.O. and J.P. are co-authors and copyright holders of the REHACOP cognitive rehabilitation program, published by Parima Digital, S.L. (Bilbao, Spain). M.D.C., A.C.Z., O.L.J., J.C.G.E., M.A.G.B. and N.I.B. have no conflicts of interest to report.

Ethical approval and informed consent The study protocol was approved by the Ethics Committee at the Health Department of the Basque Mental Health System in Spain and the Ethics Committee of the University of Deusto (approval Number: Psi-09/11–12). All subjects were volunteers and provided written informed consent prior to their participation in the study, in accordance with the Declaration of Helsinki of 1975, and the applicable revisions at the time of the investigation. All patients at the CG were provided with REHACOP rehabilitation once the trial finished.

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Paper V

CME ARTICLE

Long-term effects of cognitive rehabilitation on brain, functional outcome and cognition in Parkinson's disease

M. Díez-Cirarda[a], N. Ojeda[a], J. Peña[a], A. Cabrera-Zubizarreta[b], O. Lucas-Jiménez[a], J. C. Gómez-Esteban[c], M. Á. Gómez-Beldarrain[d] and N. Ibarretxe-Bilbao[a]

[a]*Department of Methods and Experimental Psychology, Faculty of Psychology and Education, University of Deusto, Bilbao, Biscay;* [b]*OSATEK, MR Unit, Hospital of Galdakao, Galdakao, Biscay;* [c]*Neurodegenerative Unit, Biocruces Research Institute, Neurology Service, Cruces University Hospital, Barakaldo, Biscay; and* [d]*Neurology Service, Hospital of Galdakao, Galdakao, Biscay, Spain*

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Background and purpose: Cognitive rehabilitation has demonstrated efficacy in producing short-term cognitive and brain changes in patients with Parkinson's disease (PD). To date, no study has assessed the long-term effects of cognitive rehabilitation using neuroimaging techniques in PD. The aim was to assess the longitudinal effects of a 3-month cognitive rehabilitation programme evaluating the cognitive, behavioural and neuroimaging changes after 18 months.

Methods: Fifteen patients with PD underwent a cognitive, behavioural and neuroimaging assessment at pre-treatment (T_0), post-treatment (T_1) and after 18 months (T_2). This study examined the long-term effects (from T_0 to T_2) and the maintenance of the changes (from T_1 to T_2). T1-weighted, diffusion-weighted, functional magnetic resonance imaging during both a resting-state and a memory paradigm were acquired. Voxel-based morphometry and tract-based spatial statistics were used for grey and white matter analyses. A region-of-interest-to-region-of-interest approach was used for resting-state functional connectivity (FC) and a model-based approach was used for brain activation during the memory paradigm.

Results: Patients with PD showed increased cognitive performance, decreased functional disability, increased brain FC and activation at T_2 compared with T_0 ($P < 0.05$, FDR). Moreover, patients showed maintenance of the improvements in cognition and functionality, and maintenance of the increased brain FC and activation at T_2 compared with T_1. However, significant grey matter reduction and alterations of white matter integrity were found at T_2 ($P < 0.05$, FWE).

Conclusions: Findings suggest that the improved cognitive performance and increased brain FC and activation after cognitive rehabilitation were significantly maintained after 18 months in patients with PD, despite the structural brain changes, consistent with a progression of neurodegenerative processes.

Correspondence: N. Ibarretxe-Bilbao, Department of Methods and Experimental Psychology, Faculty of Psychology and Education, University of Deusto, Bilbao, Biscay, Spain (tel.: 944139000 ext.2892; e-mail: naroa.ibarretxe@deusto.es).

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Introduction

Cognitive impairment in patients with Parkinson's disease (PD) is present from the early stages of the disease [1]. These cognitive symptoms are related to quality-of-life deterioration and functional disability in patients with PD [2]. Due to the relevance of these symptoms, specific therapeutic strategies are needed to treat cognitive deficits [3].

Cognitive rehabilitation programmes in PD have demonstrated their efficacy in improving a wide range

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of cognitive domains [4]. Previous PD studies have also shown functional brain changes after cognitive rehabilitation in the short term [5,6]. Recently, in a previous study from our group, patients with PD, after attending a 3-month cognitive rehabilitation programme, demonstrated improvements in cognition and functional disability [7], which were accompanied by increased brain functional connectivity (FC) and activation [8].

Longitudinal maintenance of cognitive improvements is one of the main goals of cognitive treatments. However, little is known about the maintenance of the cognitive improvements in patients with PD over time [9]. One study showed the persistence of some cognitive improvements over 6 months after cognitive training [10]. Another study in PD assessed the long-term (12-month) effects of cognitive rehabilitation and found that cognitive treatments could prevent cognitive decline [11]. However, another study in PD found that cognitive training, only when combined with physical activity, resulted in maintained cognitive improvements after a 6-month follow-up period [12]. To the best of our knowledge, no studies have been published using longer term periods and, to date, no study has assessed the long-term effects of cognitive rehabilitation in PD using neuroimaging techniques. Therefore, this study aimed to investigate the longitudinal effects of a cognitive rehabilitation programme evaluating the cognitive, behavioural and neuroimaging changes after an 18-month follow-up period.

Methods

Participants

Patients with PD were recruited from the Department of Neurology at the Hospital of Galdakao and from the PD Biscay Association (ASPARBI). Inclusion criteria were: (i) fulfilled the UK PD Society Brain Bank diagnostic criteria; (ii) aged between 45 and 75 years; and (iii) Hoehn and Yahr disease stage $\leq$3 and Unified Parkinson's Disease Rating Scale (UPDRS) as evaluated by the neurologist. Exclusion criteria were: (i) presence of dementia as defined by the DSM-IV-R and the Movement Disorders Society (MDS) clinical criteria; (ii) presence of other neurological illness/injury; (iii) unstable psychiatric disorders; and (iv) visual hallucinations as assessed by the Neuropsychiatric Inventory Questionnaire. Patients were symptomatically stable and were tested while on their medication. Their levodopa equivalent daily dose (LEDD) was recorded [13]. Sociodemographic characteristics are shown in Table 1.

