Structural and functional brain changes of cognitive and other non-motor dysfunctions in idiopathic and genetic Parkinson's disease

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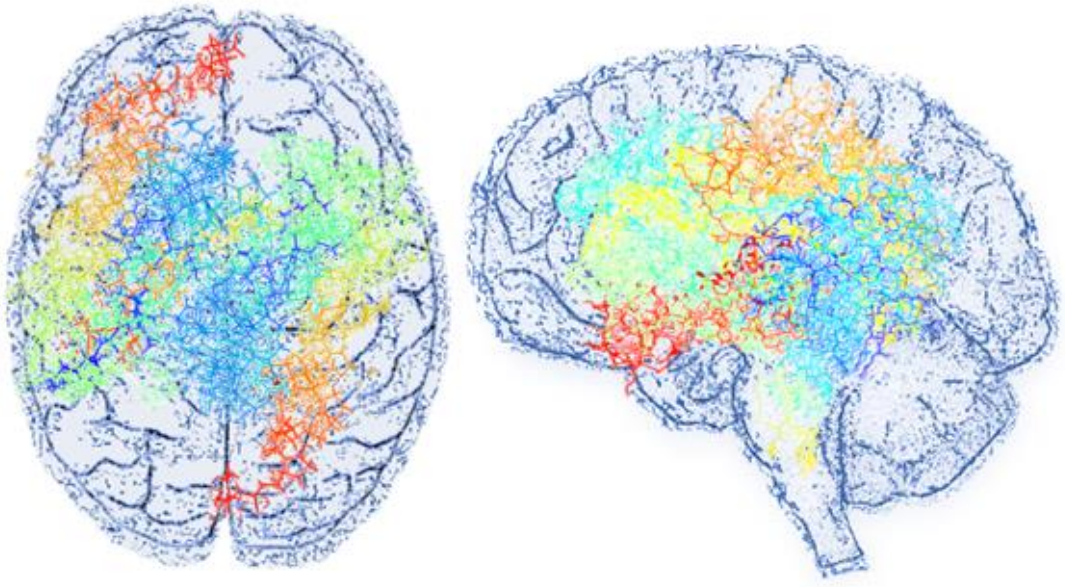

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This thesis has been carried out in the Neuropsychology of Severe Medical Conditions Research Team (coordinated by Dr. Natalia Ojeda del Pozo as Principal Investigator), in the Department of Methods and Experimental Psychology, Faculty of Psychology and Education, University of Deusto. This group has been qualified with the maximum research label by the Basque Government (Category A-Excellence).

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Dr. Naroa Ibarretxe Bilbao, Director of the Master in Clinical Neuropsychology, Assistant Professor of the Department of Methods and Experimental Psychology, Director of the present thesis; and Dr. Natalia Ojeda del Pozo, Principal Investigator of the Neuropsychology of Severe Medical Conditions Research Team, Head and Full Professor of the Department of Methods and Experimental Psychology, Director of this thesis, certify that the present thesis entitled "**Structural and functional brain changes of cognitive and other non-motor dysfunctions in idiopathic and genetic Parkinson's disease**", represents an original research work, which is presented by Olaia Lucas Jiménez to obtain the grade of Doctor of Psychology.

Director

Dr. Naroa Ibarretxe Bilbao

Director

Dr. Natalia Ojeda del Pozo

Bilbao, September 2019

A Jon,

Lo importante no es lo que nos hace el destino,
sino lo que nosotros hacemos de él
Florence Nightingale (1820-1910)

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"The single greatest cause of happiness is gratitude".
Auliq-Ice

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"No Signs of Struggle"

Growing small requires enormity of will: just sitting still in the doctor's waiting room watching the future shuffle in and out, watching it stoop; stare at you while you try not to look. Rare is an exchange: a smile of brief, wry recognition.

You are the new kid on the block. Everyone here was you once. You are still learning that growing small requires a largeness of spirit you can't fit into yet: acceptance of irritating help from those who love you; giving way and over, but not up.

You've swallowed hard the contents of the "Drink Me" bottle, and felt yourself shrink. Now, familiar furniture looms, floors tilt, and doorknobs yield only when wrestled round with both hands. It demands colossal patience, all this growing small: your diminished sleep at night, your handwriting, your voice, your height.

You are more the incredible shrinking woman than the Buddhist mystic, serene, making do with less. Less is not always more. Yet in this emptying space, space glimmers, becoming visible. Here is a place behind the eyes of those accustomed by what some would call diminishment.

It is a place of merciless poetry, a gift of presence previously ignored, drowned in the daily clutter. Here every gesture needs intention, is alive with consciousness. Nothing is automatic.

You can spot it in the provocation of a button, an arm poking at a sleeve, a balancing act at a night-time curb while negotiating the dark. Feats of such modest valor, who would suspect them to be exercises in an intimate, fierce discipline, a metaphysics of being relentlessly aware?

Such understated power here, in these tottering dancers who exert stupendous effort on tasks most view as insignificant. Such quiet beauty here, in these, my soft-voiced, stiff-limbed people; such resolve masked by each placid face. There is immensity required in growing small, so bent on such unbending grace.

Robin Morgan (2018). Dark Matter: New Poems. “*No Signs of Struggle*”
Spinifex Press 2018.

Contents

Foreword

The present thesis, presented to obtain the degree of Doctor by the University of Deusto, is the result of five studies carried out during a 4-year period at Neuropsychology of Severe Medical Conditions Research Team (P.I. Dr. Ojeda del Pozo), Department of Methods and Experimental Psychology, Faculty of Psychology and Education, University of Deusto. Three of the following articles have been published in peer reviewed international journals, as a result of the work performed, with a global impact factor of 12.155 (2018 Journal Citation Reports, published by Web of Science Group in 2019).

Study I:

Lucas-Jiménez, O., Díez-Cirarda, M., Ojeda, N., Peña, J., Cabrera-Zubizarreta, A., & Ibarretxe-Bilbao, N. (2016). Verbal Memory in Parkinson's Disease: A Combined DTI and fMRI Study. *Journal of Parkinson's Disease, 5*(4), 793–804. DOI: 10.3233/JPD-150623. [IF = 3.015; 111/256 Q2 Neurosciences].

Study II:

Lucas-Jiménez, O., Ojeda, N., Peña, J., Díez-Cirarda, M., Cabrera-Zubizarreta, A., Gómez-Esteban, J. C., Gómez-Beldarrain, M., & Ibarretxe-Bilbao, N. (2016). Altered functional connectivity in the default mode network is associated with cognitive impairment and brain anatomical changes in Parkinson's disease. *Parkinsonism and Related Disorders, 33,* 58-64. DOI: 10.1016/j.parkreldis.2016.09.012. [IF = 4.484: 32/194 Q1 Clinical Neurology].

Study III:

Lucas-Jiménez, O., Ojeda, N., Peña, J., Cabrera-Zubizarreta, A., Díez-Cirarda, M., Gómez-Esteban, J. C., Gómez-Beldarrain, M., & Ibarretxe-Bilbao, N. (2018). Apathy and brain alterations in Parkinson's disease: a multimodal imaging study. *Annals of Clinical*

and Translational Neurology, 5(7), 803-814. DOI: 10.1002/acn3.578. [IF = 4.656; 29/199 Q1 Clinical Neurology; 55/267 Q1 Neurosciences].

Study IV:

Lucas-Jiménez, O., Diez, I., Ojeda, N., Ibarretxe-Bilbao, N., Peña, J., Tijero, B., Galdós, M., Murueta-Goyena, A., Del Pino, R., Acera, M., Gómez-Esteban, J.C., & Gabilondo, I. The value of non-motor features and genetic variants of Parkison's disease for clustering Lewy body diseases. (in preparation).

Study V:

Lucas-Jiménez, O., Ibarretxe-Bilbao, N., Ojeda, N., Peña, J., Cabrera-Zubizarreta, A., Murueta-Goyena, A., Gómez-Esteban, J.C., & Gabilondo, I. Structural and functional MRI brain alterations in Lewy body diseases. (in preparation).

Glossary of Abbreviations

AD = Axial Diffusivity

ANOVA = Analysis of Variance

ASPARBI = Parkinson's disease Biscay Association

BNT = Boston Naming Test

BJLOT = Benton Judgment Of Line Orientation

BSIT = Brief Smell Identification Test

BTA = Brief Test of Attention

BVMT = Brief Visuospatial Memory Test

CIFA = Calibrated Ideational Fluency Assessment

DBS = Deep Brain Stimulation

DLB = Dementia with Lewy Bodies

DMN = Default Mode Network

DTI = Diffusion Tensor Imaging

E46K-SNCA = E46K mutation in Alpha-synuclein gene

FA = Fractional Anisotropy

FC = Functional Connectivity

FMRI = Functional Magnetic Resonance Imaging

FEW = Family Wise Error

GBA = Glucosylceramidase Beta

GDS = Geriatric Depression Scale

GM = Gray Matter

GWAS = Genome-Wide Association Studies

HC = Healthy Controls

HVLT = Hopkins Verbal Learning Test

IPD = Idiopathic Parkinson's disease

LARS = Lille Apathy Rating Scale

LB = Lewy Bodies

LBD = Lewy Body Diseases

LEDD = Levodopa Equivalent Daily Dose

LRRK2 = Leucine Rich Repeat Kinase 2

MAPT = Microtubule-Associated Protein Tau

MCI = Mild Cognitive Impairment

MD = Mean Diffusivity

MDMCI = Multiple Domain Mild Cognitive Impairment

MDS = Movement Disorder Society

MMSE = Mini-Mental State Examination

MoCA = Montreal Cognitive Assessment

MRI = Magnetic Resonance Imaging

NPI-Q = Neuropsychiatric Inventory Questionnaire

PD = Parkinson's disease

PDD = Parkinson's disease Dementia

PD-MCI = Parkinson’s disease Mild Cognitive Impairment

RD = Radial Diffusivity

REM = Rapid Eye Movement

ROI = Region of Interest

SDMCI = Single Domain Mild Cognitive Impairment

SLCT = Salthouse Letter Comparison Test

SNCA = Alpha-synuclein gene

SPSS = Statistical Package for the Social Sciences

TAP = Test de Acentuación de Palabras

TFCE = Threshold-Free Cluster Enhancement

TIV = Total Intracranial Volume

TMT = Trail Making Test

TBSS = Tract Based Spatial Statistics

UKPDSBB = United Kingdom Parkinson's disease Society Brain Bank

UPDRS = Unified Parkinson’s disease Rating Scale

UPSIT = University of Pennsylvania Smell Identification Test

VOSP = Visual Object and Space Perception Battery

VBM = Voxel Based Morphometry

WAIS-III = Wechsler Adult Intelligence Scale III

WM = White Matter

Glossary of Tables and Figures

I. Abstract

1. Abstract

1.1. Abstract

Parkinson's disease (PD) is the second most frequent neurodegenerative disease in our environment, affecting more than 300.000 people in Spain, more than 8.000 in the Basque Country, and 4.500 people approximately in Biscay. In addition, several studies have shown the socio-health impact of PD, both in terms of lower labor productivity and lower quality of life. PD is characterized by motor symptoms mainly, however, it also entails other alterations, such as visual hallucinations, mood disorders, sleep disturbances and cognitive dysfunction. In 30% of patients with PD, a deterioration of certain cognitive functions can be observed from the initial stages of the disease. These symptoms increase as the disease progresses, damaging many aspects of patients' daily lives and reducing their quality of life. Studies also show that 80% of PD patients with cognitive impairment develop dementia. In 2004, the team led by Dr. Zarranz and Dr. Gómez-Esteban described for the first time a mutation in the alpha-synuclein gene (E46K-SNCA) in a family from the Basque Country. This mutation induces a disease in the brain by Lewy bodies (the pathological paradigm of idiopathic PD) and also has a clinical phenotype superposable to more aggressive forms of PD, including early cognitive impairment and visuospatial disorders, therefore, is an excellent genetic model of idiopathic PD.

This thesis is composed by five scientific contributions, and is an attempt to characterize the pattern of brain damage underlying cognitive impairments and other non-motor dysfunctions in PD through advanced neuroimaging techniques. Firstly, the *first study* aimed to investigate the neuroanatomical and neurofunctional correlates of verbal memory deficit in PD patients. The *second study* assessed the functional connectivity within the default mode network (DMN), and the cognitive and brain correlates of the disrupted DMN functional connectivity in PD. The *third study* evaluated frontal, striatal and limbic brain changes and correlates of apathy in PD patients. The *fourth study* investigated the classification of Lewy body diseases with a comprehensive

set of non-motor features including an extensive cognitive evaluation. Finally, the *fifth study* assessed structural and resting-state functional connectivity brain differences in Lewy body diseases based on severity of non-motor symptoms.

Results revealed verbal memory deficit in PD that was related to white matter alterations in anterior cingulate and to lower brain activation in orbitofrontal regions. Structural-functional relationship underlying verbal memory deficit was also found in PD. In addition, a disruption between posterior and temporal regions within the DMN was exhibited in PD patients, even after controlling for grey matter atrophy. The disrupted DMN functional connectivity is accompanied by lower performance in verbal and visual memory, and visual abilities. Moreover, PD patients with high apathy symptoms showed fronto-striatal and fronto-limbic disruption, while PD patients with low apathy symptoms showed fronto-limbic disruption but fronto-striatal hyperconnectivity. Finally, the clinical picture of severe Lewy body diseases and most affected idiopathic PD patients is characterized by a rapidly evolving cognitive impairment that initiates in the early phase of the development of motor symptoms, and by grey matter atrophy in temporal and parietal areas, white matter alterations in corpus callosum and anterior thalamic radiation, and functional connectivity reductions between language network and dorsal-attentional and salience networks.

The characterization of the pattern of brain damage of cognitive and other non-motor features by neuroimaging and the comparison with those observed in idiopathic forms of Lewy body diseases has an invaluable utility to improve our understanding of the pathophysiology of nervous system in PD. Moreover, it could help clinicians and researchers to identify prognostic biomarkers in this disease when tested longitudinally, which in turn may support the development of effective and more personalized treatment strategies and the accuracy of diagnosis for PD patients.

Keywords: Parkinson's disease, cognition, MRI, structural, functional, resting-state, Lewy body diseases.

1.2. Resumen

La enfermedad de Parkinson (EP) es la segunda enfermedad neurodegenerativa más frecuente en nuestro entorno, afectando a más de 300.000 personas en España, a más de 8.000 en el País Vasco y a 4.500 personas aproximadamente en Bizkaia. Además, varios estudios han demostrado el impacto socio-sanitario de la EP, tanto en términos de menor productividad laboral como de menor calidad de vida.

La EP se caracteriza principalmente por síntomas motores, pero también implica otras alteraciones, como alucinaciones visuales, trastornos del estado de ánimo, trastornos del sueño y disfunción cognitiva. En el 30% de los pacientes con EP, se puede observar un deterioro de ciertas funciones cognitivas desde los estadios iniciales de la enfermedad. Estos síntomas aumentan a medida que la enfermedad progresa, dañando muchos aspectos de la vida diaria de los pacientes y reduciendo su calidad de vida. Los estudios también muestran que el 80% de los pacientes con EP con deterioro cognitivo desarrollan demencia. En 2004, el equipo liderado por el Dr. Zarranz y el Dr. Gómez-Esteban describió por primera vez una mutación en el gen de la alfa-sinucleína (E46K-SNCA) en una familia del País Vasco. Esta mutación induce una enfermedad en el cerebro por cuerpos de Lewy (el paradigma patológico de la EP idiopática) y también tiene un fenotipo clínico superponible a formas más agresivas de EP, incluyendo el deterioro cognitivo temprano y los trastornos visuoespaciales, por lo tanto, es un excelente modelo genético de EP idiopática.

Esta tesis está compuesta por cinco contribuciones científicas, y es un intento de caracterizar el patrón de daño cerebral subyacente a las deficiencias cognitivas y otras disfunciones no motoras en la EP a través de técnicas avanzadas de neuroimagen. En primer lugar, el *primer estudio* investigó las correlaciones neuroanatómicas y neurofuncionales del déficit de memoria verbal en pacientes con EP. El *segundo estudio* evaluó la conectividad funcional dentro de la red neuronal por defecto (DMN, *de sus siglas en inglés*) en pacientes con EP y las correlaciones cognitivas y cerebrales de la alteración de la conectividad funcional de la DMN en la EP. El *tercer estudio* evaluó los

cambios y correlatos cerebrales frontales, estriatales y límbicos de la apatía en pacientes con EP. El *cuarto estudio* investigó la clasificación de las enfermedades por cuerpos de Lewy mediante un conjunto completo de características no motoras, incluyendo una evaluación cognitiva exhaustiva. Finalmente, el *quinto estudio* evaluó las diferencias cerebrales estructurales y de conectividad funcional en estado de reposo en las enfermedades por cuerpos de Lewy basadas en la gravedad de los síntomas no motores.

Los resultados revelaron un déficit de memoria verbal en pacientes con EP, y éste se relacionó con alteraciones de la sustancia blanca en el cingulado anterior y con una menor activación cerebral en las regiones orbitofrontales. Se encontró también una relación estructura-función subyacente al déficit de memoria verbal en la EP. Además, se observó una interrupción entre las regiones posteriores y temporales dentro de la DMN en pacientes con EP, incluso después de controlar la atrofia en sustancia gris. La conectividad funcional de la DMN se relacionó con un menor rendimiento en la memoria verbal y visual y en las habilidades visuales. Por otra parte, los pacientes con EP con síntomas altos de apatía mostraron alteraciones frontoestriatales y fronto-límbicas, mientras que los pacientes con síntomas bajos de apatía mostraron alteraciones fronto-límbicas pero hiperconectividad frontoestriatal. Por último, el cuadro clínico de las enfermedades por cuerpos de Lewy severas y de los pacientes con EP idiopática más afectados se caracteriza por, un deterioro cognitivo de rápida evolución que se inicia en la fase inicial del desarrollo de los síntomas motores de la EP, y por la atrofia de la materia gris en las zonas temporales y parietales, las alteraciones de la materia blanca en el cuerpo calloso y la radiación talámica anterior, y la reducción de la conectividad funcional entre la red del lenguaje y las redes de atención-dorsal y de saliencia.

La caracterización del patrón de daño cerebral de las características cognitivas y otras características no motoras mediante neuroimagen, y la comparación de estos hallazgos con los observados en las formas idiopáticas de las enfermedades por cuerpos de Lewy tiene una utilidad inestimable para mejorar nuestra comprensión de la fisiopatología del sistema nervioso en la EP. Además, podría ayudar a los médicos e

investigadores a identificar biomarcadores pronósticos en esta enfermedad cuando se prueba longitudinalmente, lo que a su vez puede apoyar el desarrollo de estrategias de tratamiento más efectivas y personalizadas, y la precisión del diagnóstico para los pacientes con EP.

Palabras clave: Enfermedad de Parkinson, cognición, resonancia magnética, estructural, funcional, estado de reposo, enfermedades por cuerpos de Lewy.

