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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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la A a la derecha y la izquierda las demás.

Por si fuera poco nos ponen en un foco que tenemos que poner las palabras

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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)

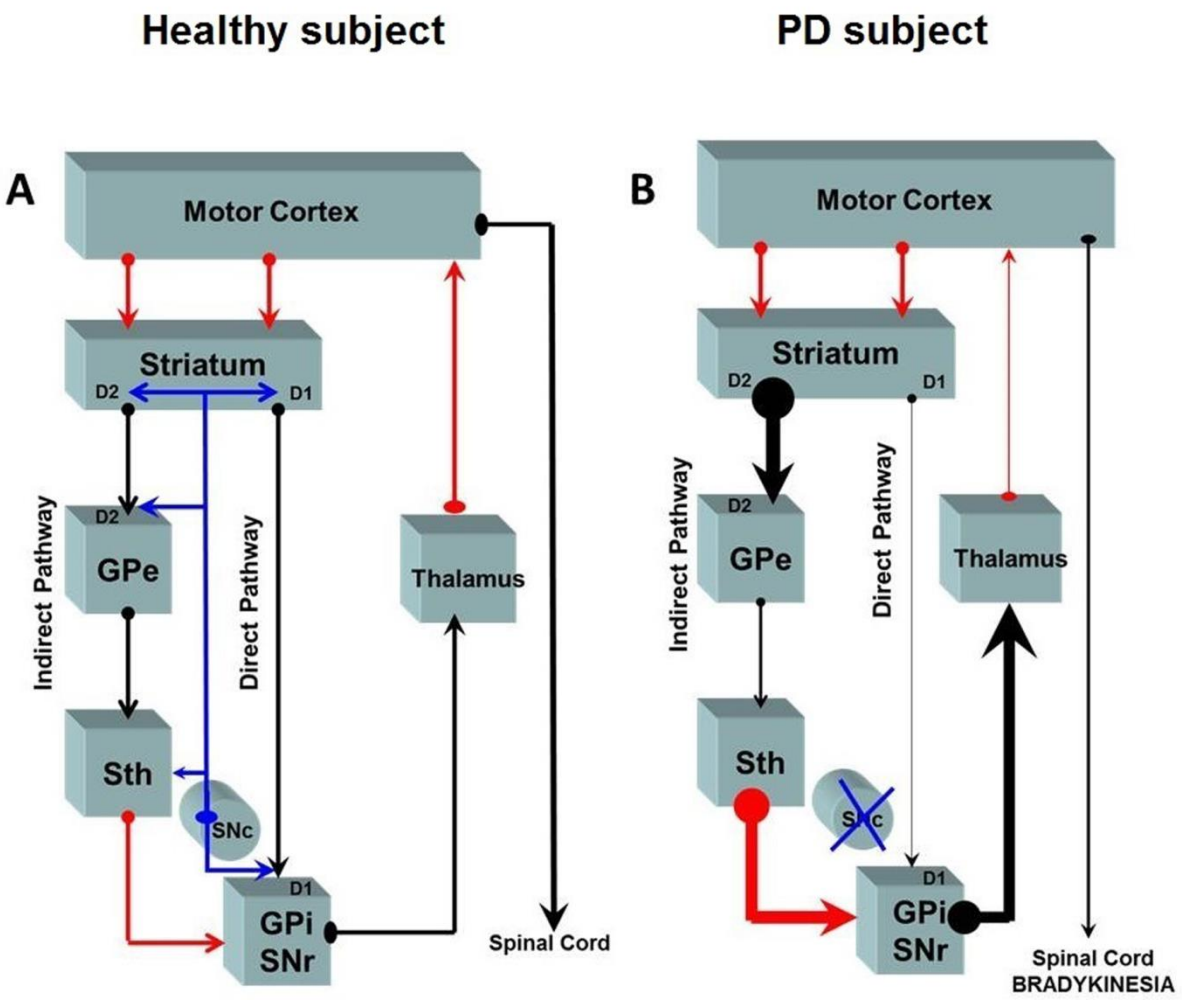


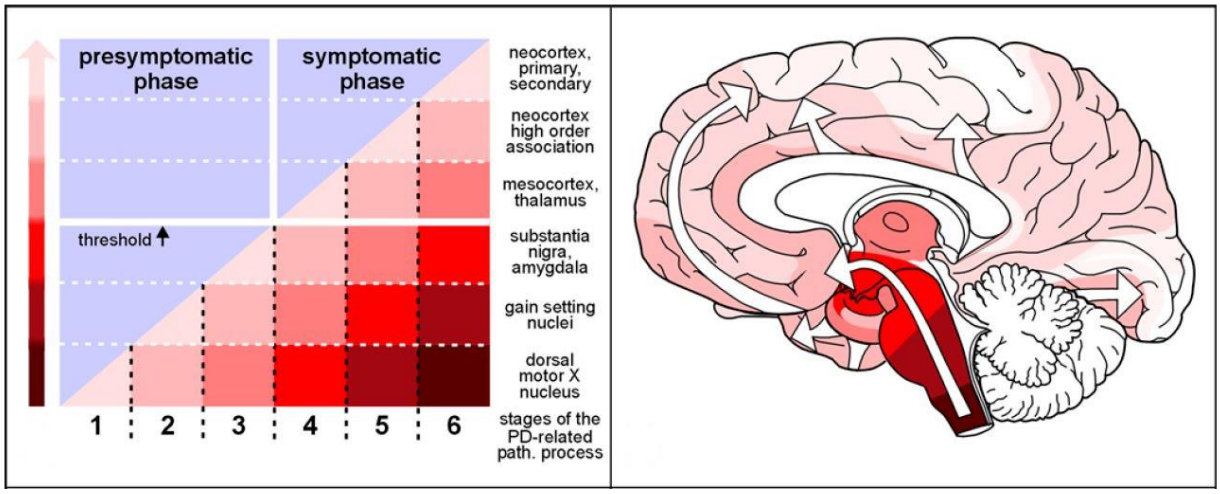