Procedure

Patients with PD were assessed at pre-treatment (T_0), post-treatment (T_1) and after 18 months (T_2). Neuroimaging changes after cognitive rehabilitation (from T_0 to T_1) were reported in 30 patients with PD (15 each in the experimental and control groups) [8]. The present study evaluated the long-term effects of cognitive rehabilitation comparing T_0 with T_2 and maintenance of the changes comparing T_1 with T_2, by reassessing the 15 patients with PD in the experimental group at T_2. This longitudinal follow-up study was part of a randomized controlled trial (NCT02118480).

Cognitive and behavioural assessment

Patients with PD underwent the same neuropsychological battery at T_0, T_1 and T_2 as previously described [7], which included the assessment of five cognitive domains: (i) processing speed (PS), including

Table 1 Sociodemographic characteristics of patients with Parkinson's disease

	Pre-treatment (T_0)		Post-treatment (T_1)		Longitudinal follow-up (T_2)		Statistics			
							T_0 vs. T_2		T_1 vs. T_2	
	Mean	SD	Mean	SD	Mean	SD	W	*P*	W	*P*
Age (years)	66.07	4.84	66.63	4.60	68.00	4.61	–	–	–	–
Gender (male)	56.25%	–	–	–	–	–	–	–	–	–
Education (years)	10.80	4.64	–	–	–	–	–	–	–	–
MMSE	27.93	1.10	27.94	1.43	28.19	1.94	−0.91	0.35	−0.70	0.47
TAP	20.40	7.10	–	–	–	–	–	–	–	–
Cognitive reserve	12.40	4.77	–	–	–	–	–	–	–	–
LEDD	646.80	406.43	612.14	367.08	641.72	374.64	−0.42	0.67	−1.46	0.14
UPDRS III	18.13	8.84	17.12	8.54	31.08	12.31	−2.79	<0.01	−3.18	<0.01
H&Y scale	1.84	0.36	1.84	0.45	2.35	0.65	−1.89	0.06	−2.34	0.02
Age of disease onset (years)	60.03	8.92	–	–	–	–	–	–	–	–

H&Y, Hoehn and Yahr; LEDD, levodopa equivalent daily dose; MMSE, Mini-Mental State Examination; TAP, pre-morbid intelligence test; UPDRS III, Unified Parkinson's Disease Rating Scale (motor scale); W, Wilcoxon.

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the Trail Making Test–A and Salthouse Letter Comparison Test; (ii) verbal memory (VM), using the Hopkins Verbal Learning Test (learning and recall) (version 3); (iii) visual memory (VIM), using the Brief Visual Memory Test (learning and recall) (version 5); (iv) executive functions (EFs), using the Stroop test (word-colour and interference scores); and (v) theory of mind (ToM), using the Happé test. The following behavioural aspects were also evaluated: (i) apathy, using the Lille Apathy Rating Scale; (ii) depression, using the Geriatric Depression Scale; and (iii) functional disability, using the World Health Organization Disability Assessment Schedule II.

Neuroimage acquisition

Structural and functional imaging data were acquired using a 3-T magnetic resonance imaging scanner (Philips Achieva TX) at OSATEK, Hospital of Galdakao. All sequences were acquired during a single session, and the same acquisition protocol was used at T_0, T_1 and T_2. The neuroimaging acquisition parameters and memory functional magnetic resonance imaging (fMRI) paradigm description are included in Appendix S1.

Neuroimage pre-processing

A comprehensive description of the neuroimaging pre-processing in grey matter (GM), white matter (WM), resting-state and memory fMRI paradigm acquisition types is included in Appendix S2.

Grey matter
Voxel-based morphometry [14] analysis was carried out using the FMRIB Software Library tools. In addition, cortical thickness changes were analysed with FreeSurfer.

White matter
Diffusion data were also pre-processed and analysed using FMRIB Software Library. Fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD) and axial diffusivity (AD) data were extracted and tract-based spatial statistics was used for longitudinal analysis.

Resting-state functional magnetic resonance imaging
The FC pre-processing and analyses were performed using the Conn FC Toolbox [15]. Whole-brain analyses were performed. Region-of-interest (ROI) analyses were also performed to test the maintenance at T_2 of the increased FC from T_0 to T_1 found in patients with PD after attending cognitive rehabilitation (Appendix S2). FC values between these ROIs were extracted from patients with PD at the three time points and entered into SPSS.

Memory functional magnetic resonance imaging paradigm
The fMRI data were pre-processed and analysed using SPM8 (Statistical Parametric Mapping). Whole-brain analyses were performed. ROI analyses were also performed to test the maintenance at T_2 of the increased brain activation from T_0 to T_1 found in patients with PD (Appendix S2). Activation values from these ROIs at the three time points were also extracted from patients with PD and entered into SPSS.

Intervention

From T_0 to T_1, patients with PD attended an integrative group-based cognitive intervention (REHACOP) over a 13-week period (three times/week; 1 h/day). They trained different cognitive functions, in the following order: attention (4 weeks; sustained, selective, alternant, divided), memory (3 weeks; verbal and visual learning, recall, recognition), language (3 weeks; verbal fluency, synonyms/antonyms), EF (2 weeks; cognitive planning, verbal reasoning) and social cognition (1 week; moral dilemmas, ToM). PS was trained during the programme because several tasks were timed. The REHACOP programme is based on the restoration, compensation and optimization of the cognitive functions, and was described extensively in a previous study [7]. Patients with PD did not receive booster sessions from T_1 to T_2.

Statistical analysis

Normality of data was tested using the Shapiro–Wilk test. To evaluate the evolution of the 15 patients with PD after attending cognitive rehabilitation, non-parametric paired *t*-tests were performed in cognitive, behavioural and neuroimaging data between T_0 and T_2 assessments and between T_1 and T_2 assessments. All neuroimaging analyses were performed at $P < 0.05$ corrected for multiple comparisons and fMRI data used LEDD as covariate [16].

Ethical statement

The study protocol was approved by the Ethics Committee at the Health Department of the Basque Mental Health System in Spain and the Ethics Committee of the University of Deusto. All subjects were volunteers and provided a written informed consent before participating in the study.