1.3. Laburpena

Parkinson gaixotasuna (PG) gure inguruan bigarren neuroendekapenezko gaixotasunik ohikoena da, 300.000 gizaki Espainian, 8.000 euskal autonomia erkidegoan eta 4.500 Bizkaian erasanduz. Gainera, zenbait ikerketek PG- ren eragina gizarte eta osasun arloetan, lan eraginkortasunaren jaitsieran eta bizi kalitatean frogatu dute.

PG batez ere sintoma motoreen bidez bereizten da, baina beste aldakuntza batzuk dakartza, ikusmenezko-haluzinazioak, aldarte eta lo desorekak eta disfuntzio kognitiboa hurrenez hurren. Gaixoen %30n, zenbait funtzio kognitiboen narriadura gaixotasunaren lehenengo egoeretatik ikus daiteke. Sintoma hauek harago doaz gaixotasuna aurrera doan ahala, gaixoaren eguneroko bizitzaren arlo ugari kaltetuz eta bere bizi kalitatea murriztuz. Ikerketek, narriadura kognitiboa duten gaixoen %80a dementzia ere garatzen dutela erakusten dute.2004an, Zarranz eta Gómez-Esteban medikuek bideratutako taldea, Euskal autonomia erkidegoko familia batean alfa-sinucleina (E46K-SNCA) genean mutazio bat deskribatu zuen lehenengo aldiz. Mutazio honek, Lewy gorputzen ondorioz (PG idiopatikoaren paradigma patologikoa) garunean gaixotasuna eragiten du eta forma agresiboagoko PG-ren fenotipo kliniko bat badauka ere, narriadura kognitibo goiztiar eta desoreka ikus-espazialak barneratuz, beraz, PG idiopatikoaren modelo genetiko bikaina da.

Tesi hau bost ekarpen zientifikoz osatuta dago. eta neuroirudi teknika aurreratuen bidez, urritasun kognitiboen azpian dauden garun-kalteak eta PG-ko beste disfuntzio ez motoreak bereizteko saiakuntza bat da. Lehenik eta behin, hasierako ikerketak PG ahozko memoria murrizketaren erlazio neuroatomikoak eta neurofuntzionalak aztertu zituen. Bigarren ikerketak, gaixoen oinarrizko sare neuronalaren barneko oinarrizko konektibitate funtzionala (DMN, ingeleseko sigletatik) eta PG-ko DMN-aren konektibitate funtzionalaren aldaketen erlazio kognitiboak eta garun-erlazioak ebaluatu zituen. Hirugarren ikerketak, PG duten pertsonen apatiaren garuneko aldaketa eta korrelatu frontal, estriatal eta linbikoa ikertu u zituen. Laugarren

ikerketan, ezaugarri ez motoreen multzo oso baten eta ebaluazio kognitibo sakon baten bitartez, Lewy gorputzen gaixotasunen klasifikazioa aztertu zen., Amaitzeko, bostgarren ikerketak, sintoma ez motoren larritasunean oinarritutako Lewy gorputzen gaixotasunetan egonaldian ematen diren aldaketa garun-egituralak eta konektibitate funtzionalak ebaluatu zituen.

Emaitzek, gaixoetan ahozko memoriaren murrizketa bat erakutsi zuten, eta honek, aurreko zingulatuko materia zuriaren aldaketekin, eta aktibitate gutxiago alde orbitofrontalekin erlazionatu zen. PG-an, ahozko memoria murrizketaren azpiko egitura-funtzio erlazio bat aurkitu zen. Gainera, DMN-aren barnean, atzekaldeko gunearen eta gune tenporalaren arteko geldiune bat ikusi zen, nahiz eta materia griseko atrofia kontrolatu ere. DMN-aren konektibitate funtzionala ikus eta ahozko memoriaren eta ikus kapazitateen errendimendu txikiago batekin erlazionatu zen. Beste aldetik, apatian sintoma altuak zituzten gaixoek desoreka fronto-estriatalak eta fronto-linbikoak erakutsi zituzten, aldiz, sintoma baxuko gaixoek desoreka fronto-linbikoak erakutsi zituzten baina frontoestriatal hiperkonektibitatea erakutsi zuten. Amaitzeko, Lewy gorputzen gaixotasun larrien eta PG idiopatikoaren gaixo kaltetsuenen ezaugarri klinikoa, sintoma motoreen hasierako garakuntza fasean hasten den eboluzio arineko kalte kognitibo batengatik eta gune tenporalean eta parietalean ematen den materia grisaren atrofiagatik, gorputz kailukarako materia zuriaren aldaketengatik eta aurreko erradiazio talamikoagatik, eta lengoaia sarearen eta albo atentzioaren sareen arteko konektibitate funtzionalaren murrizketagatik bereizten da.

Neuroirudiaren bidezko ezaugarri kognitiboen eta beste ezaugarri ez motoreen garun-kalteen patroiaren bereizgarriak eta lorpen hauen konparaketak, Lewy gorputzen gaixotasunen forma idiopatikoetan lortutakoekin, PG-ko nerbio-sistemaren fisiopatologiaren ulerkuntzan erabilgarritasun ordainezin bat daukate. Gainera, luzeetara saiatzen denean, mediku eta ikertzaileentzako gaixotasunaren iragarpen bioadierazgailuak identifikatzeko lagungarria izan daiteke. Aldi berean,

tratamendu estrategia eraginkorragoak eta pertsonalagoak; eta diagnostiko zehaztasun handiagoa PG-ko gaixoentzat sustatuko daiteke.

Hitz gakoak: Parkinson gaixotasuna, kognizioa, erresonantzia magnetikoa, estrukturala, funtzionala, atseden-egoera, Lewy gorputzen bidezko gaixotasuna.

II. Introduction

"The search for knowledge is a long and difficult task".
Fabiola Gianotti

2. Introduction

2.1. Lewy Body Diseases

James Parkinson (1755–1824) published his monograph entitled "*An Essay on the Shaking Palsy*" in 1817, and this work represented the first description of Parkinson' disease (PD) as a neurological disorder, called paralysis agitans or shaking palsy (Goetz, 2011; Kosaka, 2016). However, the pathology did not become a detached entity until 1892, when the work of Jean-Martin Charcot (1825–1893) was particularly influential in refining and expanding this early designation. Charcot recognized that PD patients do not necessarily have tremor (Przedborski, 2017; Walusinski, 2018).

In 1912, Fritz Heinrich Lewy (1885–1950) described the eosinophilic intraneuronal inclusion bodies, while studying the neuropathology of PD at Alois Alzheimer's laboratory (Munich, Germany). At that time, he called these inclusions "eosinophilic bodies" (Goedert, Spillantini, Del Tredici, & Braak, 2013; Przedborski, 2017). It was in 1919 when for the first time Konstantin Nikolaevich Tretiakoff (1892–1956) named these inclusions "Lewy bodies" (LB). Tretiakoff reported the presence of LB in substantia nigra in PD and he linked it to tremor, rigidity and nerve cell loss. This discovery was confirmed in 1938 by Rolf Hassler (1914–1984) demonstrating specifically the focal distribution of pathology, which affected more pronouncedly to the caudal and ventrolateral parts of the substantia nigra (Goedert et al., 2013; Mueller, Ballard, Corbett, & Aarsland, 2017). Years later, in 1978, Kenji Kosaka (1939–) and colleagues reported a variable distribution of LB in the brain stem, but also in the cerebral cortex; and in 1980, Kosaka and colleagues reported for the first time the term "Lewy body disease" (LBD) (Kosaka, 2016).

Then, in 1997, alpha-synuclein was shown to be the key component of LB. Nowadays, the generic term LBD is commonly used by some authors to describe neurodegenerative conditions with similar clinical phenotype, including PD, Parkinson's disease with dementia (PDD), and dementia with Lewy bodies (DLB) (Kosaka, 2016).

2.2. Parkinson's Disease: Etiology and Pathogenesis

PD is the second most common neurodegenerative disorder after Alzheimer's disease (worldwide incidence: 5 to >35 new cases per 100.000 individuals yearly) (Twelves, Perkins, & Counsell, 2003). According to current population estimations, there are at least 300.000 patients with PD and one new case per 10.000 habitants per year in Spain (García-Ramos, López Valdés, Ballesteros, Jesús, & Mir, 2016)

PD is twice more common in men than in women. The prevalence increases with age affecting 1% of the population above 65 years (Poewe et al., 2017). Idiopathic PD (iPD) constitutes 90% of PD cases, being small percentage of patients (5% to 10%) who have a genetic predisposition. Moreover, other risk factors seem to play a role in the incidence for iPD, being exposure to pesticides and traumatic brain injury risk factors in this disease (Ascherio & Schwarzschild, 2016).

PD is pathologically characterized by degeneration of dopaminergic neurons in specific areas of the substantia nigra, and the presence of LB and Lewy neurites in the surviving neurons (Goedert et al., 2013). LB, which are largely composed of intracellular protein alpha-synuclein, are a key players in this disease (Poewe et al., 2017). Several studies have shown that alpha-synuclein inclusions emerge in order in different regions of the brain, making it possible to distinguish and characterize the whole neuropathological process in six stages (Braak et al., 2003). In *stage 1*, the first alpha-synuclein inclusions occur in the olfactory bulb and/or the dorsal motor nucleus of the vagal nerves. In *stage 2*, pathology develops in the lower raphe nucleus, locus coeruleus and reticular nucleus. Stage 1 and 2 are characterized by autonomic and olfactory disturbances (Doty, 2012). By *stage 3*, pathology has reached the amygdala and the substantia nigra. In *stage 4*, the pathology worsens and the alpha-synuclein inclusions reach the anteromedial temporal cortex. Sleep and motor (bradykinesia, and rigidity, rest tremor or gait disturbance) symptoms are characteristics in stages 3 and 4 (Schapira, Chaudhuri, & Jenner, 2017). *Stage 5* is characterized by the atrophy of the secondary somatomotor areas and prefrontal cortex. Finally, in *stage 6,* LB and Lewy neurites

appear in the whole neocortex. During stages 5 and 6, most of the cognitive and emotional problems associated with advanced PD appear (Braak et al., 2003; Braak, Ghebremedhin, Rüb, Bratzke, & Del Tredici, 2004) (see Figure 1). Moreover, these six stages have been also termed as "presymptomatic phase" from stage 1 to stage 3 and "symptomatic phase" from stage 4 to stage 6 (Braak et al., 2003).

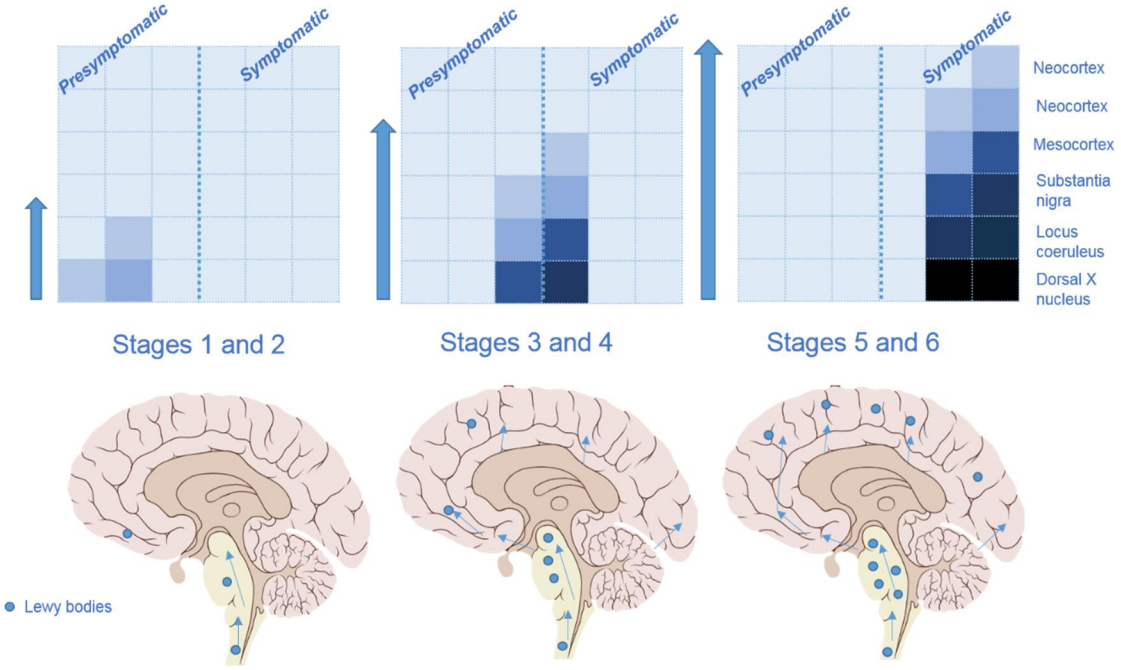

Figure 1. Progressive stages of Parkinson's disease (Braak stages).

In addition of alpha-synuclein aggregation as a central process for the development of the disease, multiple other processes have also been identified as a contributory factors, with several studies suggesting that abnormal protein clearance, mitochondrial dysfunction, oxidative stress, calcium homeostasis, and neuroinflammation play an important role in the onset and progression of PD (Cuenca et al., 2018; Kouli, Torsney, & Kuan, 2018).

PD is defined primarily as a motor disorder, with the typical symptoms being bradykinesia, resting tremor, rigidity and postural instability. Briefly, under healthy conditions, the *hyperdirect pathway* has direct connectivity from the motor cortex to the subthalamic nucleus. The substantia nigra pars compacta dopaminergic neurons

produce the activation (D1 receptors, *direct pathway*) and the inhibition (D2 expressers, *indirect pathway*) of the striatum, and these inputs posteriorly connect with the motor cortex (Poewe et al., 2017; Przedborski, 2017).

Once these both pathways (direct and indirect) are activated by the cortex, the *direct pathway* activates the globus pallidus internus and the substantia nigra pars reticulata, and the *indirect pathway* inhibits the globus pallidus externus, which inhibits the subthalamic nucleus, the globus pallidus internus and the substantia nigra pars reticulata. The correct combination of these inputs together cause the thalamus sends adequate information to the cortex. However, PD is associated with changes in these relays. The degeneration of the substantia nigra pars compacta will decrease the activation of the *direct pathway* and the inhibition of the *indirect pathway* (Bravo, Rangel-Barajas, & Garduño, 2014; Picconi, Hernández, Obeso, & Calabresi, 2018; Poewe et al., 2017). Thus, the input loss to the striatum leads to a decrease in motor activity, producing one of the most common features in PD, the bradykinesia (see Figure 2).

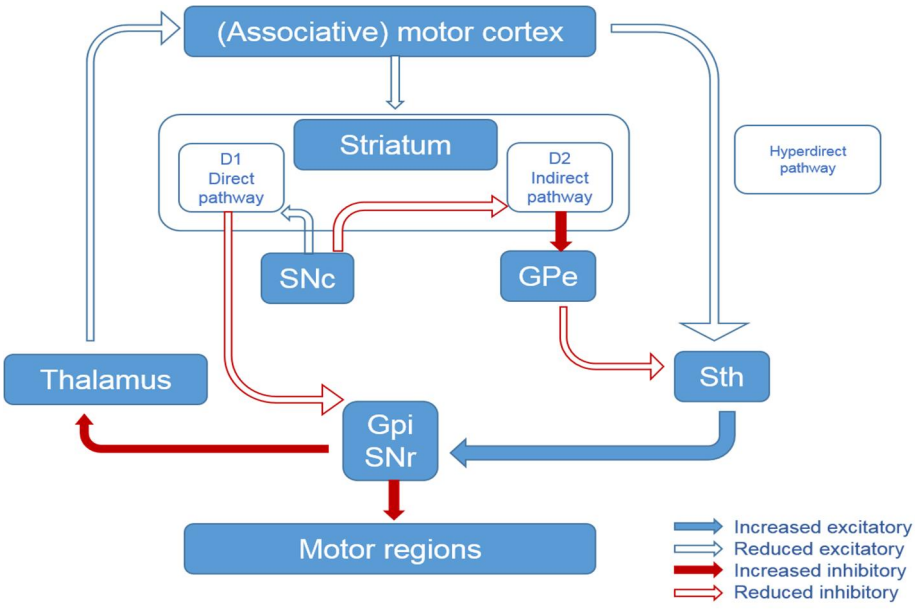

Figure 2. Motor circuits activity in Parkinson's disease. Abbreviations: SNc = Substantia nigra pars compacta; GPe = External globus pallidum; GPi = Internal globus pallidum; SNr = Substantia nigra pars reticulata; Sth = Subthalamic nucleus.

2.3. Motor and Non-motor Features of Parkinson's Disease

PD is a complex neurodegenerative disorder characterized by the triad of motor symptoms: bradykinesia, resting tremor, and rigidity, with postural instability occurring as the disease progresses. Onset of motor symptoms is unilateral in most cases, manifesting asymmetrically throughout the disease (Poewe et al., 2017; Schapira et al., 2017). Motor abnormalities are required for the diagnosis of PD (Jankovic, 2008; Postuma et al., 2015; Tolosa, Gaig, Santamaría, & Compta, 2009), but this disease is associated with other non-motor symptoms and signs. These symptoms have acquired an important role when evaluating the quality of life of PD patients and the impact on health economics, attracting a growing interest in the last years (Del Rey et al., 2018; Schapira et al., 2017).

Patients with PD also experience a variety of other non-motor symptoms such as olfactory, sleep disruption, mood disorders, autonomic disturbances and cognitive impairment throughout their disease trajectory. Some of these non-motor symptoms can precede motor symptoms, indicating that a prodromal symptomatic stage exists in PD. Therefore, non-motor symptoms may develop in the "*prodromal stage*" several years before onset of motor symptoms. In the *prodromal stage*, between 2 to 5 years prior the diagnosis, hyposmia, sleep disruption [(e.g. rapid eye movement (REM) sleep behavior disorder], depression and constipation are common features of PD (Postuma & Berg, 2016; Schapira et al., 2017; Tolosa et al., 2009). Thus, an early disease may be associated with the emergence of additional non-motor symptoms. Olfactory deficit (hyposmia or anosmia), is usually bilateral, and it ranges from 45% to 90% in PD (Doty, 2012; Ponsen et al., 2004). Indeed, the progression of hyposmia could represent an excellent clinical biomarker for early diagnosis (Doty, 2012). Sleep disorders (including insomnia, REM sleep behavior disorder, periodic limb movements, restless leg syndrome, and akathisia) usually affect 30% of PD patients, and their prevalence increases with the duration of the disease (Garcia-Borreguero, Odin, & Serrano, 2003; Iranzo, 2011; Schapira et al., 2017). Moreover, the development of hyposmia and REM sleep behavior disorder may reflect

the evolving distribution and spread of LB as described by Braak and colleagues (Braak & Del Tredici, 2017). Other common non-motor features from the *prodromal stage* are depression and constipation. Depression is considered clinically significant in 35% of PD patients (Aarsland, Påhlhagen, Ballard, Ehrt, & Svenningsson, 2012; Pont-Sunyer et al., 2015) and may predate the onset of motor symptoms (Schapira et al., 2017). Constipation (ranges from 40-50% in PD patients) is an autonomic problem related to gastrointestinal dysfunction, primary derived for the change in the dorsal motor nucleus of the vagus nerve (Knudsen, Krogh, Østergaard, & Borghammer, 2017; Schapira et al., 2017).