Figure 1 Legend: Dopaminergic pathways in healthy subjects A), and in PD subjects B). Blue arrows represent dopamine pathways; Red arrows represent excitatory pathways (GABA); Black arrows represent inhibitory pathways (glutamate). D1= dopamine receptor; D2= dopamine receptor; GPe= External globus pallidus; 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

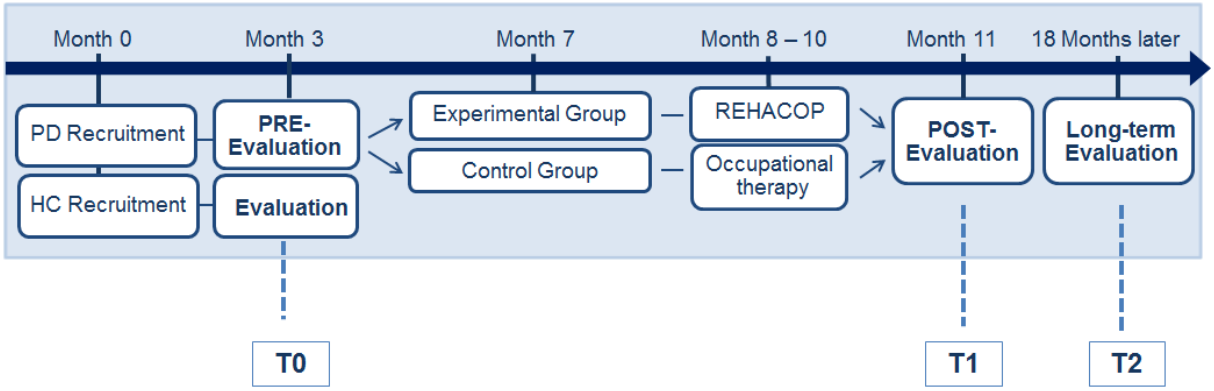


Figure 3 Legend: PD= Parkinson's disease; HC=Healthy Controls; REHACOP= Cognitive Rehabilitation Program.