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Results

Changes from T_0 to T_2

Cognitive and behavioural changes

Patients with PD showed increased performance in VM, VIM, EF and ToM, and decreased functional disability at T_2 compared with T_0 (Table 2). Moreover, there was also a statistical trend toward differences in scores on the apathy scale at T_2. *Post-hoc* analyses were performed to test the changes in the nine subscales of the apathy test and results revealed improvements in the 'Everyday productivity' ($W = 2.33$; $P = 0.02$; $r = 0.60$) and 'Lack of interest' ($W = 2.44$; $P = 0.01$; $r = 0.63$) subscales. Finally, patients with PD showed significant deterioration in UPDRS III (motor score) and a statistical trend towards a progression in disease on the Hoehn and Yahr scale at T_2 compared with T_0 (Table 1). *Post-hoc* correlation analyses showed no significant relationships between the change in UPDRS III and Hoehn and Yahr scale with the cognitive and behavioural changes at T_2.

Neuroimaging changes

Structural changes. Significant reduction in GM volume in the inferior part of the precuneus and the occipital fusiform gyrus was found at T_2 compared with T_0 (Table 3, Fig. 1). However, mean cortical thickness results showed no significant differences. Moreover, decreased WM FA was found mostly in the corpus callosum and corticospinal tract, and increased MD and RD in the posterior thalamic radiation and optic radiation, respectively, at T_2 (Table 3, Fig. 1).

Functional magnetic resonance imaging changes. Resting-state fMRI analyses showed significantly increased FC in the frontotemporal network at T_2 compared with T_0, between the perirhinal cortex [Brodmann area (BA)35L] and dorsolateral prefrontal cortex (BA9L) ($t = 4.18$; $P = 0.029$, FDR; $d = 1.08$), parahippocampal gyrus (BA36L) ($t = 4.24$; $P = 0.029$, FDR; $d = 1.09$) and fusiform gyrus (BA37L) ($t = 4.70$; $P = 0.029$, FDR; $d = 1.21$) (Fig. 2). Whole-brain analyses showed no significant differences in brain activation in the memory fMRI paradigm.

In the previous study, patients with PD showed increased FC during resting-state fMRI in the frontotemporal network and increased brain activation in the memory fMRI paradigm in the frontal and temporal areas after rehabilitation [8]. Therefore, for exploratory purposes, ROI connectivity and activation values were extracted from the 15 patients with PD

Table 2 Cognitive and behavioural changes

	Pre-treatment (T_0)		Post-treatment (T_1)		Longitudinal follow-up (T_2)		Statistics					
							T_0 vs. T_2			T_1 vs. T_2		
	Mean	SD	Mean	SD	Mean	SD	W	*P*	Effect size (*r*)	W	*P*	Effect size (*r*)
PS												
Composite score	–	–	–	–	–	–	0.79	0.427	–	0.62	0.532	–
TMTA (time)	51.47	16.83	47.87	14.89	58.53	29.73	0.1.02	0.306	–	1.42	0.155	–
Salthouse (hits)	19.07	7.19	22.07	7.77	19.00	9.01	0.19	0.842	–	2.93	**0.003**	**0.75**
VM												
Composite score	–	–	–	–	–	–	2.89	**0.004**	**0.74**	0.17	0.865	–
Learning (hits)	16.87	5.65	20.07	5.88	20.33	6.32	3.27	**0.001**	**0.84**	0.25	0.801	–
Recall (hits)	4.53	3.56	7.20	2.80	6.80	2.72	2.28	**0.023**	**0.58**	0.56	0.571	–
VIM												
Composite score	–	–	–	–	–	–	2.89	**0.004**	**0.74**	2.32	**0.020**	**0.59**
Learning (hits)	13.13	8.54	15.93	7.29	18.80	7.60	2.92	**0.003**	**0.75**	2.28	**0.023**	**0.58**
Recall (hits)	5.67	2.94	6.20	2.78	7.20	3.46	2.29	**0.022**	**0.59**	1.83	0.066	–
EFs												
Composite score	–	–	–	–	–	–	3.29	**0.001**	**0.85**	3.35	**0.001**	**0.86**
Stroop word-colour (hits)	27.67	11.54	28.87	11.21	35.47	10.26	3.12	**0.002**	**0.80**	3.11	**0.002**	**0.80**
Stroop interference	−1.03	8.04	−1.37	8.54	7.24	8.09	3.35	**0.001**	**0.86**	3.29	**0.001**	**0.85**
ToM	5.47	1.35	6.13	1.35	6.47	1.64	3.41	**0.001**	**0.88**	0.81	0.416	–
Apathy	−27.47	4.67	−28.13	4.22	−29.47	3.44	1.85	0.063	–	1.81	0.069	–
GDS	2.33	2.49	1.87	2.35	2.47	3.29	0.05	0.957	–	1.72	0.084	–
WHO-DAS-II	20.86	6.23	15.80	3.32	17.53	3.81	2.66	**0.008**	**0.68**	1.65	0.098	–

Bold values are significant at $P < 0.05$; EF, Executive Functions; GDS, Geriatric Depression Scale; PS, Processing Speed; Salthouse, Salthouse Letter Comparison Test; TMTA, Trail Making Test (part A); ToM, Theory of Mind; VIM, Visual Memory; VM, Verbal Memory; W, Wilcoxon; WHO-DAS-II, World Health Organization Disability Assessment Schedule.