Throughout the course of the disease, around 3 to 6 years before the diagnosis, other non-motor symptoms appear in the called "*early motor stage*", such as pain (ranges from 30–85% in PD patients), fatigue (in 50% of PD patients) and diplopia (ranges from 22-76% in PD patients) (Schapira et al., 2017). However, development of these features can vary between PD patients, and the incidence increases with disease progression. Following the natural history of PD, it is estimated that motor features appear when approximately 50–60% of dopaminergic neurons have been lost, and in that moment usually the diagnosis is established, being the period coincident with the so-called "*early stage-mid stage*". In this stage (variability between 4-12 years), non-motor symptoms like neuropsychiatric disorders (anxiety, apathy), hypoponia, dysphagia, and sleep fragmentation are frequent (Schapira et al., 2017).

Is in the "*late stage*", around year 8, when incontinence, sexual dysfunction, orthostatic hypotension, hallucinations, and cognitive dysfunction usually appear. These three autonomic dysfunctions reveal different complications related to bladder dysfunction or cardiovascular dysfunction. Orthostatic hypotension is a key marker of sympathetic denervation (frequency of 30–58% in PD). Visual hallucinations and delusions are present in 40% of cases of PD and are associated with subsequent dementia (Aarsland et al., 2017; Ffytche et al., 2017; Ibarretxe-Bilbao et al., 2010). Moreover, 83% of PD patients may be affected by some level of cognitive dysfunction.

2.3.1. Cognitive impairment.

Interest in cognition in PD has grown considerably over the past years due to the impact and to the high prevalence of cognitive dysfunctions in PD. The prevalence of cognitive impairment in newly-diagnosed PD patients has been described to be between 24 and 62% (Aarsland, Brønnick, Larsen, Tysnes, & Alves, 2009; Muslimović, Post, Speelman, & Schmand, 2005). By 3 years after diagnosis, up to 57% of patients have fronto-striatal or visuospatial deficits and 10% have PDD (Williams-Gray, Foltynie, Brayne, Robbins, & Barker, 2007). By 5 years, 17% of PD patients have PDD (Williams-Gray et al., 2007), by 8 years 26% (Aarsland, Andersen, Larsen, & Lolk, 2003), by 10 years 46% (Williams-Gray et al., 2013), and by 20 years 83% (Hely, Reid, Adena, Halliday, & Morris, 2008) (see Figure 3). Thus only 15% of PD patients approximately remain cognitively intact in the long-term (Aarsland et al., 2010). It is therefore important to ascertain what determines cognitive decline, and how it relates to subsequent dementia.

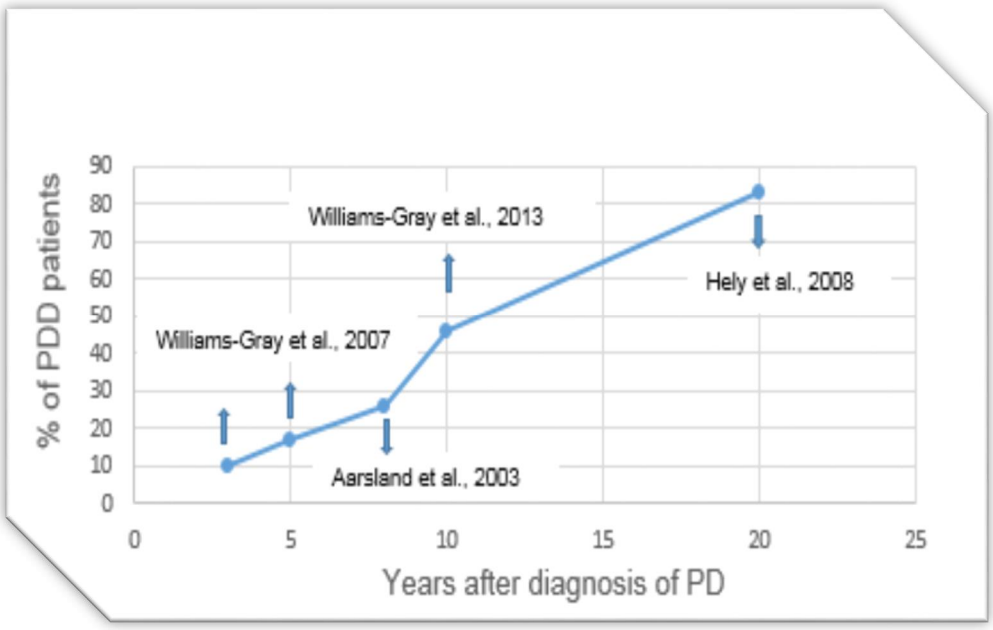

Figure 3. Proportion of affected individuals with Parkinson's disease dementia years after diagnosis of Parkinson's disease.

Traditionally, cognitive deficits have been related to a dysexecutive syndrome, affecting primarily frontal cortex (Aarsland et al., 2017; Ffytche et al., 2017). The most common cognitive deficits in newly-diagnosed PD patients revealed that attention, language, executive functions, visual abilities, and memory domains are impaired (Foltynie, Brayne, Robbins, & Barker, 2004; Muslimović et al., 2005).

From all different subtypes of memory, verbal memory impairment was found to be one of the most deficient cognitive domain with the largest effect size in PD (Aarsland et al., 2009; Muslimović et al., 2005). Nowadays, studies have shown that PD patients have impaired recall but also recognition, reporting that memory impairments in PD are not solely due to retrieval problems (Chiaravalloti et al., 2014). In addition, recognition memory deficits in PD may result partially from the impairment of learning or encoding process (Brønnick, Alves, Aarsland, Tysnes, & Larsen, 2011; Chiaravalloti et al., 2014) related to frontal lobe dysfunction (Ivory, Knight, Longmore, & Caradoc-Davies, 1999) and by the presence of frontal and medial temporal regions dysfunction (Beyer et al., 2013; Rosen et al., 2005). Indeed, recognition memory comprises two independent processes, recollective and familiarity detection; both processes involve medial temporal regions (Eichenbaum, Yonelinas, & Ranganath, 2007).

Recent clinical and research interest in cognitive manifestations of PD has set the focus on the diagnosis of mild cognitive impairment (MCI) in PD patients who have cognitive deterioration beyond what would be expected for age, but who maintain normal functional activities (Litvan et al., 2012). Therefore, a classification of MCI in PD (PD-MCI) has been established by the Movement Disorders Society (MDS) Task Force criteria (Litvan et al., 2012). The diagnosis of PD-MCI has been described as a stage between normal cognition and dementia (Petersen et al., 2001), characterized by the presence of cognitive deficits not normal for age (Goldman & Litvan, 2011). The classification for PD-MCI could be divided in two levels of assessment (see Figure 4).

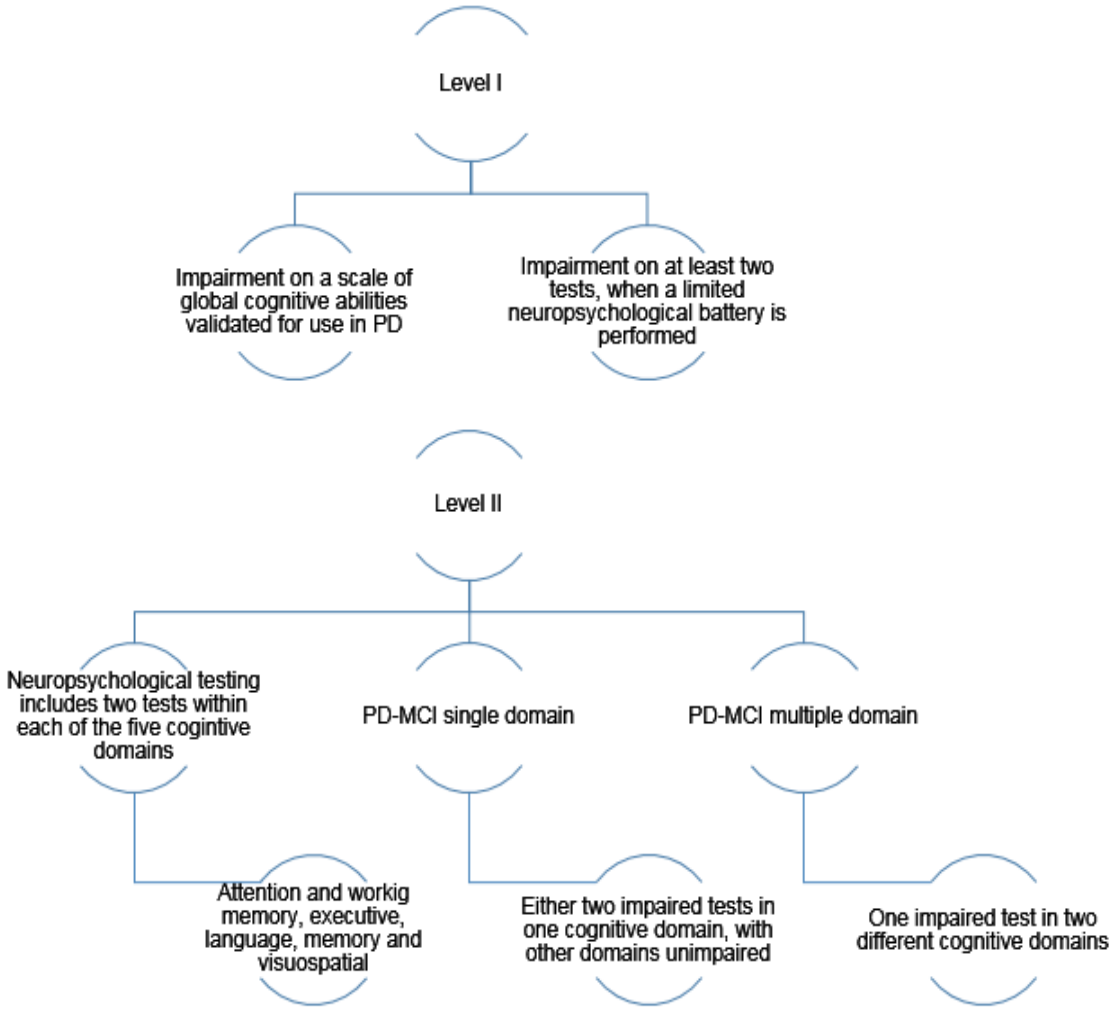

Figure 4. Specific guidelines for PD-MCI level I and level II categories (based on Litvan et al., 2012).

Level I) it is based on abbreviated assessment or a global cognitive scale such as the Montreal Cognitive Assessment (MoCA); Level II) it is based on a comprehensive assessment including two tests per cognitive domain (attention and working memory, executive functions, language, memory and visuospatial ability). Different subtypes of PD-MCI have been established (Litvan et al., 2012): Single-domain MCI (SDMCI) is diagnosed when only one cognitive domain is impaired; Multiple-domain MCI (MDMCI) if two or more cognitive domains are impaired. Moreover, cognitive deficits deteriorate with the progression of the disease and up to 80% of PD patients will develop dementia

after 10-20 years (Hely et al., 2008). This subtype classification may help clinicians to adjust and adequate treatment for PD patients, to better identify and diagnose patients with MCI in PD, and researchers to transmit the findings easier to clinicians (Litvan et al., 2012).

2.3.2. Apathy symptomatology.

The original definition of apathy proposed by Marin (Marin, 1991) is a complex neurobehavioral syndrome characterized by a lack of motivation that affects behavior, cognition, and emotion that is not attributable to an alteration of consciousness, a disturbance of intellect or emotion. It is characterized by reduced goal-directed behavior, flattened affect, and lack of interest in new stimuli, and in one's own and others' problems (Kirsch-Darrow, Fernandez, Marsiske, Okun, & Bowers, 2006; Pagonabarraga, Kulisevsky, Strafella, & Krack, 2015; Starkstein & Leentjens, 2008).

Apathy is one of the most common and disabling non-motor symptom in PD, affecting 40-60% of patients (den Brok et al., 2015; Pagonabarraga et al., 2015; Schapira et al., 2017). Moreover, apathy has been associated with poor cognitive performance and dementia (Dujardin, Sockeel, Delliaux, Destée, & Defebvre, 2009; Dujardin et al., 2007). The pathophysiological mechanisms of apathy in PD are multifactorial and incompletely understood (Pagonabarraga et al., 2015). Its high frequency in this population suggests that it may be related to frontosubcortical dysfunction as part of the overarching disease process (Isella et al., 2002; Leroi, David, & Robert, 2012). It has been postulated that apathy is related to insufficient dopamine transmission in the mesocorticolimbic pathway, and dysfunction of cholinergic, serotonergic, and noradrenergic pathways have also been implicated in apathy (García-Ramos, Villanueva, del Val, & Matías-Guíu, 2010; Levy & Dubois, 2006; Pagonabarraga et al., 2015). Therefore, increased awareness and early detection of the demographic and clinical symptoms that raise the risk of clinically significant apathy in PD, could lead to improved treatment and healthcare outcomes.

2.4. Differential Diagnosis in Parkinson's Disease

PD affects approximately 1% of people over 65 years of age (Poewe et al., 2017). The key to diagnosis PD is recognition of core features (bradykinesia plus one of tremor or rigidity). But, as the disease progresses, other motor features become apparent which are characteristic of PD, such as gait impairment (Poewe et al., 2017). However, nowadays, the non-motor symptoms are well established and can help in making the diagnosis process (Schapira et al., 2017). The United Kingdom Parkinson's Disease Society Brain Bank (UKPDSBB) represented the first formal diagnostic criteria proposed for PD (Hughes, Daniel, Kilford, & Lees, 1992), and it consists in three-step process. 1) Diagnosis of a parkinsonian syndrome; 2) Exclusion criteria for PD; and 3) Prospective supportive criteria for PD. Later, in 2015, the ad hoc MDS Task Force proposed new clinical diagnostic criteria for PD (called the MDS-PD criteria) (Postuma et al., 2015) (see Table 1).

To assess disease severity and for quantitative assessment of progression, multi-domain scales are usually employed in the diagnosis of PD, follow-up, as well as in research settings. The Unified Parkinson Disease Rating Scale (UPDRS) (Martínez-Martín et al., 1994; Movement Disorder Society Task Force on Rating Scales for PD, 2003) is composed of four subscales: I) Mentation, behavior and mood (assesses behavioral problems such as intellectual decline, hallucinations, and depression); II) Activities of daily living (assesses patients' perceptions of their ability to carry out activities of daily living, including dressing, walking, and eating); III) Motor examination [covers the motor evaluation of disability and includes ratings for tremor, slowness (bradykinesia), stiffness (rigidity), and balance]; IV) Complications [covers a number of treatment complications including ratings of involuntary movements (dyskinesia), painful cramps (dystonia), and irregular medication responses (motor fluctuations)].

Table 1

Diagnostic criteria for Parkinson's disease and dementia with Lewy bodies

MDS PD diagnosis (Postuma et al., 2015)	DLB diagnosis (McKeith et al., 2017)
Diagnosis of parkinsonism Bradykinesia *Plus one of* Tremor or Rigidity **Exclusion criteria** Cerebellar abnormalities; Supranuclear gaze palsy; Diagnosis of behavioral variant of frontotemporal dementia or primary progressive aphasia within 5 years of disease onset; Parkinsonian features restricted to the lower limbs for more than 3 years; Treatment with a dopamine receptor blocker or dopamine depleting agent consistent with drug-induced parkinsonism; Absence of a response to high-dose levodopa despite at least moderate disease severity; Cortical sensory loss, clear limb ideomotor apraxia, or progressive aphasia; Normal functional imaging of the dopaminergic system ("DAT scan"); Diagnosis of alternative condition causing parkinsonism which could be causing the symptoms **Supportive criteria** Clear beneficial response to dopaminergic therapy Presence of levodopa-induced dyskinesia; Rest tremor of a limb; The presence of either olfactory loss or cardiac sympathetic denervation on MIBG scintigraphy **Red flags** Rapid progression of gait impairment leading to wheelchair use within 5 years; Absence of progression of motor symptoms over 5 years; Early bulbar dysfunction; Inspiratory respiratory dysfunction; Severe autonomic failure (5 years of disease); Recurrent falls (3 years of onset); Disproportionate anterocollis or contractures within 10 years of disease onset; Absence of any of the common non-motor features despite 5 years of disease; Unexplained pyramidal signs Bilateral symmetrical parkinsonism **For the diagnosis of clinically established PD** Parkinsonism; Absence of exclusion criteria At least 2 supportive criteria **For the diagnosis of clinically probable PD** Parkinsonism Absence of exclusion criteria Balanced numbers of supportive criteria and red flags	**Diagnosis of DLB** Dementia, defined as a progressive cognitive decline of sufficient magnitude to interfere with usual daily activities. Prominent or persistent memory impairment evident with progression. Deficits on tests of attention, executive function and visuo-perceptual ability may be especially prominent and occur early. **Core clinical features** *(the first three typically occur early and may persist throughout the course)* Fluctuating cognition with pronounced variations in attention and alertness; Recurrent visual hallucinations; REM sleep behaviour disorder; One or more spontaneous cardinal feature of parkinsonism **Supportive clinical features** Severe sensitivity to antipsychotic agents; postural instability; repeated falls; syncope or other transient episodes of unresponsiveness.; severe autonomic dysfunction e.g. constipation, orthostatic hypotension, urinary incontinence; hypersomnia; hyposmia; hallucinations in other modalities; systematized delusions; apathy, anxiety and depression **Indicative biomarkers** Reduced dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET; Abnormal (low uptake) MIBG myocardial scintigraphy Polysomnographic confirmation of REM sleep without atonia **Supportive biomarkers** Relative preservation of medial temporal lobe structures on CT/MRI scan; Generalised low uptake on SPECT/PET perfusion/metabolism scan with reduced occipital activity +/- the cingulate island sign on FDG-PET imaging; Prominent posterior slow wave activity on EEG with periodic fluctuations in the pre-alpha/theta range **Probable DLB can be diagnosed if:** Two or more core clinical features of DLB are present, with or without the presence of indicative biomarkers or Only one core clinical feature is present, but with one or more indicative biomarkers; Probable DLB should not be diagnosed on the basis of biomarkers alone **Possible DLB can be diagnosed if:** Only one core clinical feature of DLB is present, with no indicative biomarker evidence, or One or more indicative biomarkers is present but there are no core clinical features **DLB is less likely:** In the presence of any other physical illness or brain disorder or If parkinsonian features are the only core clinical feature and appear for the first time at a stage of severe dementia

Note. DLB should be diagnosed when dementia occurs before, or concurrently with parkinsonism. The term PDD should be used to describe dementia that occurs in the context of well-established PD.