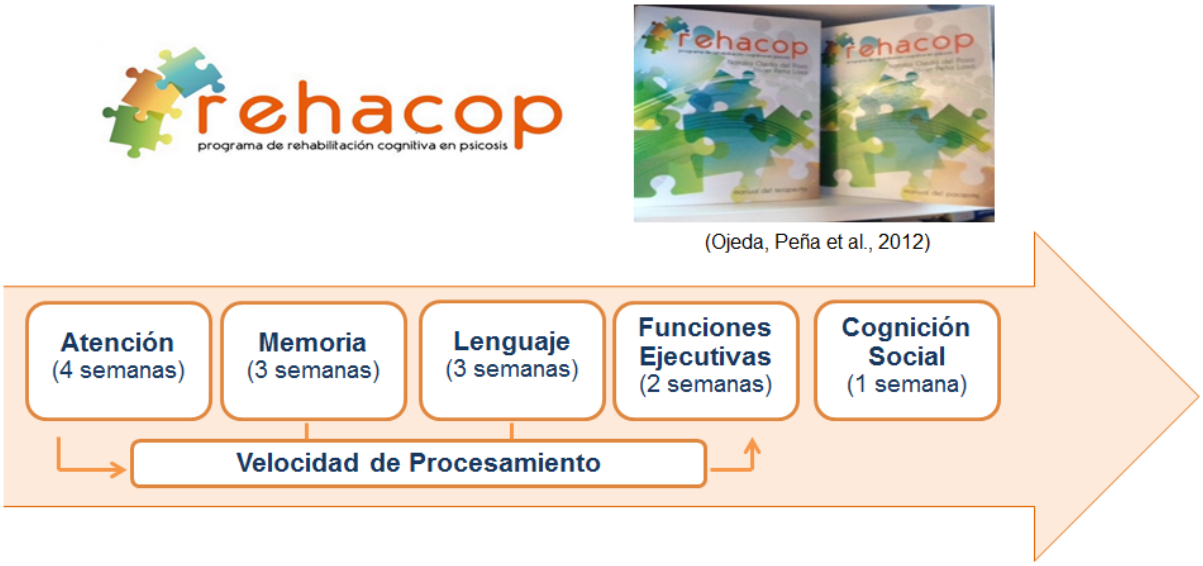
4.3 REHACOP: Integrative cognitive rehabilitation program

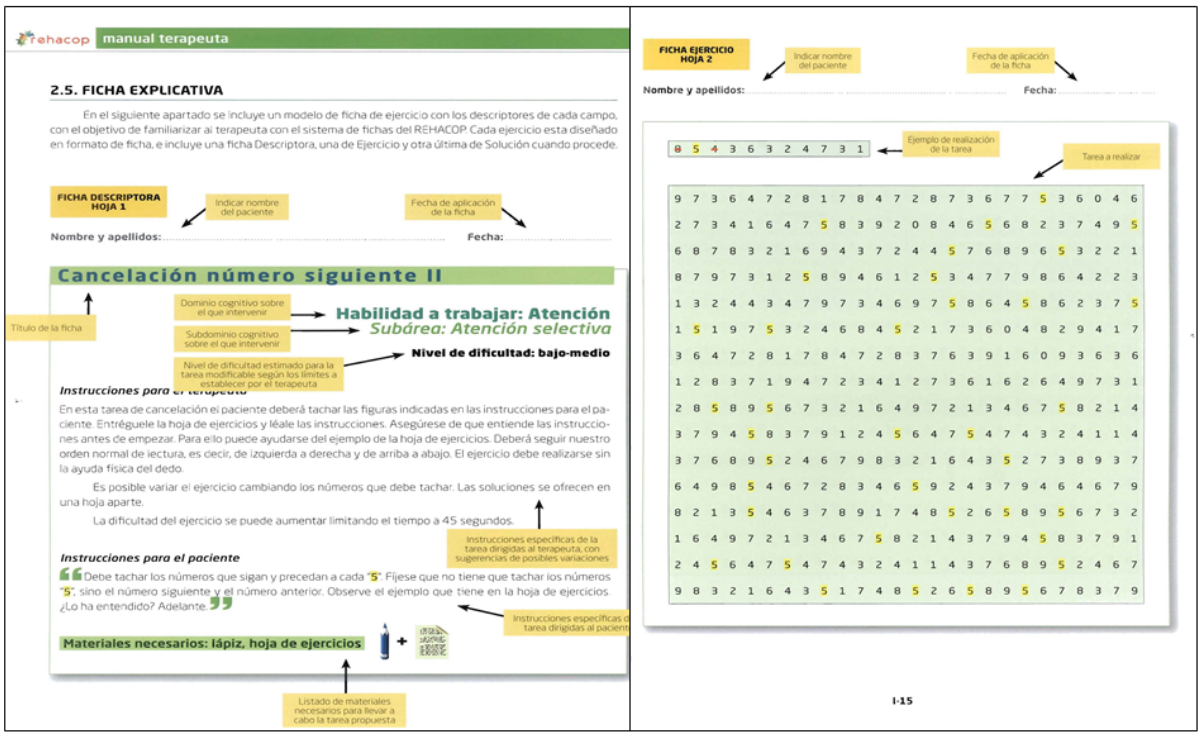
The cognitive rehabilitation program used in the present thesis is the REHACOP (www.rehacop.deusto.es). REHACOP is a structured program using paper-pencil tasks (based on restoration, compensation, and optimization strategies of rehabilitation) with a gradual level of cognitive effort and demand. REHACOP 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)].