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Table 3 Structural grey matter (GM) and white matter (WM) changes from T_0 to T_2

		MNI coordinates					
	Cluster (voxels)	*x*	*y*	*z*	*t*	*P*	Cohen's *d*
GM volume							
Baseline (T_0) > longitudinal follow-up (T_2)							
R precuneus/intracalcarine/lingual gyrus	90	6	−60	10	6.12	0.02	1.58
L occipital fusiform gyrus	85	−22	−70	−14	6.26	0.02	1.61
WM indices							
Baseline (T_0) > longitudinal follow-up (T_2)							
FA							
L callosal body	19879	−18	−22	35	3.71	0.001	0.95
R corticospinal tract	649	32	−13	46	4.89	0.03	1.26
	98	26	−18	12	1.84	0.04	0.47
Baseline (T_0) < longitudinal follow-up (T_2)							
MD							
R posterior thalamic radiation (including optic radiation)	5805	30	−59	18	4.84	0.02	1.25
RD							
R optic radiation	7543	22	−60	33	3.51	0.02	0.90
R corticospinal tract	179	28	−11	43	3.58	0.04	0.92

FA, Fractional Anisotropy; L, Left; MD, Mean Diffusivity; R, Right; RD, Radial Diffusivity. Cluster size denotes the extent of the cluster of significant voxels. Montreal Neurological Institute (MNI) coordinates refer to the location of the most statistically significant voxel in the cluster. Results are shown at $P < 0.05$, FWE corrected.

assessed at the three time points ($T_0/T_1/T_2$). Results showed that the brain FC and activation values in the specific ROIs at T_2 were higher compared with T_0, although they were reduced compared with T_1 (Fig. 3).

Changes from T_1 to T_2

Cognitive and behavioural changes

Patients with PD showed no significant changes in PS, VM, ToM, apathy, symptoms of depression or functional disability and showed increased performance in VIM and EF at T_2 compared with T_1 (Table 2).

Neuroimaging changes

Structural changes. We found no significant changes in GM volume or mean cortical thickness. However, WM indices showed significantly decreased FA and increased MD, RD and AD at T_2 compared with T_1 (Table S1, Fig. S1).

Functional magnetic resonance imaging changes. No significant changes were found during the memory fMRI paradigm from T_1 to T_2. During resting-state, patients with PD showed decreased FC within the default-mode network between BA33 and the posterior cingulate cortex ($t = 5.07$; $P = 0.02$, FDR; $d = 1.31$). In addition, patients with PD also showed increased FC between the somatomotor network and default-mode network, specifically between BA5–BA28 ($t = 4.62$; $P = 0.047$, FDR; $d = 1.19$) and bilateral BA7–BA30 (right: $t = 4.41$; $P = 0.01$, FDR; $d = 1.13$; left: $t = 5.22$; $P = 0.03$, FDR; $d = 1.34$) (Fig. S2).

Discussion

This study aimed to investigate the long-term (18-month) effects of an integrative cognitive rehabilitation programme in PD, assessing cognitive, behavioural and neuroimaging changes. Results showed that the improvements found from baseline to post-treatment in cognition and functional disability [7], and the increased FC and activation [8], were still present after an 18-month follow-up.

Findings revealed increased cognitive performance in most cognitive domains in the long-term compared with baseline, which supports the long-term effects of cognitive rehabilitation. In the previous study, after attending a 3-month cognitive rehabilitation programme, patients with PD improved in PS, VIM, ToM and tendency to change in VM [7]. In the present study, patients with PD showed maintenance of these cognitive improvements in the long term. Previous studies in PD showed maintenance of cognitive improvements after 6 months [10,12] and 12 months [11]. This study found that cognitive improvements could be maintained for a longer period of time. The REHACOP is a structured programme based on the theoretical models of the neuropsychological rehabilitation (restoration, compensation and optimization). Therefore, the combination of these three orientations as well as the combination of function training and strategy training could have helped to maintain these improvements over time. However, reduced performance in the Salthouse Letter Comparison test also been found. We hypothesized that booster sessions

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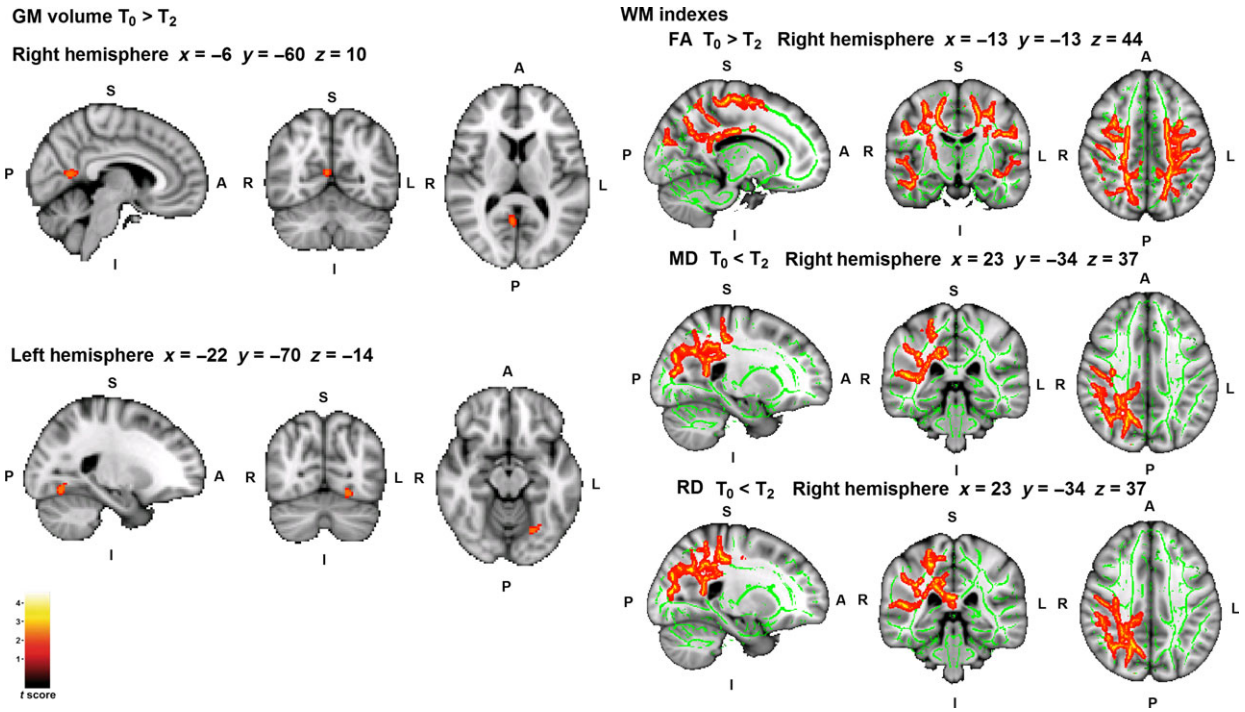

Figure 1 Whole-brain structural changes from T_0 to T_2. Significant grey matter (GM) and white matter (WM) regions are shown in red/yellow; the WM skeleton is shown in green. A, Anterior; FA, Fractional Anisotropy; I, Inferior; L, Left; MD, Mean Diffusivity; P, Posterior; R, Right; RD, Radial Diffusivity; S, Superior. Coordinates are shown in Montreal Neurological Institute space. Results are shown at $P < 0.05$ corrected for multiple comparisons. [Colour figure can be viewed at wileyonlinelibrary.com].