The other most widely scale to classify the course of PD is the Hoehn & Yahr scale (Hoehn & Yahr, 1967). The Hoehn & Yahr original scale measures motor dysfunction with a 5-point stage: Stage 1) unilateral symptoms; Stage 2) bilateral symptoms; Stage 3) bilateral symptoms with balance impairment but independent physically; Stage 4) severe disability but unassisted walking; and Stage 5) confinement to bed or wheelchair if unassisted. Later, a modified scale was developed with two intermediate stages: Stage 1.5) unilateral + axial symptoms; and Stage 2.5) mild bilateral symptoms with recovery on pull test (Goetz et al., 2004).

Although UPDRS and Hoehn & Yahr scales are useful to diagnose, some other disorders, like DLB, multiple system atrophy, progressive supranuclear palsy or corticobasal syndrome can mimic iPD, and on occasion, the correct diagnosis only becomes apparent with time (Kouli et al., 2018). A recent meta-analysis of 11 studies showed that diagnostic accuracy at first visit is about 80% (Rizzo et al., 2016) , but these findings highlight the need for biomarkers to enhance diagnostic confidence in PD (Poewe et al., 2017). Only postmortem studies reveal a definitive diagnosis of PD, relying on the degeneration of the substantia nigra with the presence of LB and Lewy neurites.

One of the most common form of dementia after Alzheimer's disease or PDD is DLB, characterized by the presence of LB in neocortical and paralimbic areas, and Alzheimer-type lesions. DLB is characterized by progressive cognitive impairment together with fluctuating levels of attention, visual hallucinations, REM sleep behavior disorder, and parkinsonism (McKeith et al., 2017). In both disorders, PDD and DLB, there is a clinical and pathological overlap. Current diagnostic criteria state that is DLB if the cognitive symptoms develop within the first year of the emergence of parkinsonism (see Table 1) (Kouli et al., 2018; McKeith et al., 2017).

Therefore, PD and DLB clearly manifest a heterogeneous clinical syndromes and this variability in the clinical phenotype seems to suggest the existence of several subtypes of the disease. Cluster analysis uses a hypothesis-free data-driven approach to divide patients according to clinical features. Several previous studies used cluster

analysis to define clinical PD subtypes based on motor severity, motor complications, some non-motor features, and age at onset (Van Rooden et al., 2010). Phenotypes can characterize specific subgroups of patients which are more sensitive to faster conversion to dementia. Assuming that homogeneous groups of patients are more likely to share pathological and genetic features, recognition of different subgroups of patients may be relevant for research on underlying pathophysiology, with crucial consequences for our understanding of disease progression, prognosis and treatment strategies.

2.5. Treatment in Parkinson's Disease

The certainty of the diagnosis of PD improves following a positive response to treatment. Currently, there is no cure for PD, but a number of pharmacological and non-pharmacological treatments offer benefits in terms of controlling the motor and non-motor symptoms (Deng, Wang, & Jankovic, 2018).

The main pharmacological treatment for PD is Levodopa-based preparations, designed to replace the dopamine in the depleted striatum. Levodopa is an effective drug, but when the disease advances, significant side effects constitute an important part of the illness experienced by PD patients. Dopamine agonists are other pharmacological treatment common in PD, usually used for young PD patients.

Other treatments to motor function are inhibitors of monoamine oxidase B "MAO-B", catechol-O-methyltransferase "COMT" inhibitors, anticholinergics, and amantadine (Connolly & Lang, 2014; Deng et al., 2018). These treatments are used to control the symptoms of PD, but none of them alter the course of the disease. While these drugs can offer significant improvements to motor function, they may lead to problematic adverse effects, particularly as the disease progresses. Hence, a number of promising novel approaches are currently under investigation such as gene therapies, immunotherapies targeting alpha-synuclein gene (SNCA) (Deng et al., 2018), stem-cell treatment (Stoker, 2018), physical exercise, or deep brain stimulation (DBS) (Dallapiazza et al., 2018). DBS is a surgical intervention treatment for improving motor symptoms of PD among well-selected patients (Okun, 2012). All of these treatments

have shown great efficacy against motor symptoms, however, non-motor symptoms are still present in the disease.

Non-pharmacological treatments, such as repetitive transcranial magnetic stimulation “rTMS”, transcranial direct current stimulation “t-DCS”, physical exercise, acupuncture, and cognitive rehabilitation have demonstrated distinct levels of efficacy to treat non-motor symptoms such as depression, apathy or cognitive dysfunction in PD (Seppi et al., 2019). Among treatments against cognitive impairment, neuropsychological rehabilitation has proven to be effective in improving cognition and even functional disability (Cerasa et al., 2014; Díez-Cirarda et al., 2016, 2017; Edwards et al., 2013; París et al., 2011; Peña et al., 2014; Petrelli et al., 2014, 2015; Sammer, Reuter, Hullmann, Kaps, & Vaitl, 2006; Zimmermann et al., 2014).

That is, benefits from neuropsychological rehabilitation can be transferred to other variables that have not been trained directly. It is for this reason that determining cognitive impairment profiles in LBD can help us to improve neuropsychological rehabilitation programs, assuming greater effectiveness in both reducing cognitive dysfunctions as well as functional disability. Future studies are needed integrating both pharmacological and non-pharmacological intervention with the ultimate aim of improving the quality of life of people with PD.

2.6. Magnetic Resonance Imaging in Parkinson’s Disease

PD is a heterogeneous neurological disorder with a variety of motor and non-motor symptoms since the early phase of the disease. The underlying mechanisms of these symptoms are not fully understood, and neuroimaging techniques are a key component to better understand the neural basis of the PD patients’ brain. Nowadays, there is an increased interest in structural and functional magnetic resonance imaging (MRI) analyses using multimodal neuroimaging approach. Moreover, different images can be acquired such as T1-weighted images, diffusion weighted images and task-based or resting-state functional MRI (fMRI) images in order to understand the impact of abnormalities in PD.

2.6.1. T1-weighted structural magnetic resonance imaging.

The identification of structural changes in the brain is increasingly important in the study of neurodegenerative diseases. It can be used to identify causes of cognitive impairment, and it has also become important in the differential diagnosis of the disease. The most widely methods to assess grey matter (GM) changes in PD have been surface-based and voxel-based cortical thickness analyses, and voxel-based-morphometry (VBM) analyses.

Surface-based analysis and voxel-based cortical thickness are designed to measure cortical thinning (or thickness) and allow investigation into how these variables relate to pathological, clinical, cognitive or genetic variables (Dale, Fischl, & Sereno, 1999). Both techniques are able to detect subtle regional changes in brain structure which has contributed to the recognition of structural imaging as a potential biomarker (Karas et al., 2003; Mak, Su, Williams, & O'Brien, 2015). VBM is one automated technique (Ashburner & Friston, 2000; Wright et al., 1995) that detects differences in regional GM density while accounting for global brain shape differences. The technique typically uses T1-weighted images and performs statistical tests across all voxels in the image to identify volume differences between groups.

2.6.1.1. Grey matter brain changes.

GM MRI studies have been extensively used to differentiate PD from other entities. According to the literature, decreased GM volume of the substantia nigra is found in PD compared to healthy controls (HC) (Ziegler et al., 2013). Moreover, several studies have shown putamen and caudate atrophy in PD (*review* De Micco, Russo, & Tessitore, 2018). Taken these results together, they suggest that striatal GM studies may be useful in detecting PD-related pathology, especially at the time of disease onset.

In addition, apart from purely striatal result, in terms of cortical GM volume, several studies have found decreased volume in the frontal, temporal, occipital, parietal and limbic areas (De Micco et al., 2018). Nevertheless, other studies regarding cortical GM volume, have demonstrated no GM changes when compared with HC (De Micco et

al., 2018). Taken into account both striatal and cortical GM results, the pattern of GM loss in PD differs between cortical and subcortical regions, with marked striatal atrophy earlier, and cortical atrophy later in the disease (Lewis et al., 2016). Thus, by merging PD patients from different stages as well as with or without cognitive impairment a methodological bias could be introduced, explaining conflicting results from studies including patients at different disease and cognitive stage, along with methodological issues.

2.6.1.2. Grey matter brain correlates of cognition.

Structural brain changes associated with cognitive impairment in PD have been of interest, showing high sensitivity and specificity to differentiate PD from other disorders. In particular, pre-frontal and hippocampal GM atrophy was shown in early stage PD patients compared with HC, and this atrophy correlated with impaired performance on tests of verbal memory (Beyer et al., 2013; Brück, Kurki, Kaasinen, Vahlberg, & Rinne, 2004). Reduced GM volume regions, including the temporal and parietal cortices, amygdala, thalamus putamen and hippocampus, have also been found in PD (Melzer et al., 2012), with the latter structure particularly associated with impairment in memory encoding performance (Camicioli et al., 2003; Chen, Guang Fan, Liu, & Wang, 2015; Gao et al., 2017; Weintraub et al., 2012). In addition, executive functioning and visuospatial abilities' performance was associated with GM density in the bilateral parahippocampal region, right fusiform gyrus and bilateral frontal cortices in PD (Gao et al., 2017; Nagano-Saito et al., 2005). Indeed, attention-executive test performance and volume loss in the bilateral inferior and medial frontal gyrus as well as in the right middle temporal cortex has been found in PD (Unger et al., 2010). In addition, one study showed that GM lower volume in orbitofrontal cortex correlated with decision-making and facial emotion recognition in PD patients (Ibarretxe-bilbao et al., 2009). Finally, a recent study with VBM showed that lower GM volume in the nucleus basalis of Meynert may predict development of cognitive impairment in PD patients (Wilson, Schulz, Pagano, & Ferna, 2018). In summary, different patterns of cognitive

deficits are associated with GM atrophy in specific cortical areas, and may lead to the definition of specific GM biomarkers able to predict the development of cognitive impairment over time.

2.6.1.3. Grey matter brain correlates of other non-motor features.

Evidence of GM abnormalities related to other non-motor features in PD is scarce. Regarding olfaction, PD patients' scores in University of Pennsylvania Smell Identification Test (UPSIT) were positively correlated with GM volume changes in the left putamen, right thalamus and right caudate nucleus (Campabadal et al., 2017).

Apathy in PD has been associated with GM in caudate nucleus, accumbens and several frontal regions (Carriere et al., 2014; Martinez-Horta et al., 2016; Reijnders et al., 2010). Recently, one study showed reduced GM volume in the left inferior, middle and medial frontal gyrus, right anterior cingulate and the left superior temporal gyrus correlated with increasing apathy severity in PD patients (Alzahrani, Antonini, & Venneri, 2016).

In summary, GM studies of non-motor features have been applied to define neural correlates in PD. The presence of these GM abnormalities supports the hypothesis that evolution of LB-related neurodegeneration toward limbic areas may enhance the progression of behavioral symptoms in specific groups of PD patients (Marras & Chaudhuri, 2016).

2.6.2. Diffusion-weighted magnetic resonance imaging.

In order to enhance the knowledge about white matter (WM) changes in PD, diffusion tensor imaging (DTI) allows the study of the structure of cerebral tissue, such as the trajectories in WM bundles and the orientation of fibers. DTI is a noninvasive imaging approach used to analyze the diffusivity in brain tissues and to infer WM tracts throughout the brain. It is sensitive to the flow of water molecules (Mori et al., 2002; Mori & Zhang, 2006). Two crucial measures that can be used are the fractional anisotropy (FA) and the mean diffusivity (MD) (Basser & Pierpaoli, 1996). FA is a measure that reflects the degree of diffusivity of water molecules in the different

directions and can inform understanding of the microstructural organization of the tensors. The closer to 1 the FA value is, the more anisotropic this diffusion is. Conversely, for an FA value close to 0, the movement of water molecules would be isotropic, suggesting damaged tissue when measured in WM (Schulte, Sullivan, Müller-Oehring, Adalsteinsson, & Pfefferbaum, 2005). MD refers to the overall diffusion of water molecules within the brain. Increased MD suggests degeneration of the tissue (Atkinson-Clement, Pinto, Eusebio, & Coulon, 2017). While this is generally accepted, changes in FA or MD values can be explained by other cellular changes unrelated to WM integrity, or by crossing fibers (Atkinson-Clement et al., 2017). Additionally, DTI provides an estimate of diffusivity along (axial diffusivity; AD) and perpendicular (radial diffusivity; RD) to the main fiber direction. AD decrease is indicative of axonal damage and RD increases in response to demyelination (Winklewski et al., 2018). DTI data can be analyzed by tract based spatial statistics (TBSS) (Smith et al., 2006) and voxel-based analyses, which entail a whole-brain unbiased hypothesis-free approach, and by probabilistic tractography approach, which estimates the most likely fiber orientation at each voxel tracing a single tract (in contrast with deterministic tractography).

2.6.2.1. White matter brain changes.

DTI may offer an opportunity to detect biomarkers to monitor disease progression as well as predict future disease prognosis. Several studies have reported decreased FA within the substantia nigra in PD patients compared to HC (Zhang et al., 2015). In fact, recent meta-analyses supports the use of this measure to differentiate accurately PD patients from HC (Atkinson-Clement et al., 2017; Cochrane & Ebmeier, 2013). Moreover, in one study with drug-naïve PD patients, substantia nigra offered 100% sensitivity and specificity in differentiating PD patients from HC (Vaillancourt et al., 2009). More recently, one study demonstrated reduced putamen-ipsilateral susbtantia nigra density applying probabilistic tractography in PD patients compared with HC (Theisen et al., 2017).

At a cortical level, one study detected microstructural abnormalities not only at the level of substantia nigra, but also in the thalamus, motor, premotor and supplementary motor areas, and the postcentral gyrus in PD patients compared to HC (Zhan et al., 2012). Additionally, the study of Karagulle-Kendi and colleagues (Karagulle-Kendi, Lehericy, Luciana, Ugurbil, & Tuite, 2008) showed decreased FA in medial frontal cortex in PD. Finally, a recent study in early PD patients (Nigro et al., 2016), showed a disruption in the structural connectivity in motor (basal ganglia) and non-motor regions (limbic, olfactory). In summary, DTI studies support the presence of a disrupted structural WM, which may characterize PD patients from controls and explain symptoms development and severity.

2.6.2.2. White matter brain correlates of cognition.

Despite the clinical relevance of cognitive decline, neuropathological correlates in PD are still under debate (Hely et al., 2008). However, WM changes are emerging as an important neuroanatomical correlate of cognitive dysfunction in PD. One study revealed that FA reduction in the bilateral posterior cingulate correlated with cognitive parameters (Matsui et al., 2007), confirming the role of cingulate for verbal and visuospatial functions in PD.

Memory impairment has been associated with diffusivity changes in the fornix, and with WM alterations in the right anterior corona radiata in PD (Zheng et al., 2014). Moreover, impairments in executive function have been associated with WM alterations in the frontal and parietal regions in PD (*review* Hall & Lewis, 2019), including the left anterior limb of the internal capsule and genu of corpus callosum (Zheng et al., 2014). Attention impairments have been related to anterior and posterior cingulate cortex in PD (*review* Hall & Lewis, 2019), including posterior thalamic radiation, and retrolenticular limb of the internal capsule (Zheng et al., 2014). The linguistic performance was related to left internal capsule, right sagittal striatum, the genu of the corpus callosum and the anterior corona radiata in PD (Zheng et al., 2014). In addition,

theory of mind in PD was related to precuneus and the parietal lobe after controlling for executive functions (Díez-Cirarda et al., 2015).

Finally, the study of Kamagata and colleagues (Kamagata et al., 2013) showed that WM FA values were lower in the prefrontal cortex and the genu of the corpus callosum in PDD patients when compared to PD patients with normal cognition. Moreover, there was a significant correlation between the Mini-Mental State Examination (MMSE) scores and the prefrontal and callosal FA values. In summary, WM studies might contribute to the identification of brain alterations in PD patients prior to the development of dementia.

2.6.2.3. White matter brain correlates of other non-motor features.

Regarding WM abnormalities, non-motor features, including mood disorders have been very few investigated. Hyposmia is well-known in PD, and characteristic of the prodromal phase. One study revealed reduced FA in the WM adjacent to gyrus rectus in hyposmic and anosmic PD patients when compared to HC and PD patients without severe olfactory dysfunction (Ibarretxe-Bilbao, Junque, et al., 2010). They also showed a significant correlation between UPSIT scores and FA measures extracted from WM adjacent to primary olfactory cortex and right gyrus rectus (Ibarretxe-Bilbao, Junque, et al., 2010).

Some studies have been found about depression (Huang et al., 2014; Li et al., 2010), one about apathy (Carriere et al., 2014), and no studies regarding anxiety WM correlates in PD. Depressive PD patients showed decreased FA values in the bilateral medial dorsal thalamus (Li et al., 2010), and revealed a negative correlation between WM microstructural changes within the thalamus and depression severity (Li et al., 2010). However, this is in contrast with other study in which tractography was used and no differences across PD groups were found (Surdhar et al., 2012). In addition, PD patients with visual hallucinations showed higher MD values in the posterior regions of the hippocampus compared to non-visual hallucinations PD patients and HC (Yao et al.,

2016). However, methodological heterogeneity along with technical difficulties to define WM correlates boundaries has determined some conflicting results to date.

2.6.3. Functional magnetic resonance imaging.

FMRI has been widely used to study abnormal patterns of brain connectivity at rest and activation during a variety of tasks in PD. Two fMRI approaches exist to study brain activations: task-based fMRI and resting-state fMRI. The first method includes the performance of a task during the fMRI acquisition eliciting the activation of task specific areas. The second method consists in measuring neural activations at rest, asking the subjects to be awake and do not perform any particular task.

2.6.3.1. Task-based brain changes and correlates.

Task-based fMRI techniques consist of assessing regional blood-oxygen-level-dependent "BOLD" signal intensity during the performance of a given behavioral task compared with the signal intensity during a control condition. One meta-analysis showed that PD patients in OFF-time had lower activation of the right posterior putamen and an increased activity of the superior parietal lobule relative to HC during motor performances (Herz, Eickhoff, Løkkegaard, & Siebner, 2014).

Regarding cognition, in a recent study, PD patients revealed higher activation in the dorsal attention and frontoparietal networks compared to HC in attentional task (Boord, Madhyastha, Askren, & Grabowski, 2017; Madhyastha, Askren, Boord, & Grabowski, 2014), interpreting that PD patients required more neural resources to perform the task than HC. In another recent study investigating working memory, PD patients (off-state) showed reduced activation in the left prefrontal and bilateral parietal cortices, associated with lower working memory performance (Simioni, Dagher, & Fellows, 2017). In line, one study found that PD patients had reduced activation in fronto-striatal circuitry compared with cognitively normal PD patients and HC while performing a working memory task (Lewis, Dove, Robbins, Barker, & Owen, 2003). Additionally, other study found that PD patients, compared with HC, presented

increased task-related activity in the left dorsolateral prefrontal cortex during a visuospatial n-back working memory task (Trujillo et al., 2015).