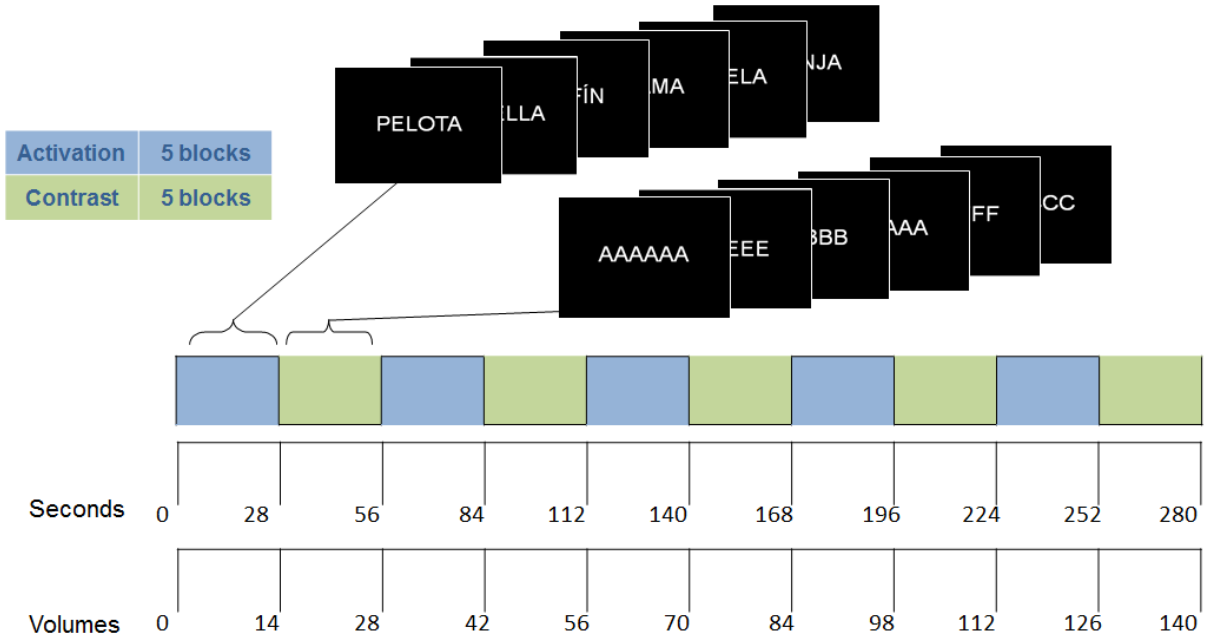
The memory fMRI paradigm consisted of words presented inside a 3T magnet with Visual Digital MRI Compatible High Resolution Stereo 3D glasses and Presentation® version 10.1 (Neurobehavioral Systems), running on Windows XP. They were also given two controls (one in each hand) connected to a MR-compatible 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"

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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