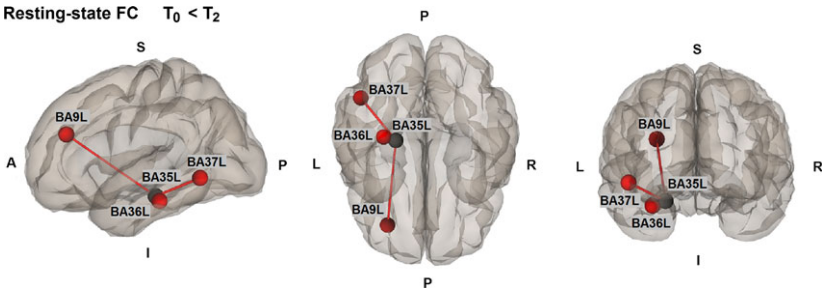

Figure 2 Whole-brain functional connectivity (FC) changes from T_0 to T_2. Red line, increased FC at T_2 compared with T_0; black point, seed; red points, targets. A, Anterior; BA, Brodmann area; I, Inferior; L, Left; P, Posterior; R, Right; S, Superior. Results are shown at $P < 0.05$ corrected for multiple comparisons. [Colour figure can be viewed at wileyonlinelibrary.com].

might have been useful for the maintenance of this specific cognitive domain.

Another important finding of the study was that functional disability and some aspects of apathetic symptomatology could be maintained after 18 months. It is important to mention that the functional disability score in the present study was decreased in the long term compared with baseline, but slightly increased compared with post-treatment. More research is needed to evaluate the long-term effects on functional outcome with longer periods of time and the possible benefits of booster sessions. Nevertheless, the fact that transfer effects on behavioural aspects could be maintained over time in PD is an important finding with regard to the efficacy of cognitive rehabilitation programmes.

Regarding neuroimaging results, patients with PD showed that both increased brain connectivity during resting-state fMRI and increased brain activation during the memory fMRI paradigm found in patients with PD after rehabilitation [8] were still present at follow-up. In the previous study, patients with PD after cognitive rehabilitation showed increased FC in the frontotemporal network (BA9L–BA20 bilateral) from baseline to post-treatment [8], and results from this study showed increased FC in the same network

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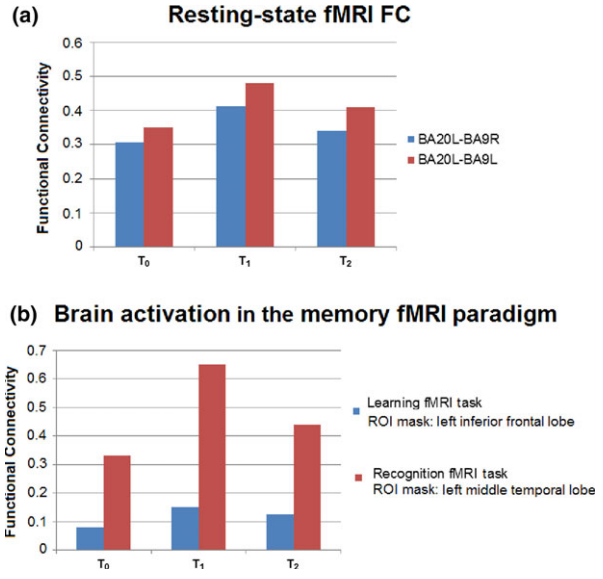

Figure 3 Neuroimaging changes with region of interest (ROI) analyses from patients with Parkinson's disease (PD) at three time points. (a) Values represent the functional connectivity of patients with PD between the two ROIs at the three time points. ■, BA20L–BA9R; ■, BA20L–BA9L. (b) Values represent the brain activation of patients with PD in the ROI mask at the three time points. ■, learning fMRI task, ROI mask: left inferior frontal lobe; ■, recognition fMRI task, ROI mask: left middle temporal lobe. [Colour figure can be viewed at wileyonlinelibrary.com].

in the long-term compared with baseline. Interestingly, the same brain area in the frontal lobe (BA9L) maintained the increased FC with the temporal lobe. Moreover, after 18 months, the brain connectivity and activation values from specific ROIs were increased compared with baseline, but decreased compared with post-treatment. We hypothesized that the reduction of FC in the long-term compared with post-treatment could be related to the progression of the neurodegenerative disease, which may result in a future decline of the cognitive improvements.

Furthermore, neuroimaging assessment detected structural changes consistent with a progression of neurodegenerative processes. Slight GM reduction in the occipital and parietal lobes was detected at long-term follow-up. Previous PD studies assessing the progression of the disease found GM reduction in the same brain areas [17,18]. Moreover, the neurodegenerative process was mostly detected in alterations of WM integrity. Patients with PD showed bilateral reduced FA and increased MD and RD mostly in the posterior part of the right hemisphere. We have to be cautious when interpreting WM indices, but literature suggests that FA, MD and RD could be biomarkers for microstructural brain tissue integrity, membrane cell density and myelin integrity respectively [19]. A recent PD study also found alterations in WM integrity with disease progression, showing FA reduction and AD and RD increment after 12 months in the frontal, temporal and occipital lobes, including the corpus callosum [20]. Finally, the degenerative process of patients with PD was also reflected in the deterioration of motor symptoms. The progression of motor symptoms is part of the evolution of PD [21], and this study found that, despite the motor evolution, the non-motor symptoms of the disease can be improved.

This is the first study in PD to use neuroimaging techniques to assess the long-term effects of cognitive rehabilitation. Neuroimaging data provide insight into the brain changes that are associated with cognitive and behavioural changes, and they show the cerebral bases of cognitive rehabilitation. Findings reinforce the efficacy of cognitive improvements after training, and support the long-term effects of cognitive treatments.