In one study, PD patients showed reduced activation in the orbitofrontal cortex and frontal poles indicating a dysfunction in memory-related networks in these patients (Ibarretxe-Bilbao et al., 2011). Interestingly, at follow-up, PD patients showed progressive activation and deactivation of the recognition memory network (Segura et al., 2013). Moreover, many studies suggested that the fronto-striatal network hypo-activation can mediate executive deficits in PD patients (Monchi et al., 2004; Monchi, Petrides, Mejia-Constain, & Strafella, 2007; Monchi, Petrides, Petre, Worsley, & Dagher, 2001; Nagano-Saito et al., 2014). Moreover, PD patients showed lower activation of the amygdala and fusiform gyrus compared with HC in both "on" and "off" states during an fMRI study using angry and fearful facial expressions (Tessitore et al., 2002). Finally, in another study, it has been described that, during dual tasks, PD patients recruited a striatal territory (ventro-posterior putamen) not engaged during either the cognitive or the motor task alone, and that this recruitment is not seen in HC (Nieuwhof et al., 2017). Regarding olfaction, PD patients showed hyperactivation in the inferior frontal gyrus, anterior cingulate gyrus, and the striatum (Moessnang et al., 2011; Westermann et al., 2008).

2.6.3.2. Resting-state brain changes and correlates.

In resting-state fMRI, there is no explicit task, thus, it can be employed even in patients who have difficulty complying with fMRI tasks. Comparisons of different conditions to identify activations cannot be made, and the most frequently used techniques are based on the coherence of signal variation across the brain, i.e., functional connectivity (FC) (Baggio & Junqué, 2019; Niethammer, Feigin, & Eidelberg, 2012). Therefore, it can be used to assess the intrinsic functional organization of the brain or connectivity networks (activity across distant brain regions). According to a meta-analysis related to motor symptoms, the most consistent resting-state functional

alteration across different studies in PD subjects is the reduced activity in the posterior putamen, which correlates with a worse motor impairment (Herz et al., 2014).

One intrinsic connectivity network that is consistently identified in resting-state is the default-mode network (DMN). This network involves the medial prefrontal cortex, posterior cingulate cortex, precuneus, and lateral parietal and medial temporal cortices (van Eimeren, Monchi, Ballanger, & Strafella, 2009). The DMN consistently decreases its activity when compared with activity during these relaxed nontask states (Raichle, 2015). Other intrinsic connectivity networks are frontoparietal, dorsal-attentional, visual, sensorimotor, and salience network.

The association between resting-state DMN connectivity and cognitive performance in PD was first suggested in the study of Tessitore and colleagues (Tessitore et al., 2012). In that study, PD patients showed FC alterations in the right medial temporal lobe and bilateral inferior parietal cortex (Tessitore et al., 2012). Several studies have demonstrated FC reduction of the DMN since the early phases of PD (Putcha, Ross, Cronin-Golomb, Janes, & Stern, 2015; Tessitore et al., 2012; van Eimeren et al., 2009) in PD patients with MCI (Amboni et al., 2014; Díez-Cirarda et al., 2018; Zhan et al., 2018) and with dementia (Chen et al., 2015; Dubbelink et al., 2014; Zhan et al., 2018).

Moreover, some studies have demonstrated a relationship between DMN connectivity and cognitive functions such as memory and visuospatial processing (Baggio, Segura, Sala-Llonch, et al., 2015; Ibarretxe-Bilbao et al., 2011; Rektorova, Krajcovicova, Marecek, Novakova, & Mikl, 2014; Tessitore et al., 2012). Other studies revealed that PD patients with cognitive deficits also showed altered FC of other networks such as dorsal-attention, fronto-parietal, salience and associate visual networks (*review* Filippi, Elisabetta, Piramide, & Agosta, 2018).

Finally, regarding FC, abnormal prefrontal-limbic network connectivity has been demonstrated in depressed PD patients (Surdhar et al., 2012). In addition, PD patients with olfactory impairment had decreased connectivity between the posterior cingulate cortex and bilateral primary sensory areas, right frontal areas, and right parietal areas,

and had an enhancement of striatocortical connectivity compared to PD patients with normal olfaction (Sunwoo et al., 2015). Apathetic PD patients showed reduced FC in fronto-striatal areas (Baggio, Segura, Garrido-Millan, et al., 2015).

In PD patients with visual hallucinations, occipital-cortico-striatal connectivity was significantly higher than in patients without hallucinations (Yao et al., 2014). In addition, hallucinations have been associated with functional abnormalities in primary visual cortex and visual associative cortices in PD (Meppelink et al., 2009). Therefore, the characterization of the pattern of brain damage by neuroimaging and the comparison of these findings between LBD may help to improve our understanding of the pathophysiology of nervous system damage and to identify prognostic biomarkers in PD.

2.7. Genetic Forms of Parkinson's Disease

Although most cases of PD are idiopathic, there is a small percentage of patients that report a family history (10–15%) or have Mendelian inheritance (5%). These cases have provided crucial clues to the mechanisms underlying the neuropathology of PD (Deng et al., 2018; Kim & Alcalay, 2017).

The genes that have been found to potentially cause PD are assigned a "PARK" name in the order they were identified. To date, at least 23 PARK genes for Parkinsonism have been identified by the HUGO Gene Nomenclature Committee (see Table 2) (Cuenca et al., 2018; Del Rey et al., 2018; Kouli et al., 2018). These include autosomal dominant genes (e.g., SNCA) and autosomal recessive genes (e.g., PRKN, and PINK1) conforming a total of 23 loci and 19 disease-causing genes (Deng et al., 2018; Kouli et al., 2018). In autosomal dominant inheritance, one mutated copy of the gene in each cell is sufficient for a person to be affected while in autosomal recessive inheritance, both copies of the gene in each cell have mutations. In addition to PD-causative mutations, genome-wide association studies (GWAS) have identified other common genetic variants such as microtubule-associated protein tau gene (MAPT) or glucosylceramidase beta (GBA) which contribute to increase PD susceptibility (Deng et al., 2018). The variants in MAPT and SNCA loci showed the strongest association with PD risk across populations, while

Table 2

PARK genes involved in Parkinson's disease (Adapted from Kouli et al., 2018, and from Deng et al., 2018)

Locus (OMIM)	Gene Symbol by HGNC	Inheritance	Description	Clinical features
PARK1 PARK4	SNCA	AD	α-synuclein (SNCA)	Classic PD phenotype caused by PARK1 missense mutations. Duplication/triplications of PARK4 produce early-onset PD with dementia, autonomic dysfunction, and rapid progression.
PARK2	PRKN	AR	parkin RBR E3 ubiquitin protein ligase	Early-onset PD, slow progression, often features of dystonia
PARK3	Unknown	AD	PD 3 (Unclear)	Late-onset
PARK5	UCHL1	AD	ubiquitin C-terminal hydrolase L1	Classical PD—only one family, findings not since replicated
PARK6	PINK1	AR	PTEN-induced putative kinase 1	Early-onset PD, slow progression
PARK7	DJ-1	AR	Parkinsonism-associated deglycase	Early-onset PD, slow progression
PARK8	LRRK2	AD	Leucine-rich repeat kinase 2	Classical PD with less frequent dementia and slower progression
PARK9	ATP13A2	AR	Cation-transporting ATPase 13A2	Early-onset (adolescence), atypical parkinsonism with dementia, spasticity and supranuclear palsy (Kufor–Rakeb syndrome)
PARK10	Unknown	Unclear	PD 10 (Unclear)	Late-onset
PARK11	GIGYF2	AD	GRB10 interacting GYF protein 2	Classical PD
PARK12	Unknown	X-linked	PD 12 (Unclear)	Late-onset
PARK13	HTRA2	AR	HtrA serine peptidase 2	Classical PD
PARK14	PLA2G6	AR	Calcium-independent phospholipase A2 enzyme	Early onset with atypical features (dystonia parkinsonism)
PARK15	FBX07	AR	F-box protein 7	Early onset with atypical features (pallido-pyramidal syndrome)
PARK16	Unknown	Unclear	PD 16 (Unclear)	Late-onset
PARK17	VPS35	AD	Vacuolar protein sorting-associated protein 35	Classical PD
PARK18	EIF4G1	AD	Eukaryotic translation initiation factor 4 gamma 1	Classical PD
PARK19	DNAJC6	AR	HSP40 Auxilin	Early-onset PD, slow progression
PARK20	SYNJ1	AR	Synaptojanin 1	Parkinsonism with dystonia and cognitive decline
PARK21	DNAJC13	AD	Receptor-mediated endocytosis 8 (RME-8)	Classical PD
PARK22	CHCHD2	AD	Coiled-coil-helixcoiled-coil-helix domain containing 2 gene	Early-onset, late-onset
PARK23	VPS13C	AR	Vacuolar protein sorting-associated protein 13C	Early-onset PD, rapid progression

Note. OMIM = Online Mendelian Inheritance in Man; HGNC = HUGO Gene Nomenclature Committee; AD = Autosomal Dominant; AR = Autosomal Recessive; PD = Parkinson's disease

common variants in Leucine-rich repeat kinase 2 (LRRK2) increase the risk of PD only in Asian populations but not in Europeans (Farrer et al., 2007; Lu et al., 2008). In addition, mutations in GBA show a more severe Parkinsonism than idiopathic patients, earlier age-at-onset and more frequently dementia (Thaler et al., 2017).

In conclusion, since 1997, when the first PD-associated mutation "A53T" was discovered in SNCA, the number of PD-related genes as risk factors has exponentially increased, suggesting an important role in the etiology of the disease (Del Rey et al., 2018). Therefore, the use of relevant biological data such as genotype information on PD might be extremely useful to refine PD classification and characterize specifically patients which are more sensitive to faster conversion to dementia.

2.8. E46K Mutation of Alpha-synuclein

It was in 1997 when the SNCA gene was identified due to a missense mutation "A53T" in an adult-onset autosomal-dominant PD phenotype, and subsequently, other mutations in SNCA were identified (Del Rey et al., 2018; Deng et al., 2018; Poewe et al., 2017). SNCA-linked mutations are a key player in PD, and are considered a rare condition, highly-penetrant and clinically aggressive genetic model of pure LBD. In 2004, Zarranz and colleagues described for the first time the third known point mutation in the SNCA gene (E46K substitution in SNCA) in a family with autosomal dominant PD and DLB (Zarranz et al., 2004). In particular, the mutation produces glutamic acid substitution by lysine in position 46 of the alpha-synuclein gene (E46K-SNCA). Neuropathological examination revealed extensive LB and Lewy neurites in cortical and subcortical structures that met the pathological criteria for DLB. Since the first description, nine individuals of the original family in which the E46K mutation was identified were followed (see Figure 5).

The clinical profile of E46K symptomatic carriers is characterized by a rapidly evolving cognitive impairment (Somme et al., 2011) that begins in the early phase of motor symptoms of PD and appears to debut as an alteration of subsequent cortical functions. In addition, all carriers developed early alterations in the sleep architecture

(Zarranz et al., 2005) and a dysfunction of the autonomic nervous system with sympathetic cardiac denervation (Tijero et al., 2010; Tijero et al., 2013) that may precede the cognitive and motor manifestations of PD.

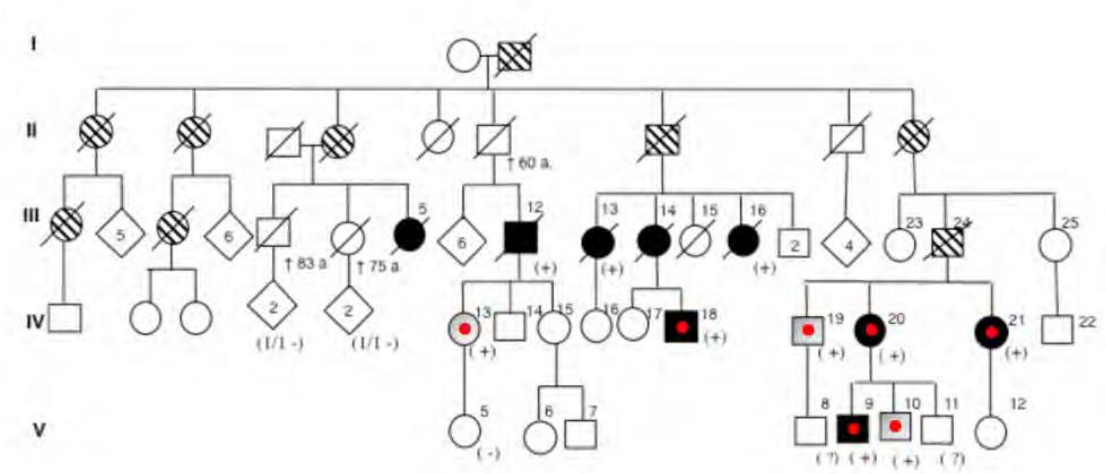

Figure 5. Family tree for E46K-SNCA gene mutation carriers. Legend = hashed symbol: history of affectation; filled symbol: involvement confirmed by personal medical examination; slashed symbol: deceased; the index case III-34 is indicated by an arrow; gray symbols are asymptomatic carriers of the mutation; red dots indicate the seven subjects selected for the current study.

The histological post-mortem of the brains of two E46K mutation carriers demonstrated that they met the criteria of DLB (Zarranz et al., 2005). However, this evaluation was performed in advanced stages of the disease, when the disease was already present. The characterization of the pattern of cognition and brain impairment of E46K mutation carriers by neuroimaging and the comparison of these findings with those observed in idiopathic forms of LBD may help to improve our understanding of the pathophysiology of nervous system damage in PD. Moreover, could help us to identify prognostic biomarkers in this disease, which in turn may support the development of effective neuroprotective drugs for PD.

III. Approach, General objectives, and Hypotheses

"Set your goals high, and don't stop till you get there".
Bo Jackson

3. Approach, General Objectives and Hypotheses

The present thesis consists of five studies examining the structural and functional brain changes of cognitive and other non-motor features in idiopathic and genetic PD patients.

3.1. Study I

"Verbal memory in Parkinson's disease: A combined DTI and fMRI study"

Background

Verbal memory is one of the mostly impaired cognitive domain in PD. While significant progress has been made to determine the functional role of specific GM areas underlying verbal memory deficit in PD, very little is known about the relationship between these regions and their underlying WM structures.

Objectives

- The first objective was to investigate verbal memory, FA and brain activation differences between PD patients and HC.
- The secondary goal was to explore the neuroanatomical and neurofunctional correlates of verbal memory in PD.
- Additionally, third goal was to investigate the relationship between these neuroanatomical and neurofunctional verbal memory correlates in PD.

Hypotheses

- PD patients would show lower performance in the verbal memory fMRI paradigm, would have less WM FA, and lower functional brain activation during fMRI paradigm compared to HC.
- Verbal memory fMRI performance would be related to functional brain activity in the frontal and temporal regions and would correlated with FA in the WM tracts adjacent to those regions in PD.

- There would be an association between the WM microstructure FA and functional brain activation in those frontal and temporal regions in PD.

3.2. Study II

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

Background

The relevance of the DMN has been emphasized in several neuropsychiatric diseases, and some studies have investigated the DMN in the context of PD. FMRI studies have confirmed the crucial role played by the DMN in cognitive processing both in normal aging and neurodegenerative disorders. However, most neuroimaging studies assessing the DMN only had one single imaging modality making it difficult to investigate structural and functional changes in PD patients. Moreover, studies usually assess cognition with one general measure instead of extensive cognitive battery assessing several domains. To our knowledge, this is the first study assessing DMN FC disturbances and its brain GM volume and WM indexes cognitive correlates.

Objectives

- The first objective was to investigate the resting-state FC between the regions of the DMN in PD patients compared with HC. At the same time, we investigated cognitive differences, and GM volume and WM indexes differences in the DMN areas.
- The second objective was to explore the cognitive, GM volume and WM correlates of the FC DMN disturbances in PD.

Hypotheses

- PD patients would have lower FC, GM volume and WM in the DMN, and lower cognitive performance.
- Decreased FC in the DMN would be related to GM atrophy, lower WM, and diminished cognitive performance in PD patients.

3.3. Study III

"Apathy and brain alterations in Parkinson's disease: A multimodal imaging study"

Background

Apathy is one of the most common and disabling non-motor symptom in PD affecting 40% of patients. Apathy has been associated with lower cognitive performance and dementia. Although the neurochemical substrates of apathy remain poorly characterized, dopamine deficits affecting fronto-striatal and limbic regions have been suggested to play an important role in the pathophysiological bases of apathy in PD. However, no studies have investigated symptoms of apathy in PD patients when the diagnosis of apathy has not yet been established.

Objectives

- The aim of the study was to investigate brain changes of frontal, striatal and limbic pathways through three different neuroimaging modalities (GM, WM, and resting-state FC) in PD patients with high and low symptoms of apathy compared to HC.
- The second objective was to study brain correlates of frontal, striatal and limbic pathways related to high and low symptoms of apathy in PD patients.

Hypotheses

- PD patients with high symptoms of apathy would show fronto-striatal deficits compared with PD patients with low symptoms of apathy and HC.
- Apathy symptoms in PD group with high symptoms of apathy would correlate with brain fronto-striatal deficits.

3.4. Study IV

"The value of non-motor features and genetic variants of Parkinson's disease for clustering Lewy body diseases"

Background

PD is a heterogeneous condition with marked variability in terms of clinical presentation and disease progression. However, the use of exclusively clinical data to define PD subtypes may be insufficient. Therefore, the evolution of cognitive impairment in patients with genetic PD is important to determine whether specific domain impairment phenotypes can be identified. These domains could characterize subgroups of iPD patients which are more sensitive to faster conversion to dementia.

Objective

- The objective of this study was to classify iPD using cluster analysis with a comprehensive set of non-motor features, including an extensive cognitive evaluation, and involving three genetic PD variants with different degrees of LB pathology.

Hypothesis

- Cluster organization parameters would showed several subtypes differing in severity of non-motor features. Severe iPD patients would show pattern-specific cognitive disabilities related to visual abilities, and severe motor manifestations with marked axial symptoms.

3.5. Study V

"Structural and functional MRI brain alterations in Lewy body diseases"

Background

Although clinical abnormalities have been reported in diagnosis of LB pathologies, imaging studies are particularly important in the identification of patients in the prodromal phase. Therefore, the characterization of the pattern of brain damage by neuroimaging and the comparison of these findings between idiopathic and genetic PD may help to improve our understanding of the pathophysiology of nervous system damage and to identify prognostic biomarkers in this disease.

Objectives

- The aim was to evaluate structural (T1 and diffusion-weighted images) and resting-state functional MRI brain differences in LBD (idiopathic and genetic PD and DLB) based on severity of the non-motor symptoms.
- The second objective was to investigate specific differences between iPD patients and severe LBD (symptomatic E46K-SNCA carriers and DLB patients).