Some limitations should be taken into account. First, this study did not include a long-term follow-up of the control group. Several PD studies showed that the normal course of brain activity is the decrement of FC and activation as the disease progresses, these decrements being correlated with clinical and cognitive decline [22,23]. These previous findings support the significance of the present study and suggest that, despite the absence of a control group, findings from this study are promising and important for the field of neurorehabilitation in PD. Moreover, the Stroop test was used to evaluate EF, but other tests, such as the Wisconsin Card Sorting Test, would be more representative. Furthermore, language domain was not included in the assessment. Finally, it would be interesting to evaluate the long-term effects of cognitive rehabilitation with booster sessions.

Conclusions

Findings suggest the long-term maintenance of the cognitive, functionality and brain changes after attending a 3-month cognitive rehabilitation programme. These findings support the possibility that cognitive rehabilitation programmes in PD might prevent cognitive deterioration even after 18 months, and showed brain plasticity in a neurodegenerative disease, which encourages the replication of these findings.

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Disclosure of conflicts of interest

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Whole-brain white matter changes from T_1 to T_2.
Figure S2. Whole-brain functional connectivity changes from T_1 to T_2.
Table S1. White matter indices changes from T_1 to T_2.
Appendix S1. Neuroimaging acquisition parameters.
Appendix S2. Neuroimaging pre-processing.

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VI. Discussion

6. General Discussion

The objective of this thesis was to evaluate the brain correlates of cognitive impairment and assess the efficacy of cognitive rehabilitation in brain, behavioral aspects and cognition in PD.

The *study I* aimed to investigate the brain correlates of ToM deficit in PD patients. Results showed presence of ToM deficit in PD patients, and this deficit correlated with GM volume decrease and WM alterations. Specifically, ToM deficit correlated with GM volume decrease in the left medial frontal cortex, inferior frontal gyrus, anterior cingulate gyrus, precentral gyrus, and postcentral gyrus, all regions known to be involved in ToM performance (Carrington & Bailey, 2009; Rizzolatti & Craighero, 2004; Schurz et al., 2014). Similar results have been obtained in other pathologies such as progressive supranuclear palsy (Ghosh et al., 2012) autism spectrum disorder, schizophrenia (Sugranyes, Kyriakopoulos, Corrigall, Taylor, & Frangou, 2011) and Alzheimer´s disease (Kumfor et al., 2014). WM alterations also showed relationship with ToM deficit in PD, in the superior longitudinal fasciculus (adjacent to the parietal lobe) and WM tracts adjacent to the frontal lobe. The superior longitudinal fasciculus connects the dorsolateral prefrontal cortex with the parietal areas (Makris et al., 2005), involving all cortical areas related to ToM performance (Schurz et al., 2014). In addition, the uncinate fasciculus and inferior fronto-occipital fasciculus adjacent to the orbitofrontal cortex also showed significant associations with ToM deficit in PD. These findings add evidence to previous studies that related the ability to process social and emotional information to the frontal lobes in PD (Bodden et al., 2010; Carrington & Bailey, 2009; Ibarretxe-Bilbao et al., 2009; Monetta et al., 2009; Poletti et al., 2011; Poletti et al., 2012; Rizzolatti & Craighero, 2004; Schurz et al., 2014), and to the uncinate fasciculus and inferior fronto-occipital fasciculus in other pathologies (Barnea-Goraly et al., 2004; Von Der Heide, Skipper, Klobusicky, & Olson, 2013). Moreover, previous studies have demonstrated

that ToM was related to executive functioning (Costa et al., 2013; Monetta et al., 2009). PD patients involved in this study also showed associations between ToM and executive dysfunction. Interestingly, after controlling for executive functions, the relationship between ToM deficit and WM remained significant for WM areas adjacent to the precuneus and the parietal lobe. As we hypothesised, the prefrontal and medial frontal clusters may mostly represent the influence of executive functions on ToM. The strength of the correlation between ToM deficit and WM in PD remained significant mainly in WM tracts adjacent to the parietal lobe and precuneus. Results suggest that ToM should be considered as an independent cognitive function, and ToM deficits cannot be only understood as a consequence of executive dysfunction. With all, findings may suggest that the frontal component of ToM is due to the influence of executive functions and that "pure ToM" is related to the precuneus and parietal lobe. To summarise, this study reinforces the presence of ToM impairment in PD, and the findings suggest associations with GM volume in the prefrontal cortex, precentral gyrus and somatosensory cortex, and with WM alterations in the right superior longitudinal fasciculus and corticospinal tract (adjacent to the parietal lobe), and WM tracts adjacent to the orbitofrontal cortex. However, after controlling for executive functions in the regression analysis, the associations of prefrontal regions with ToM deficit were no longer significant. This may suggest that the frontal component of ToM is due to the influence of executive functions and that "pure ToM" is related to the precuneus and parietal lobe.

The *study II* aimed to evaluate the dynamic FC characteristics of PD patients with MCI diagnosis and with normal cognition. Cognitive impairment is a common symptom in PD patients and dynamic FC has been described as a more accurate approach to measure FC over time. Results revealed two different connectivity states in the whole sample, a hyper-connected state and a hypo-connected state. The sparsely connected state was present 78% of the time. Interestingly, the same number of FC states was found in a recent dynamic FC study