Hypotheses

- Severe LB pathology patients would show greater brain alterations compared to mild, moderate or normal LB pathology patients.
- DLB patients would show greater brain alterations, followed by E46K-SNCA carriers with marked occipital alterations, and finally by iPD patients.

IV. Methods

"The true method of knowledge is experiment."
William Blake

4. Methods

The present thesis is part of two larger projects: *Project 1*) "Neuroanatomical and neurofunctional correlates of different types of mild cognitive impairment in Parkinson's disease" funded by Department of Health of the Basque Government (2011111117), Department of Education and Science of the Basque Government (Team A; IT946-16); *Project 2*) "Study by neuroimaging of carriers of E46K mutation of alpha-synuclein gene as a model of idiopathic Lewy body disease" funded by Michael J. Fox Foundation (RRIA2014; 10189) and Instituto de Salud Carlos III (PI14/00679).

Therefore, methods section for both projects will be divided in *Project 1* (Study I, Study II and Study III) and in *Project 2* (Study IV and Study V).

Project 1 (Study I, Study II and Study III)

4.1. Study Sample

The sample included PD patients recruited from the Department of Neurology of Galdakao Hospital and from the PD Biscay Association (ASPARBI). HC were also recruited, matched with patients by age, sex, and years of education (1:1 ratio). PD patients were enrolled in the study according to the following inclusion/exclusion criteria (see Table 3).

Table 3

Inclusion and exclusion criteria for the Project 1 (Study I, Study II and Study III).

Inclusion criteria	Exclusion criteria
♦ Diagnosis of PD based on the UK PD Society Brain Bank diagnostic criteria ♦ Age between 45-75 years ♦ Hoehn & Yahr disease stage ≤ 3 (Hoehn & Yahr, 1998) ♦ UPDRS evaluated by the neurologist (Martínez-Martín et al., 1994)	♦ Dementia as defined by the DSM-IV-R (American Psychiatric Association, 2003) and the MDS clinical criteria for PD dementia ♦ Scores on the Mini Mental State Examination (MMSE) < 24 (Lobo et al., 2001) ♦ Other neurological illness/injury (e.g., traumatic brain injury) ♦ Unstable psychiatric disorders (e.g., schizophrenia) ♦ Visual hallucinations evaluated with Neuropsychiatric Inventory Questionnaire ♦ Patients with depression or a score > 5 on Geriatric Depression Scale (GDS-15) ♦ Patients unable to undergo MRI or conditions incompatible with optimal pre-processing of MRI data (e.g., hemorrhage)

4.2. Neurological, Neuropsychological and other Non-motor Features Assessment

All participants underwent a neurological, neuropsychological and clinical/functional assessment (see Table 4), which will be explained in more detail below.

Table 4

Neurological, neuropsychological and other non-motor features assessment in Project 1 (Study I, Study II and Study III).

Area	Test
Neurological assessment	
PD Rating Scale	Unified PD Rating Scale
	Hoehn and Yahr Scale
Medication	Levodopa Equivalent Daily Dose
Neuropsychological assessment	
Premorbid intelligence	Word Accentuation Test
Global cognition	Mini-Mental State Examination
Attention & Working memory	Brief Test of Attention
	Stroop Test (Word & Color)
	Digits test Wechsler Adult Intelligence Scale III
Processing speed	Trail Making Test (A)
	Salthouse Letter Comparison Test
Verbal memory	Hopkins Verbal Learning Test- Revised
Visual memory	Brief Visual Memory Test- Revised
Language	Boston Naming Test
Verbal fluency	Calibrated Ideational Fluency Assessment (phonemic and semantic)
Executive functions	Trail Making Test (B)
	Stroop Test (Word-Color & Interference)
Visuospatial abilities	Visual Object and Space Perception
	Clock Drawing Test (draw + copy)
Other non-motor features assessment	
Depression	Geriatric Depression Scale (15-items)
Apathy	Lille Apathy Rating Scale
Neuropsychiatry symptoms	Neuropsychiatric Inventory Questionnaire

4.2.1. Neurological assessment.

The neurological exam was exclusively administered to the PD sample and by two experienced neurologists. Three scales were administered with the aim of evaluating PD-related features such as motor impairment and medication. Moreover, age of disease onset and years of disease evolution were also recorded.

PD Rating Scale. PD participants' stage and course of the disease was measured by means of UPDRS (Martínez-Martín et al., 1994) and Hoehn and Yahr Scale (Goetz et al., 2004).

Medication. Medications, dosages and frequencies were used to calculate Levodopa equivalent daily dose (LEDD; mg/d) (Tomlinson et al., 2010).

4.2.2. Neuropsychological assessment.

All participants underwent an extensive neuropsychological battery. The battery included assessments to evaluate premorbid intelligence, global cognitive status, attention and working memory, processing speed, verbal memory, visual memory, language, verbal fluency, executive functions and visual abilities. The assessment was also administered by a trained neuropsychologist in one session.

Premorbid intelligence. Premorbid intelligence was evaluated through the Word Accentuation Test (Test de Acentuación de Palabras, TAP) (Gomar et al., 2011) the Spanish version of the National Adult Reading Test. The participant had to read 30 words taking into account the accentuation. The scale ranged from 0 to 30 according to the utilization of an adequate or inadequate accentuation.

Global cognitive status. The MMSE (Folstein et al., 1975) test was used as screening measure to assess global cognition. In the MMSE the participant is instructed to perform activities related to attention and calculation, recall, language, ability to follow simple commands and orientation.

Attention and working memory. These cognitive domains were evaluated by Brief Test of Attention (BTA) (Schretlen, Brandt, & Bobholz, 1996), Backward Digits Subtest of the Wechsler Adult Intelligence Scale III (WAIS-III) (Weschler, 1997), and

Stroop Test (word and color) (Golden & Freshwater, 2002). In the BTA test the participant is asked to count the number of numbers and the number of letters in 10 strings. In the Forward Digits Subtest of WAIS-III the participant had to repeat sequences of numbers aloud at a pace of one number per second in direct order. Finally, the Stroop test consists of three trials; in the word-trial the participant is asked to read aloud the words (red, blue and green) as quickly as possible (time frame 45"); in the color-trial the participant is asked to read a sheet with series of four X "XXXX" (printed in red, blue or green) as quickly as possible (time frame 45").

Processing speed. Trail Making Test – A (TMT-A) (Reitan, 1985) and Salthouse Letters Comparison Test (SLCT) (Salthouse & Babcock, 1991) were used to assess processing speed. In the TMT-A the participant was asked to connect the numbers in ascending order (1 to 25) as quickly as possible (time frame 90"). In the Salthouse Test the participant is instructed to compare the pairs of letter strings and to write "I" if they are equal and "D" if they are dissimilar in both sheets (3 or 6 letters) as quickly as possible (time frame for each sheet 30").

Verbal and visual memory. Learning and long-term recall performance on the Hopkins Verbal Learning – Revised (Brandt, 1991) (HVLT-R; version 2) and on the Brief Visual Memory Test – Revised (Benedict, 1997) (BVMT-R; version 1) were utilized. In the HVLT-R the participant is asked to repeat as many as words as she/he can recall (learning 3 trials), and after 20 minutes is asked to freely recall the list of words (long-term recall). In the BVMT-R the participant is asked to draw six figures as accurately as possible after 10 seconds of visually observation each time (learning 3 trials), and after 20 minutes is asked to freely recall the figures (long-term recall).

Language ad verbal fluency. These domains were evaluated through the abbreviated version of the Boston Naming Test (BNT) (Allegri et al., 1997) and the Calibrated Ideational Fluency Assessment (CIFA) (Schretlen & Vannorsdall, 2010). In the BNT test the participant is told to tell the name of each picture and is given about 20" to respond for each trial (15-items). If the participant fails to give the correct response,

the examiner at her or his discretion may give the patient a phonemic/semantic cue. In the semantic fluency task of CIFA test the participant is asked to say as many animals as possible for one minute, as well as supermarket items for another minute. In the phonetic fluency task the participant is instructed to say as many words beginning with the letter "P" as possible for three minutes.

Executive functions. Trail Making Test – B (TMT-B) (Reitan, 1985) and Stroop Test (word-color and interference) (Golden & Freshwater, 2002) were administered to evaluate executive functions. In the TMT-B test the participant was asked to connect 25 encircled items (numbers from 1 to 13; letter from A to L) alternating between numbers (ascending) and letters (alphabetically) as quickly as possible (time frame 300") Finally, in the third trial of the Stroop test (word-color trial), the participant is asked to read the color ink in which each word is presented (color words printed in incongruent colors) as quickly as possible (time frame 45").

Visual abilities. For visual abilities the Clock Drawing Test (Cacho, García-García, Arcaya, Vicente & Lantada, 1999) (draw and copy) and the Visual Object and Space Perception (VOSP) battery (Warrington & James, 1991) (cubes and incomplete letters) were used. In the Clock Drawing Test the participant is asked to free draw and to copy a clock showing the time 11:10. In the VOSP cubes, 10 boards are presented and the participant is asked to identify how many solids (cubes) there are on each board; in the VOPS incomplete letters, 20 incomplete letters are shown and the participant is asked to name or identify them.

4.2.3. Other non-motor features assessment.

Additionally, some clinical and functional aspects were evaluated. The assessment was also administered by a trained neuropsychologist.

Depressive symptoms. The Geriatric Depression Scale (Yesavage & Sheikh, 1986) (GDS-15) was utilized to evaluate depressive symptoms. Higher scores represent a higher degree of depression (ranged from 0 to 15).

Apathy symptoms. The Lille Apathy Rating Scale (LARS) (Sockeel et al., 2006) was administered to assess apathy and consists of 33 items, including nine subscales. These subscales were summed into a total apathy score with a possible range of -36 to 36, being LARS scores closer to -36 indicative of normality and scores closer to 36 indicative of apathy.

Neuropsychiatric symptoms. The Neuropsychiatric Inventory Questionnaire (Kaufer et al., 2000) (NPI-Q) was administered to assess neuropsychiatric symptoms. The test includes 10 items (delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, euphoria, apathy, disinhibition, irritability, and aberrant motor behavior). The total scores of subscales were ranged from 0 to 120, with higher scores indicating more frequent and severe symptoms.

4.3. Neuroimaging Acquisition

MRI data were acquired on a 3T MRI (Philips Achieva TX) at OSATEK, Hospital of Galdakao (Biscay, Spain). All MRI sequences were acquired during a single session and by an experienced radiologist.

T1-weighted Turbo Field Echo 3D images were obtained in a sagittal orientation (anterior-posterior phase) (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 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).

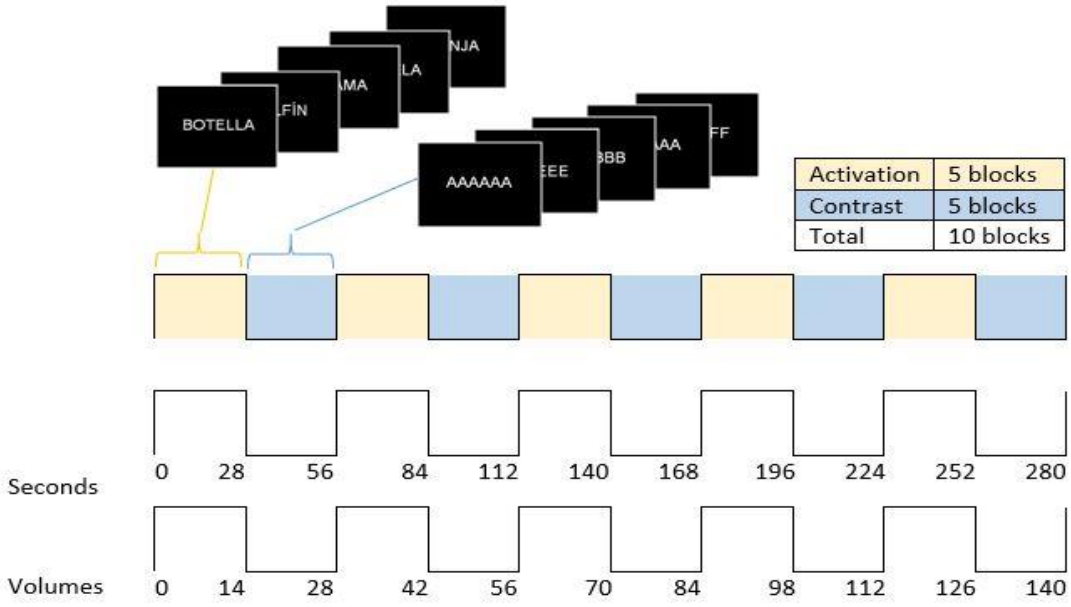

Figure 6. Memory fMRI paradigm representation (block-design).

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) (activation condition). 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.

4.4. Neuroimaging Preprocessing and Analyses

T1-weighted MRI, diffusion-weighted MRI, resting-state fMRI and memory fMRI paradigm data preprocessing was carried out with different techniques explained below. Moreover, different analyses were employed depending on the study, therefore, the studies will be named.

4.4.1. Voxel-Based morphometry (Study II and Study III).

VBM analysis (Douaud et al., 2007) was carried out using the FMRIB Software Library (FSL v 5.0.9) (Smith et al., 2004) tools for GM. First, structural images were brain-extracted and GM segmented before being registered to the Montreal Neurological Institute 152 standard space using non-linear registration. The resulting images were averaged and flipped along the x-axis to create a left-right symmetric, study-specific GM template. Second, all native GM images were non-linearly registered to this study-specific template and "modulated" to correct for local expansion (or contraction) due to the non-linear component of the spatial transformation. The modulated GM images were then smoothed with an isotropic Gaussian kernel with a sigma of 3.5 mm (8 mm FWHM).

Specifically, for *Study II* analyses, regions of interest (ROIs) were located and labelled anatomically with the Harvard-Oxford Cortical Atlas. The ROIs selected were posterior and anterior cingulate cortex, medial prefrontal cortex, bilateral medial temporal lobe, bilateral inferior parietal cortex, and precuneus. Then, differences between PD and HC groups were analyzed with a randomized tool (5000 permutations) and with threshold-free cluster enhancement (TFCE) in FSL. Statistical threshold for analysis was set at $p < 0.05$ corrected for multiple comparisons using family wise error (FWE). Mean volume values of the ROIs were obtained to perform statistical analyses in Statistical Package for the Social Sciences (SPSS).

Specifically, for *Study III* analyses, ROIs were located and labelled anatomically with the Harvard-Oxford Cortical Atlas. The regions selected were bilateral frontal pole, superior frontal gyrus, middle frontal gyrus, inferior frontal gyrus pars triangularis and opercularis, precentral gyrus, frontal medial cortex, juxtapositional lobule cortex

(formerly supplementary motor cortex), cingulate gyrus anterior division and frontal orbital cortex, amygdala, and striatum was also included (bilateral caudate, putamen, pallidum and nucleus accumbens). ROI mask was created with these regions included. Then, differences between groups were analyzed with a randomized tool (5000 permutations) and with TFCE and with cluster-based in FSL with ROI-to-ROI methodology. Total Intracranial Volume (TIV), UPDRS-III (motor) and MCI were introduced as covariates in between-group analysis. Statistical threshold for analysis was set at $p < 0.05$ corrected for multiple comparisons using FWE and exploratory analyses using $p < 0.001$ (uncorrected, K > 30 voxels) were also explored.

4.4.2. Tract-Based Spatial Statistics (Study I, Study II and Study III).

Diffusion data were analyze using FSL v.5.0.9. First, each subject's images were concatenated and radiologically oriented. Then, the data were corrected for motion and eddy currents, brain-extraction BET was performed, and the diffusion gradients (bvecs) were rotated to be corrected accordingly. Then, all FA, MD, RD and AD images were obtained by fitting a tensor model to the raw diffusion data using FDT "DTIFIT". TBSS (Smith et al., 2006) were then used for group comparisons. Using TBSS, the data were prepared to apply a nonlinear registration of all FA images into standard space. The mean FA image was created using a threshold of 0.2 and thinned to create a "mean FA skeleton" which represents the centres of all tracts common to the group. AD data were analyzed using "tbss non FA" script from TBSS, which applies the original non lineal registration to the AD data, merges all subjects warped AD data into a 4D file, then projects this onto the original mean FA skeleton, and creates the 4D projected data. The same process was repeated for MD and AD.

Specifically, for *Study I* analyses, specific predefined WM ROIs were selected, based on the JHU White-Matter Tractography Atlas, as follows: anterior cingulate fasciculus, posterior cingulate fasciculus, and uncinate fasciculus. TBSS differences between PD and HC groups were analyzed with a randomized tool (5000 permutations) and TFCE in FSL. Statistical threshold for analysis was set at $p < 0.05$ corrected for

multiple comparisons using FWE. Mean indexes values of the predefined ROIs were obtained to perform statistical analyses in SPSS.

For *Study II* analyses, specific predefined WM ROIs were selected, based on the JHU White-Matter Tractography Atlas, as follows: corpus callosum body, anterior cingulate fasciculus, posterior cingulate fasciculus, inferior longitudinal fasciculus, and inferior fronto-occipital fasciculus. Then, differences between PD and HC groups were analyzed with a randomized tool (5000 permutations) and with TFCE in FSL. Statistical threshold for analysis was set at $p < 0.05$ corrected for multiple comparisons using FWE. Mean indexes values of the predefined ROIs were obtained to perform statistical analyses in SPSS.

For *Study III* analyses, specific predefined WM ROIs were selected, based on the JHU White-Matter Tractography Atlas, as follows: anterior thalamic radiation, body of corpus callosum, internal capsule, superior longitudinal fasciculus, cingulum and uncinate fasciculus. For TBSS analyses, a ROI mask was created with these regions included. Then, differences between groups were analyzed with a randomized tool (5000 permutations) and with TFCE and with cluster-based in FSL with ROI-to- ROI methodology. TIV, UPDRS-III (motor) and MCI were introduced as covariates in between-group analysis. Statistical threshold for analysis was set at $p < 0.05$ corrected for multiple comparisons using FWE and exploratory analyses using $p < 0.001$ (uncorrected, $K > 30$ voxels) were also explored.

4.4.3. Model-driven approach for Memory fMRI paradigm (Study I).

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 Montreal Neurological Institute 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).

For memory fMRI paradigm analyses ROIs selected were inferior orbitofrontal cortex and medial temporal lobe. Beta values (brain activation > contrast) were extracted from each anatomically defined bilateral ROI using the Anatomical Automatic Labelling atlas and the MarsBar toolbox (http://marsbar.sourceforge.net/) for both learning and recognition tasks to examine significant differences between groups ($p < 0.005$ corrected for multiple comparisons by Bonferroni's procedure).