in PD and also the sparsely connected was significantly more present (Kim et al., 2017). Specifically, the present study analyzed the dynamic FC pattern in PD patients with MCI and with normal cognition. Results of this study showed that PD patients with MCI diagnosis exhibited dynamic FC alterations in mean dwell time, spending significantly less time in the state characterized by hypo-connectivity compared with the HC. Moreover, PD-MCI patients showed increased number of changes between FC states compared with the HC. Contrary to PD-MCI patients, there were no significant differences in dynamic FC indexes between PD-NC and HC. However, despite not finding significant differences, PD-NC patients showed slight increased state transitions compared to the HC. The previous dynamic FC study in PD subjects without MCI diagnosis showed no significant differences in state transitions compared to HC, but the number of transitions was also slightly elevated compared to HC (Kim et al., 2017). Results in both studies might represent a gradual dysfunctional pattern in PD patients that increases with more severe cognitive deterioration. Moreover, FC differences between PD-MCI, PD-NC and HC in each dynamic FC state were also investigated. PD-MCI patients in this study showed reduced FC in the hypo-connected state compared with the HC, showing reduced inter-network connectivity mostly between the somatomotor network and cognitive control networks, but also between the somatomotor network and visual network, between the somatomotor network and auditory network, between the cognitive control network and visual network and between the subcortical network and default-mode network. Previous studies in PD-MCI patients also found reduced FC compared with the HC (Baggio et al., 2015; Göttlich et al., 2013). The disconnection between networks has only been found in the PD-MCI group, while PD-NC patients showed no significant differences compared with the HC. These results, added to previous results in PD patients with MCI (Amboni et al., 2015; Baggio et al., 2015; Gorges et al., 2015; Lucas-Jiménez et al., 2016), support that reduced connectivity is linked to the presence of cognitive deficits in PD patients. Dynamic

FC alterations in PD-MCI patients were accompanied by impairment in graph topological parameters in two nodes located in the somatomotor network (right BA4 and left BA6). The reduced betweenness centrality in the node BA6 (left hemisphere) in PD-MCI group suggests a poorer communication between the adjacent nodes in the network. Moreover, results showed a loss of efficiency when transferring the information in the node BA4 (right hemisphere). Both nodes were located in the somatomotor network and remarkably, most of the reduced FC found in the PD-MCI group, was located between these two nodes and other brain regions. This may suggest that the reduced efficiency when transferring the information in the somatomotor network could have influenced the poorer FC between the somatomotor network and other networks in PD-MCI patient. With all, this is the first study to assess the dynamic FC characteristics in PD-MCI and PD-NC. Findings suggest that the temporal properties of FC in PD could add relevant information about the neural substrates of PD-MCI deterioration, and its differences with PD-NC patients. Moreover, graph theoretical analyses could add information to the FC results in order to better understand the neurobiological processes of cognitive deterioration in PD.

Due to the relevance and the high prevalence of cognitive deficits in PD, therapeutic strategies are needed to treat cognitive decline. Therefore, the *study III* aimed to investigate the efficacy of cognitive rehabilitation on improving cognitive functions and behavioral aspects in PD patients. Previous studies that assessed the efficacy of cognitive rehabilitation in PD have been focused on few cognitive domains. Therefore, this study aimed to investigate the efficacy of an integrative cognitive rehabilitation program, which trained attention, memory, language, executive functions, social cognition and processing speed. Patients after attending a cognitive rehabilitation program showed improvements in processing speed, visual learning and memory and ToM. Results from this study reinforce previous findings of cognitive rehabilitation in PD patients and support its efficacy on improving cognition

(Hindle et al., 2013; Leung, 2015). Moreover, PD patients after intervention also showed reduced functional disability. These results suggest that cognitive rehabilitation programs not only improve cognitive functions but also could have an impact on functional outcome, and support that benefits can be transferred to other variables that have not been trained directly during the cognitive program. This study is the first randomized controlled trial of cognitive training that has demonstrated a significant improvement in functional disability in PD. Previous studies also evaluated the efficacy of cognitive rehabilitation on quality of life aspects, but no significant results were found (París et al., 2011), and authors related the findings to the duration of treatment. The present study used an integrative cognitive rehabilitation program that lasted 3 months; therefore, the duration of treatment could be a critical factor in order to find changes in functionality in PD patients.

Few studies have evaluated whether a cognitive rehabilitation program could produce cerebral changes in PD patients. Therefore, the *study IV* aimed to evaluate the structural and functional cerebral changes related to an integrative cognitive rehabilitation program in patients with PD. Results show that patients with PD increased their brain connectivity and brain activation after rehabilitation. Specifically, PD patients that received cognitive rehabilitation showed increased brain connectivity between the left inferior temporal lobe and the bilateral dorsolateral prefrontal cortex. In this study, the cognitive function of attention was trained during 4 weeks and interestingly, a previous resting-state fMRI study in PD patients also found increased brain connectivity in the dorsolateral prefrontal cortex after attention rehabilitation (Cerasa et al., 2014). Furthermore, the fronto-temporal network connects the prefrontal with the temporal cortex, both areas related to other cognitive functions trained in the cognitive rehabilitation program, such as executive functions (Nagano-Saito et al., 2005), language, verbal fluency (Pereira et al., 2009b), memory (Cabeza & Nyberg, 2000; van Paasschen et al., 2013) and ToM (Díez-Cirarda et al., 2015). Results

also showed that the experimental group had increased brain activation after cognitive rehabilitation during the learning and recognition tasks of the memory fMRI paradigm. Specifically, during the learning fMRI task, PD patients had increased brain activation in the left inferior frontal area after rehabilitation. Furthermore, during the recognition fMRI task, the PD patients showed increased brain activation in the left middle temporal lobe after intervention. These results are coherent with previous literature because the frontal lobe is known to be involved in memory performance in PD in both encoding and retrieval processes (Cabeza & Nyberg, 2000; Eichenbaum, Yonelinas, & Ranganath, 2007) and the temporal lobe has been associated with the retrieval process (Cabeza & Nyberg, 2000). Furthermore, this study also assessed whether cognitive rehabilitation programs could be related to GM changes. As expected by the authors, no significant differences in GM volume after three months of cognitive rehabilitation were found. Finally, the brain connectivity and activation values in the experimental group at post-treatment correlated with the final performance in cognitive functions. With all, these findings suggest that integrative cognitive rehabilitation programs have an impact on cerebral activation and connectivity in PD patients. In addition, significant and positive relationships between the brain connectivity and activation and cognitive performance have been found in PD patients after attending cognitive rehabilitation.