4.4.4. Data-driven approach for Resting-state fMRI (Study II and Study III).

Resting-state fMRI data were acquired during a so-called resting-state block. Subjects were instructed to both engage in any particular activity, to keep their eyes closed and not fall asleep. Once the resting-state fMRI acquisition finished, the radiologist asked the participants whether they fell sleep and no patient reported. Foam padding and headphones were used. FC pre-processing was carried out using CONN Functional Connectivity Toolbox 15.h (Whitfield-Gabrieli & Nieto-Castanon, 2012). First, each subject's 214 functional images were realigned and unwarped, co-registered with structural data, slice-timing corrected (bottom-up), spatially normalized into the standard Montreal Neurological Institute space, outlier detected (ART-based scrubbing) and smoothed using a Gaussian kernel of 8 mm FWHM. All pre-processing steps were conducted using default pre-processing pipeline for volume-based analyses (to Montreal Neurological Institute-space). T1 structural data were segmented in GM, WM and cerebrospinal fluid and normalized in the same default pre-processing pipeline. One major point is reducing the noise via the anatomical CompCor approach. This method extracts principal components (5 each) from WM and cerebrospinal fluid time series. These components are added as confounds in the denoising step of the CONN toolbox (Whitfield-Gabrieli & Nieto-Castanon, 2012). The six head motion parameters derived

from spatial motion correction were also added as confounds. As recommended, band-pass filtering was performed with a frequency window of 0.008 to 0.09 Hz (Weissenbacher et al., 2009). In addition, ART-based scrubbing regressors' files were included as within-subject covariates in CONN toolbox.

Specifically, for *Study II* analyses, seed regions were the same ROIs as for VBM analyses (DMN regions). Seed-to-voxel group comparisons were assessed using cluster-level inference at p (FWE) < 0.05 at a height threshold of p< 0.001 (uncorrected) in CONN Functional Connectivity Toolbox 14.p. LEDD data was used as covariate in the analysis based on previous findings. FC values of significant differences were obtained to perform statistical analyses in SPSS.

For *Study III*, seed regions were bilateral frontal lobe regions and amygdala and target regions included bilateral striatum. FC differences were assessed with ROI-to-ROI methodology with CONN Functional Connectivity Toolbox 15.h. TIV, UPDRS-III, MCI and LEDD data were used as covariates. Statistical threshold was set at p < 0.05 corrected for multiple comparisons using false discovery rate and exploratory analyses using p < 0.001 (uncorrected, K > 30 voxels) were also explored.

4.5. Statistical Analyses

4.5.1. Study I.

The Shapiro-Wilk test was used to assess the distribution of the data. Independent-samples t-tests were conducted to analyze the differences in the clinical and socio-demographic variables between PD patients and HC. Behavioral data (responses) and brain activation (beta values) from the verbal recognition memory fMRI task were not normally distributed. Therefore, Mann-Whitney U test was used to examine differences between PD and HC groups on those variables. To assess differences in FA and brain activation from the verbal learning memory fMRI task independent-samples t-tests were conducted. Analyses were corrected for multiple comparisons with Bonferroni correction. Partial non-parametric correlations were conducted to investigate all correlations in PD patients controlling for disease stage and disease duration. For HC

group, Spearman's Rho tests were conducted to assess correlations between behavioral data from the verbal recognition memory fMRI task and FA and brain activation from the verbal learning and recognition memory fMRI tasks. Finally, for normally distributed variables in HC group, Pearson's product-moment correlations were measured to examine the structural and functional relationship. Correlational analyses were corrected for multiple comparisons with Bonferroni correction. Statistical analyses were performed using the statistical package SPSS.

4.5.2. Study II.

Normality of data was tested, using the Kolmogorov-Smirnov test. Sociodemographic, clinical and neurological characteristics were compared, using the two-tailed t-test or Chi-squared χ^2 test. All cognitive measures were converted into z scores, based on the pooled PD group, and all composite cognitive domains maintained satisfactory internal consistency. Processing speed (Cronbach $\alpha = 0.86$) was quantified, based on the TMT - A and SLCT. For verbal fluency ($\alpha = 0.89$), CIFA (semantic and phonetic) fluency test was used. For verbal learning and memory ($\alpha = 0.92$), learning and long-term recall performance on the HVLT-R (version 2) was utilized. For visual learning and memory ($\alpha = 0.97$), learning and long-term recall performance on the BVMT-R (version 1) was used. For visual abilities, the Clock Drawing Test (order and copy) and VOSP Battery (incomplete letters and cubes) were used ($\alpha = 0.76$). Executive functioning ($\alpha = 0.73$) was determined, based on the Backward Digits Subtest of the WAIS-III and the Stroop test, using the word-color and interference scores.

Between-group differences were compared using age, gender and education as covariates. Pearson's partial correlations, including as covariates age, gender, education, LEDD, UPDRS III, Hoehn and Yahr stage and disease duration were performed in PD. Pearson's partial correlations, including as covariates age, gender and education were performed in HC. Two outliers were excluded for correlation analyses in PD group using boxplots to avoid false correlations. Finally, a hierarchical multiple regression analysis was conducted to examine if the age, GM atrophy, as well as WM alteration predicted the

FC differences between the regions of the DMN in PD patients. The predictor variable of age was entered in the first block; the predictor variables of GM atrophy correlates were entered in the second step, the final predictor variables of WM alteration correlates were entered in the third block. The criterion variable was FC differences. To obtain adjusted mean differences in change scores and correlations, we used bootstrapping. Effect size (Cohen's d and 95% confidence interval) was calculated, based on the change in the score differences between groups. Cohen's d values of 0.20, 0.50 and 0.80 were considered small, medium and large, respectively. Post-hoc analyses were carried out to test whether FC differences and correlates were related to structural GM abnormalities. Statistical analyses were performed, using the statistical package SPSS program.

4.5.3. Study III.

Normality of data was tested using the Shapiro-Wilk test. Categorical data were analyzed with χ^2 test. Significant differences in variables were compared using the Analysis of Variance (ANOVA) test or Kruskal– Wallis test for three-group comparisons and two-tailed t-tests or U-Mann–Whitney test for two-group comparisons. Significant results' average of each participant was extracted for correlational analyses. To obtain adjusted mean differences we used bootstrapping. Effect size was calculated with Cohen's d. To study brain correlates of apathy, Spearman Rho correlations between significant neuroimaging results (structural and resting-state fMRI) and four factors of apathy were performed in PD patients with high symptoms of apathy and PD patients with low symptoms of and HC. Additionally, further post-hoc analyses were also carried out to examine the relationship between structural and resting-state functional MRI in PD patients (high or low symptoms of apathy) and HC using the Spearman Rho correlation test. For the correlations, outliers were excluded and the scores were initially adjusted for TIV, UPDRS-III, LEDD, and MCI by means of linear regressions and the resulting nonstandard residuals were utilized in the correlations.

4.6. Ethics Statement

The study protocol was approved by the Ethics Committee at the Health Department of the Basque Mental Health System in Spain (CEIC-E 2011111117) 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, in accordance with the Declaration of Helsinki of 1975. All data and images obtained in the study will be anonymized at the time of acquisition and the anonymity of this information will be permanently protected by the research team. No data that could lead to the identification of the participants of the study will be published in the works derived from this research (Organic Law 15/1999, of 13 December on the protection of personal data).

Project 2 (Study IV and V)

4.1. Study Sample

The sample included idiopathic (PD and DLB) and genetic (E46K, PARK2, LRRK2) LBD patients recruited from the Department of Neurology of Cruces University Hospital and from ASPARBI. HC were recruited to approximately match older symptomatic E46K carriers in age and sex. LBD patients were enrolled in the study according to the following inclusion/exclusion criteria (see Table 5).

Table 5

Inclusion and exclusion criteria for the Project 2 (Study IV and Study V)

Inclusion criteria	Exclusion criteria
♦ Written informed consent ♦ Minimum reliability criteria for OCT acquisition ♦ **Study---group specific inclusion criteria* ♦ Confirmed detection of mutation in gene (E46K, LRRK2, PARK2 carriers) ♦ No family history (1st order) of a syndrome suggestive of PD or DLB (Control group: non---familiar PD, non---familiar DLB and HCs) ♦ Diagnosis of PD based on the UK PD Society Brain Bank diagnostic criteria ♦ Diagnosis of probable DLB by revised criteria for the clinical diagnosis of DLB (non---familiar DLB)	♦ Any progressive neurological disorder other than PD, any medically inestable condition or any limiting psychiatric disease ♦ History of substance abuse in the last 5 years (including alcoholism and severe tabaquism) ♦ Patients unable to undergo MRI: reduced renal clearance (screening: eGFR<45ml/min), history of severe hypersensitivity to gadolinium---DTPA, claustrophobia ♦ Previous diagnosis of Diabetes Mellitus or impaired fasting glucose (≥126mg/dL or ≥200 mg/dL after oral glucose tolerance test) ♦ Ophtalmological or drug---related causes for retinal impairment different from PD or major difficulties for retinal evaluation

4.2. Neurological, Neuropsychological, and other Non-motor Features Assessment

The tests and questionnaires shared in both projects have been explained previously in the section "*4.2. Neurological, neuropsychological and other non-motor features assessment*" of the *Project 1*. Therefore, tests previously explained only will be named, and the characteristics of the tests and questionnaires of *Project 2* that have not

been previously mentioned in *Project 1* will be detailed below. A summary of the assessment is provided in Table 6.

Table 6

Neurological, neuropsychological and other non-motor features assessment in Project 2 (Study IV and Study V)

Area	Test
Neurological assessment	
PD Rating Scale	Unified PD Rating Scale
	Hoehn and Yahr Scale
Medication	Levodopa Equivalent Daily Dose
Neuropsychological assessment	
Global cognition	Montreal Cognitive Assessment
Attention & Working memory	Trail Making Test (A)
	Digits test Wechsler Adult Intelligence Scale III
Processing speed	Symbol Digit Modality Test
	Salthouse Letter Comparison Test
Memory	Hopkins Verbal Learning Test- Revised
	Brief Visual Memory Test- Revised
Verbal fluency	Calibrated Ideational Fluency Assessment (phonemic and semantic)
Executive functions	Trail Making Test (B)
	Modified Wisconsin Shorting Card Test
Visuospatial abilities	Benton's Judgment of Line Orientation Test (H-form)
	Clock Drawing Test (draw)
Other non-motor features assessment	
Depression	Geriatric Depression Scale (15-items)
Apathy	Lille Apathy Rating Scale
Fatigue	Fatigue Severity Scale
Dysautonomia	Valsalva pressure recovery time
	Heart rate response variability to deep breathing
	Orthostatic Hypotension
Olfaction	Brief Smell Identification Test
Vision	Low Contrast Visual Acuity
	Photopic Contrast Sensitivity

4.2.1. Neurological assessment.

The neurological exam was exclusively administered to the PD sample and by three experienced neurologists. Three scales were administered with the aim of evaluating PD-related features and medication (UPDRS, Hoeh & Yahr and LEDD). Moreover, age of disease onset and years of disease evolution were also recorded.

4.2.2. Neuropsychological assessment.

All participants underwent an extensive neuropsychological battery. The battery included assessments to evaluate, global cognitive status, attention and working memory, processing speed, verbal memory, visual memory, verbal fluency, executive functions and visual abilities.

Global cognitive status. General cognition was assessed with MoCA (Nasreddine et al., 2005). In the MoCA test the participant is asked to perform different types of cognitive abilities (ranged 0 to 30) evaluating visuospatial, naming, memory, attention, language, abstraction, delayed recall and orientation.

Attention and working memory. This domain was evaluated with Backward Digits Subtest of the WAIS-III (Weschler, 1997) and TMT-A (Reitan, 1985).

Processing speed. SLCT (Salthouse & Babcock, 1991) and Symbol Digit Modalities Test (SDMT) (Smith, 1973) were used to evaluate this domain. In the SDMT the participant is instructed to write in the empty space beneath each symbol the fitting number according to the reference key (several symbols are matched with specific numbers) as quickly as possible (time frame 90").

Verbal and visual m*emory*. Verbal memory was evaluated with long-term recall of the HVLT-R (version 1) (Brandt, 1991) and visual memory with long-term recall of the BVMT-R (version 1) (Benedict, 1997)

Verbal fluency. The domain was assessed with the CIFA test (semantic and phonetic) (Schretlen & Vannorsdall, 2010).

Executive functions. TMT-B (Reitan, 1985) and *the* Modified Wisconsin Card Sorting Test (Categories) (M-WCST) (Schretlen, 2010) were used to evaluate executive

functions. In the M-WCST the participant is asked to make categories with a total of 48 cards. The category is changed every six correct answers and the examiner informs the participant if their choice is correct or incorrect.

Visual abilities. This domain was assessed with Benton's Judgment of Line Orientation Test (H-form) (BJLOT) (Benton, Varney, & Hamsher, 1978) and Clock Drawing Test draw (Cacho et al., 1999). In the BJLOT the participant is instructed to match 30-items (line segments of varying spatial orientation) with a set of longer lines on a response card.

4.2.3. Other non-motor features assessment.

Additionally, some other non-motor symptoms were evaluated. The assessment was also administered by a trained neuropsychologist and neurologist.

Depressive symptoms. GDS-15 (Yesavage & Sheikh, 1986) was utilized to assess depressive symptoms.

Apathy symptoms. These symptoms were evaluated with LARS (Sockeel et al., 2006).

Fatigue symptoms. Physical and mental fatigue symptoms were evaluated by means of the Fatigue Severity Scale (FSS) (Krupp, LaRocca, Muir-Nash, & Steinberg, 1989). This scale is conformed of nine items with seven answer options each (1 = totally disagree / 7 = totally agree).

Dysautonomia. We recorded orthostatic hypotension with tilt table test, and blood pressure recovery time following termination of Valsalva maneuver back to baseline (seconds) (Vogel, Sandroni, & Low, 2005). Heart rate response (variability) to deep breathing was measured as the mean heart rate range in 6 respiration cycles (Task Force of the EU Society, 1996).

Olfaction. Olfaction was assessed with Brief Smell Identification Test (BSIT) (Doty, Marcus & Lee, 1996) composed of 12 odorants embedded on scent strips that are released when scratched with a pencil tip.

Vision. Binocular low contrast visual acuity was assessed with 2.5% Sloan charts at 4 meters (Precision Vision, La Salle, IL) and photopic contrast sensitivity with the Pelli-Robson chart (Metropia Ltd., Cambridge, UK) at 1 meter with 280 lux chart luminance).

4.3. Neuroimaging Acquisition

MRI data were acquired on a 3T MRI (Philips Achieva TX) at OSATEK, Hospital of Galdakao. All MRI sequences were acquired during a single session and by an experienced radiologist.

T1-weighted Turbo Field Echo 3D images acquisition was obtained in a sagittal orientation (TR = 7.4 ms, TE = 3.4 ms, matrix size = 228 x 218mm; flip angle = 9°, FOV = 250 x 250 x 180mm, slice thickness = 1.1 mm, 300 slices, voxel size = 0.98 × 0.98 × 0.60 mm, acquisition time = 4′55″).

Diffusion-weighted images were obtained, in an axial orientation in an anterior-posterior phase direction using a single-shot EPI sequence (TR = 7540 ms, TE = 76 ms, matrix size = 120 x 117mm; flip angle = 90°, FOV = 240 x 240 x 132mm, slice thickness = 2 mm, no gap, 66 slices, voxel size = 1.67 × 1.67 × 2.0 mm, acquisition time = 9′31″) with two identical repetitions (32 uniformly distributed directions b = 1000 s/mm2 and 1 b = 0 s/mm2).

The resting-state fMRI was obtained in an axial orientation in an anterior-posterior phase direction using sequence sensitive to blood oxygen level dependent (BOLD) contrast and multi-slice gradient echo EPI sequence (TR = 2100 ms, TE = 27 ms, matrix size = 80x79mm, flip angle = 80°, FOV = 240x240x146mm, slice thickness = 3 mm, 214 scans, voxel size = 3.00 × 3.00 × 3.00 mm, acquisition time = 7′40″).

4.4. Neuroimaging Preprocessing and Analyses

T1-weighted MRI, diffusion-weighted MRI and data-driven approach for resting-state fMRI preprocessing and analysis was carried out only for Paper V.

Preprocessing was carried out using VBM, TBSS and CONN Functional Connectivity Toolbox as previously described in *"4.4. Neuroimaging preprocessing and analyses"* in *Project 1*.

GM, WM and FC differences between the three clusters were performed with ANOVA and student-t test analyses. GM and WM analyses were performed with a randomized tool (5000 permutations) and with TFCE. Statistical threshold for analysis was set at $p < 0.05$ corrected for multiple comparisons using FEW. FC differences were assessed with ROI-to-ROI methodology and statistical threshold was set at $p < 0.01$ corrected for multiple comparisons using false discovery rate. LEDD data was included as covariate due to its influence in resting fMRI signal. The ROIs selected were based on the FC atlas networks of CONN toolbox: DMN, Sensorimotor, Visual, Salience/ Cingulo-Opercular, Dorsal Attention, Fronto Parietal / Central Executive, Language and Cerebellar. For specific network information see CONN network cortical ROIs HCP-ICA (Whitfield-Gabrieli & Nieto-Castañon, 2012). To assess GM, WM and FC differences between iPD (all and from clusters) and severe LB pathology patients (symptomatic E46K and DLB) student t-tests were performed with age as covariate. Same neuroimaging analyses as describe above were employed.

4.5. Statistical Analyses

4.5.1. Study IV.

To optimize the performance of clustering analyses, we selected the clinical variables that best differentiated patients and HC using Random Forest Classifier (RFC). According to RFC, we chose the following variables for hierarchical clustering analysis: age (demographics); BSIT (olfaction); orthostatic hypotesion, blood pressure recovery time, heart rate response variability (autonomic testing); low contrast visual acuity and photopic contrast sensitivity (visual function); GDS (depressive symptoms); Backward digits WAIS-III and TMTA (attention and working memory); MWCST categories and TMTB (executive functions); semantic and phonetic fluency (language); HVLT-R and BVMT-R (memory); BJLOTH and Clock drawing test (draw) (visuospatial functions);

SDMT and SPCT (processing speed). The former variables were converted to z scores to conduct hierarchical clustering analysis, which was performed including all study subjects, both patients and HC. Features exclusively related to the disease were not included in the analysis and were used post-hoc to compare patients within clusters.

The hierarchical clustering analysis is based on a bottom up approach. Complete linkage criterion was used minimizing the maximum distance between observations of pairs of clusters. k = 3 was selected to offer a good combination of model fit and parsimony. For each identified cluster, we obtained the average (centroid) z score of each variable included to perform hierarchical clustering analysis. All analyses were performed with Scikit-Learning running under Python version 3.6.5 (Pedregosa et al., 2011).

Normality of data was tested using the Shapiro-Wilk test. Categorical data were analyzed with the $\chi 2$ test. Significant differences in variables were compared using the ANOVA test or Kruskal-Wallis test and two-tailed t-tests or U-Mann Whitney test for two-group comparisons. Differences between clusters were analyzed with $\chi 2$ and ANOVA Tukey-corrected as post-hoc tests for pairwise comparisons. Statistical analyses were performed, using the statistical package SPSS program. In addition, to summarize the obtained clusters in graphical representations with only 2 variables defining each subject, we used two different dimensionality reduction techniques: principal component analysis and linear discriminant analysis.