Finally, the last goal of cognitive rehabilitation programs is the long-term maintenance of the changes. However, few studies have been performed in PD. Therefore, the *study V* aimed to investigate the long-term (18-month) effects of an integrative cognitive rehabilitation program in PD, assessing cognitive, behavioral and neuroimaging changes. Results showed that the improvements found from baseline to post-treatment in cognition and functional disability, and the increased FC and activation (Díez-Cirarda et al., 2016), were still present after an 18-month follow-up. Findings revealed increased cognitive performance in most cognitive domains at long-term compared to the baseline, which supports the long-term

effects of cognitive rehabilitation. Another important finding of the study was that functional disability and some aspects of apathetic symptomatology could be maintained after 18 months. Regarding neuroimaging results, PD patients showed maintenance of brain changes at long-term. The increased brain connectivity during resting-state fMRI and the increased brain activation during the memory fMRI paradigm found in PD patients after rehabilitation were still present at follow-up. In the previous study, PD patients after cognitive rehabilitation showed increased FC in the fronto-temporal network (BA9L–BA20 bilateral) from baseline to post-treatment, and results from this study showed increased FC in the same network in the long-term compared to baseline. Interestingly, the same brain area in the frontal lobe (BA9L) maintained the increased FC with the temporal lobe. Moreover, after 18 months, the brain connectivity and activation values from specific ROIs were increased compared to baseline, but reduced compared to post-treatment. The reduction of FC could be related with the progression of the neurodegenerative disease which may result in a future decline of the cognitive improvements. Furthermore, neuroimaging assessment detected structural changes consistent with a progression of neurodegenerative processes. Slight GM volume reduction and alterations of WM integrity and diffusivity were found in PD patients at long-term compared to baseline. Finally, the degenerative process of PD patients was also reflected in the deterioration of motor symptoms, which is part of the evolution of PD (Hoehn & Yahr, 1967). However, despite the motor and structural brain deterioration, the non-motor improvements and brain activity changes could be maintained over time. In conclusion, this is the first study in PD that used neuroimaging techniques to assess the long-term effects of cognitive rehabilitation. Neuroimaging data provide insight into the brain changes that are associated with cognitive and behavioral changes, and they show the cerebral bases of cognitive rehabilitation. Findings from this study reinforce the efficacy of cognitive improvements after training, and support the long-term effects of cognitive treatments.

VII. Conclusions

7. Conclusions

The main conclusions of the thesis, derived from the five studies, can be summarized as follows:

- PD patients showed ToM impairment, which was related to WM integrity and diffusivity alterations and GM volume decrease in prefrontal and parietal areas. In addition, after controlling for executive functions, the relationship between ToM deficit and WM remained significant for WM areas adjacent to the precuneus and the parietal lobe.

- PD patients with MCI showed dynamic FC alterations compared to HC, including reduced *mean dwell time* in the hypo-connected state and increased number of *state transitions.* In addition, these dynamic FC alterations were accompanied by graph theoretical dysfunctions, such as reduced *clustering coefficient* and reduced *betweenness centrality* in the somatomotor network. These alterations were not present in PD patients with normal cognition. Therefore, dynamic FC is a novel neuroimaging approach that could add relevant information in the neurobiological bases of MCI diagnosis in PD.

- An integrative cognitive rehabilitation program is effective on improving cognitive functions, such as processing speed, visual memory and ToM in PD. In addition, PD patients also showed reduced functional disability after cognitive rehabilitation. Findings in this study support the efficacy of cognitive rehabilitation in PD, and suggest that benefits from cognitive treatments can be transferred to clinical variables that have not been trained directly during the cognitive program.

- PD patients after attending cognitive rehabilitation showed brain functional changes, such as increased functional connectivity in the fronto-temporal network during resting-state

and increased brain activation in the frontal and temporal lobes during a fMRI memory paradigm.

- Cognitive rehabilitation effects on brain, functional disability and cognition in PD were maintained after 18 months follow-up, despite the structural brain changes and evolution of motor symptoms, consistent with a progression of the neurodegenerative process.

Conclusiones

Las principales conclusiones de la tesis, derivadas de los cinco estudios, se pueden resumir de la siguiente manera:

- Los pacientes con EP mostraron un deterioro de ToM, que se relacionó con la integridad y la difusividad de sustancia blanca y la disminución del volumen de sustancia gris en las áreas prefrontal y parietal. Además, después de eliminar la influencia de las funciones ejecutivas, la relación entre el déficit de ToM y la sustancia blanca siguió siendo significativa para las áreas adyacentes al precuneus y al lóbulo parietal.

- Los pacientes con EP con deterioro cognitivo mostraron alteraciones de conectividad funcional dinámica en comparación con personas sanas, revelando un menor tiempo de permanencia en el estado de conectividad funcional caracterizado por la hipoconectividad y también mostraron un mayor número de transiciones entre los estados de conectividad funcional. Además, estas alteraciones se acompañaron de alteraciones en parámetros de teoría de grafos sobre todo en la red cerebral somatomotora. Estas alteraciones no estaban presentes en pacientes con EP con cognición normal. Por lo tanto, el análisis de la conectividad funcional dinámica es un nuevo enfoque para los análisis de neuroimagen que podría añadir información relevante sobre las bases neurobiológicas del diagnóstico de deterioro cognitivo en la EP.

- Un programa integral de rehabilitación cognitiva es efectivo para mejorar las funciones cognitivas, como la velocidad de procesamiento, la memoria visual y ToM en la EP. Además, los pacientes con EP también mostraron una discapacidad funcional

reducida después de la rehabilitación cognitiva. Los hallazgos en este estudio respaldan la eficacia de la rehabilitación cognitiva en la EP, y sugieren que los beneficios de los tratamientos cognitivos pueden transferirse a variables clínicas que no se han entrenado directamente durante el programa cognitivo.

- Los pacientes con EP después de asistir a la rehabilitación cognitiva mostraron cambios cerebrales funcionales, incluyendo una mayor conectividad funcional en la red fronto-temporal durante el estado de reposo y mayor activación cerebral en los lóbulos frontal y temporal durante el paradigma de memoria dentro de la resonancia.

- Los efectos de la rehabilitación cognitiva en los cambios cerebrales, la discapacidad funcional y la cognición se mantuvieron después de 18 meses de seguimiento en pacientes con EP, a pesar de los cambios estructurales en el cerebro y la evolución de los síntomas motores, que van acorde con el proceso neurodegenerativo de la EP.

VIII. References

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