4.5.2. Study V.

Demographic and clinical variables were tested for normality using the Shapiro-Wilk test. ANOVA or $\chi 2$ test were used to assess differences between groups. Bonferroni post-hoc analysis was performed between groups and bootstrapping was used to obtain adjusted mean differences based on 1.000 subsamples. Finally, effect size was calculated with Cohen's d, considering 0.2, 0.5 and 0.8, small, medium and large effect sizes respectively. The SPSS was used to perform statistical analyses.

4.6. Ethics Statement

The study protocol was approved by the Ethics Committee at the Health Department of the Basque Mental Health System in Spain (CEIC-E PI2014154). All patients were volunteers who provided written informed consent to participate in the study, in accordance with the Declaration of Helsinki of 1975. All data and images obtained in the study will be anonymized at the time of acquisition and the anonymity of this information will be permanently protected by the research team. No data that could lead to the identification of the participants of the study will be published in the works derived from this research (Organic Law 15/1999, of 13 December on the protection of personal data).

V. Results

“Projects we have completed demonstrate what we know, future projects decide what we will learn”.
Dr. Moshin Tiwana

5. Results

Study I

"Verbal memory in Parkinson's disease: A combined DTI and fMRI study"

Study II

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

Study III

"Apathy and brain alterations in Parkinson's disease: A multimodal imaging study"

Study IV

"The value of non-motor features and genetic variants of Parkinson's disease for clustering Lewy body diseases"

Study V

"Structural and functional MRI brain alterations in Lewy body diseases"

Study I

Verbal Memory in Parkinson's Disease: A Combined DTI and fMRI Study

Journal of Parkinson's Disease
IF = 3.015; 111/256 Q2 Neurosciences

Study II

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

Parkinsonism & Related Disorders
IF = 4.484: 32/194 Q1 Clinical Neurology

Study III

Apathy and brain alterations in Parkinson's disease: a multimodal imaging study

Annals of Clinical and Translational Neurology
IF = 4.656; 29/199 Q1 Clinical Neurology; 55/267 Q1 Neurosciences

Study IV

The value of non-motor features of Parkinson's disease for clustering Lewy body diseases

2019
In preparation

Study V

Structural and functional MRI brain alterations in Lewy body diseases

2019
In preparation

VI. Discussion

"Follow the evidence to where it leads, even if the conclusion is uncomfortable". Steven James

6. Discussion

The objective of this thesis was to investigate structural and functional brain changes of cognitive and other non-motor dysfunctions in idiopathic and genetic PD patients.

The *Study I* aimed to investigate the brain correlates of verbal memory deficit in PD patients, and the relationship between these verbal memory correlates in PD. Results showed presence of verbal recognition memory deficit in PD patients, accompanied with WM alterations in the anterior cingulate tract, and lower brain activation in the inferior orbitofrontal cortex compared to HC. Specifically, brain activation in the inferior orbitofrontal cortex correlated with verbal recognition memory impairment in PD patients. In addition, a relationship between lower brain activation in the inferior orbitofrontal cortex and WM lower integrity of the uncinate fasciculus was found in PD. Similar results have been obtained in other studies regarding verbal memory deficit (Elgh et al., 2009; Ibarretxe-Bilbao et al., 2011; Muslimović et al., 2005). WM microstructural changes in the right anterior cingulate cortex in PD have also been found in other studies (Gattellaro et al., 2009; Kamagata et al., 2013), as well as lower brain activation in the inferior orbitofrontal cortex (Ibarretxe-Bilbao et al., 2011; Segura et al., 2013). In this study, brain activation alteration of the left inferior orbitofrontal cortex also showed relationship with verbal memory deficit. These results are in line with previous literature (Ibarretxe-Bilbao et al., 2011; Segura et al., 2013) which has also revealed decreased activation in the orbitofrontal cortices and in the medial temporal areas in PD.

Previous studies have been conducted to our understanding of cognitive functioning in PD using DTI (Cochrane & Ebmeier, 2013; Kamagata et al., 2013; Melzer et al., 2013; Theilmann et al., 2013; Vaillancourt et al., 2009; Zheng et al., 2014) and fMRI (Ibarretxe-Bilbao et al., 2011; Atsuko Nagano-Saito et al., 2014; Rottschy et al., 2013; Segura et al., 2013; van Eimeren et al., 2009) separately, but little is known about brain correlates' relationship. Finally, a structure-function relationship was found

between WM FA of the right uncinate fasciculus and brain activation of the left inferior orbitofrontal cortex during the verbal learning memory fMRI task. The uncinate fasciculus is a bidirectional WM tract that projected to the orbitofrontal cortex supports error-related processing in interaction with anterior cingulate and lateral prefrontal cortex (Turken & Swick, 2008).

With all, findings may suggest that the lower performance in verbal memory in PD is related to the lower brain activation in orbitofrontal cortices during the verbal recognition memory fMRI task. In addition, the orbitofrontal cortices that correlated in the verbal recognition memory fMRI task are the same regions that correlated with FA of the uncinated fasciculus during the verbal learning memory fMRI task. To summarize, these results suggest that fronto-temporal involvement in the learning process affects subsequent recognition memory impairment in PD and to our knowledge, represents a first step toward integrating functional and structural data in the domain of verbal memory in PD. Therefore, supporting the idea that learning is an essential part of the memory process and cerebral correlates of memory impairment are found in PD, early identification of this deficit could be helpful to develop specific neuropsychological rehabilitation program including the management of memory as a key point.

The *Study II* not only aimed to investigate verbal memory deficit, but also investigated cognitive impairment in PD more extensively. Specifically, this study explored whether FC is disrupted between the regions of the DMN in PD and how this connectivity is related to cognition, brain GM structure and WM integrity and diffusivity. Indeed, the DMN is a key network in cognitive processing both in normal aging and neurodegenerative disorders (Agosta et al., 2012; Sambataro et al., 2010). Results showed FC reduction between the regions of the DMN associated with decreased cognitive performance, GM volume and WM integrity in PD. PD patients exhibited decreased FC between the posterior cingulate cortex and medial temporal lobe, accompanied with decreased cognitive performance in all domains studied, decreased GM volume in anterior and posterior cingulate, precuneus, medial temporal lobe and

inferior parietal cortex, and WM FA reduction in adjacent tracts when compared with HC. The significant FC reduction was found with LEDD data as covariate, and after controlling for GM atrophy, the FC difference between posterior cingulate and left medial temporal remained significant. Previous studies reported similar results within the DMN FC alteration in PD (Disbrow et al., 2014; Tessitore et al., 2012). Moreover, results of Study II showed that DMN FC disruption was associated with verbal and visual memory and visual abilities deterioration, even when controlling for GM atrophy. These relationships are in line with previous studies which also demonstrated a relationship between DMN connectivity and cognitive functions such as memory and visuospatial processing (Baggio et al., 2015; Ibarretxe-Bilbao et al., 2011; Tessitore et al., 2012). In addition, FC disruption correlated with GM volume of the posterior cingulate and precuneus, and WM FA of inferior longitudinal and posterior cingulate fasciculi, suggesting that the posterior region of the DMN is the most affected area. With all, the strength of this study is that is the first to demonstrate that DMN alteration in PD is associated with a defined and focal pattern of brain GM volume and WM FA abnormalities centered on the posterior cingulate and subsequent connections to the medial temporal, which revealed a lower performance in verbal and visual memory and visual abilities. This study highlights the close relationship between functional and anatomical changes and its effect on cognitive performance, and highlights the importance of investigating PD using a multimodal approach. Indeed, memory impairment is again a key domain in PD, not only during the memory paradigm task but even at rest. Early identification of this disruption could be helpful to develop specific neuropsychological rehabilitation program including the management of these cognitive deficits as a key factor. Moreover, qualitatively, memory is one of the domains that most affects the quality of life and daily life of PD patients.

Despite of the growing interest on cognition in PD as described in the introduction, some other non-motor features apart from MCI can appear in the early-stage of PD, for example apathy. Recent meta-analyses have shown that the prevalence

of apathy is close to 40% in PD (den Brok et al., 2015; Pedersen, Larsen, Alves, & Aarsland, 2009), being one of the most common non-motor symptom, and it is associated to poor cognitive performance and dementia (Dujardin et al., 2007; Simuni & Sethi, 2009).

Therefore, the *Study III* aimed to investigate brain changes and correlates of frontal, striatal, and limbic pathways related to subclinical symptoms of apathy in PD patients. Results revealed that distinct structural and functional brain alterations are present in PD patients with high or low symptoms of apathy. Those apathy symptoms were associated with these alterations controlling for TIV, UPDRS-III (motor), LEDD and MCI. Specifically, PD patients with high symptoms of apathy showed increased WM diffusivity in body corpus callosum, cingulum, uncinate and superior longitudinal fasciculi compared with HC, and increased WM diffusivity in corpus callosum compared with PD patients with low symptoms of apathy. However, no GM differences were found between groups. Few studies have investigated WM brain changes and correlates of apathy in PD (Carriere et al., 2014; Yang Zhang et al., 2018), and different results were found. One study revealed no significant differences (Carriere et al., 2014) while one recent study showed significant FA differences in the corpus callosum between apathetic and non-apathetic PD patients and a correlation with apathy scores measured with LARS (Zhang et al., 2018). In addition, PD patients with high symptoms of apathy revealed FC decrement in frontostriatal and fronto-limbic pathways compared with HC, but only fronto-striatal FC decrement when compared with PD patients with low symptoms of apathy.

These results go in line with the study of Baggio and colleagues (Baggio et al., 2015) in which apathetic PD patients showed FC reductions in limbic, striatal and frontal regions. Moreover, PD patients with low symptoms of apathy exhibited FC reduction between amygdala and accumbens (fronto-limbic) and FC hyperconnectivity in frontostriatal pathway compared with HC. This hyperconnectivity is an interesting result which could suggest a compensatory mechanism in the disease. Previous studies also

showed that hyperconnectivity might be a common response in the pre-symptomatic phases, because, as the disease progresses, a critical loss of resources may result in gradual increment of FC in other areas (Gorges et al., 2015; Hillary et al., 2015), specifically in striatal pathways (Hacker, Perlmutter, Criswell, Ances, & Snyder, 2012), and even in other pathologies (Farb et al., 2013; Kadhka et al., 2013; Kos, van Tol, Marsman, Knegtering, & Aleman, 2016; Meda et al., 2012). Apart from brain changes, correlates of apathy also were found. Fronto-striatal FC and WM diffusivity alterations were associated with symptoms of apathy in PD patients with high symptoms of apathy, and the fronto-striatal hyperconnectivity was associated with reduction of symptoms of apathy in PD patients with low symptoms of apathy. Finally, structural-functional MRI relationship in PD patients with high symptoms of apathy was observed, revealing that the higher the WM diffusivity, the lower the fronto-striatal FC. In summary, findings could suggest that in PD patients with low symptoms of apathy a hyperconnectivity is present, but with greater subclinical symptoms of apathy (PD patients with high apathy symptoms), the fronto-striatal pathway is affected showing an hypoconnectivity related to specific WM diffusivity alterations. This pattern could be considered as a cross-disease model for early symptoms of apathy helping clinicians to be aware of first symptoms and developing new therapies to management them. Moreover, the decrement of these symptoms could improve many aspects of patients' daily lives and increase their quality of life.

It is clear that non-motor features play a key role in PD. Moreover, PD is a heterogeneous condition with marked variability in terms of clinical presentation and disease progression. These non-motor symptoms increase as the disease progresses, damaging many aspects of patients' daily lives and reducing their quality of life. Studies also show that 80% of PD patients with cognitive impairment develop dementia (Hely et al., 2008). In 2004, the team led by Dr. Zarranz and Dr. Gómez-Esteban described for the first time in a family from the Basque Country (Spain) a mutation in the alpha-synuclein gene (E46K-SNCA) that induces a disease in the brain by LB (the pathological

paradigm of iPD) and also has a clinical phenotype superposable to more aggressive forms of PD, including early cognitive impairment and visuospatial disorders, being an excellent genetic model of iPD.

Therefore, the *Study IV* aimed to classify idiopathic LBD using cluster analysis with a comprehensive set of non-motor features, including an extensive cognitive evaluation, and involving three genetic PD variants with different degrees of LB pathology. Results showed three clusters of subjects including Cluster 1 or "Normal-to-mild": young iPD (< 60 years) classified together with most HC and the variable LB burden genetic PD variants (PARK2 and LRRK2) characterized by having normal-to-mild cognitive disabilities and mild-to-moderate motor disability with few axial symptoms; Cluster 2 or "Mild-to-moderate": old iPD patients (>60 years) classified together with the lowest symptomatic E46K-SNCA, PARK2 carriers and HCs, characterizing by having mild-to-moderate cognitive and motor disabilities with few axial symptoms; and Cluster 3 or "Severe": old iPD (>60 years) classified together with all DLB and the most symptomatic E46K-SNCA carriers, characterized by having severe pattern-specific cognitive disabilities (visual attention, perception, processing speed, memory and executive functions) and severe motor PD manifestations with marked axial symptoms. Until now, some publications have used clustering analyses to identify PD subtypes based on non-motor symptoms (Erro et al., 2016; Pont-Sunyer et al., 2015; Yang, Kim, Yun, Kim, & Jeon, 2014), were usually three or four phenotypes are identified.

The first cluster analysis was performed by Graham and Sagar (1999), who introduced three subtypes as 'motor only', 'motor and cognition' and 'rapid progression'. Several clustering solutions have identified two clusters of 'old age-at-onset and rapid disease progression' and 'young age-at-onset and slow disease progression' (Van Rooden et al., 2010). Furthermore, our study suggested the existence of a specific PD phenotype (cluster 3) that was identified irrespective of disease duration and which included marked axial motor manifestations and severe non-motor disability. Interestingly, and in line with the Study III, a recent study by Erro and colleagues (Erro et al., 2016)

reported a non-hierarchical cluster analysis identifying three subgroups of PD patients where apathy was found to be one of the most important classifiers. In summary, findings suggest the potential value of incorporating genetic PD variants in data-driven Ipd classification algorithms and the usefulness of non-motor PD features, especially visual cognition abnormalities, to facilitate the identification of aggressive LBD. It will be of considerable interest to continue following these subtypes, to observe to what degree these differences in progression persist over the longer term. Finally, typical clustering solutions present cluster characteristics at the group level, using mean values, which make it impossible to place individuals into a distinct subgroup, and so apply the solutions to real-life practice. Findings could help clinicians to be aware of patient profile with few specific tests while symptoms are in the first stages.

Finally, although non-motor features have been reported in diagnosis of LB pathologies, neuroimaging studies are particularly important in the identification of this subjects in the prodomic phase. Therefore, *Study V* aimed to evaluate structural and resting-state fMRI brain measures in the three previous clusters of genetic and idiopathic LB pathology identified. Additionally, specific differences between iPD patients and severe LB pathology (symptomatic E46K-SNCA carriers and DLB patients) were further analyzed.

Specifically, results showed structural and functional MRI brain alterations in cluster 3 “Severe” and cluster 2 “Mild-to-moderate” compared to cluster 1 “Normal-to-mild”. “Severe” cluster showed GM atrophy in temporal and parietal areas, WMraidl alterations in corpus callosum and anterior thalamic radiation, and FC reductions between language network and dorsal attention and salience networks. “Mild-to-moderate” cluster revealed GM atrophy in fronto-temporal areas, and FC reduction between salience and language networks. No significant alterations were found in “Normal-to-mild” cluster. Additionally, specific GM, WM and FC reductions in severe LB pathology patients (DLB+E46K) compared to all iPD patients were found. Moreover, WM diffusivity reduction of the uncinate fasciculus, and FC reduction in posterior-

frontal areas in DLB patients compared to symptomatic E46K carriers was found. Some studies have found similar results regarding structural brain alterations (Beyer, Larsen, & Aarsland, 2007; Burton, McKeith, Burn, Williams, & O'Brien, 2004) and FC brain alterations (Kobeleva et al., 2017; Peraza et al., 2015). In summary, findings suggest pattern of brain damage in LBD and across different spectrum (cluster 1,2 or 3) of iPD. This characterization may help to improve our understanding of the pathophysiology of nervous system damage in LBD and to identify prognostic biomarkers in this disease when tested longitudinally. Findings could be used to develop a more efficient personalized approach for clinical trials and treatment strategies for individuals with different subtypes of LB pathology.

VII. Conclusions

"Projects we have completed demonstrate what we know—future projects decide what we will learn." Dr. Moshin Tiwana

7. Conclusions

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

- PD patients showed verbal recognition memory impairment, which was related to brain activation reduction in frontal areas. Structural-functional relationship was found, specifically, frontal brain activation was related to WM FA of the uncinate fasciculus in PD. Findings suggest that impaired recognition might reflect deficient memory consolidation that is related to the influence of the learning process and to underlying fronto-temporal degeneration.

- PD patients showed reduced FC, GM volume and WM FA within the areas of the DMN. The FC disruption of the DMN was associated with decreased cognitive performance in memory and visual abilities, lower GM volume and lower WM FA in PD. This study highlights that the disrupted FC between posterior and temporal areas of the DMN is accompanied by memory and visual abilities deficits even after controlling for GM atrophy.

- PD patients with high symptoms of apathy showed fronto-striatal and fronto-limbic hypoconnectivity while PD patients with low symptoms of apathy showed fronto-limbic hypoconnectivity but fronto-striatal hyperconnectivity. Findings suggest that the increased pattern of connectivity accompanied by lower apathetic symptomatology, might be the initial manifestation of compensatory mechanisms for dysfunctional limbic pathway.

- Clustering analyses showed three groups of LBD patients classified irrespective of disease duration. Current results suggest that the clinical picture of severe LBD, including DLB patients, E46K-SNCA carriers, and most affected PD patients is

characterized by a rapidly evolving cognitive impairment that initiates in the early phase of the development of motor symptoms of PD.

- Severe LBD group composed of DLB patients, E46K-SNCA carriers, and most affected PD patients showed GM volume reduction in temporal and frontal areas, and WM FA reduction mainly in anterior thalamic radiation compared to moderate and mild LBD patients. In addition, severe LBD patients also exhibited reduced FC between language and dorsal-attentional networks, and between language and salience networks.

Conclusiones

Las principales conclusiones de esta tesis, derivadas de los cinco estudios, pueden resumirse como sigue:

- Los pacientes con EP mostraron un deterioro de la memoria de reconocimiento verbal, que se relacionó con la reducción de la activación cerebral en las áreas frontales. Se encontró una relación estructura-función, específicamente, la activación cerebral frontal se relacionó con la sustancia blanca del fascículo uncinado en la EP. Los hallazgos sugieren que el reconocimiento alterado podría reflejar una consolidación deficiente de la memoria que está relacionada con la influencia del proceso de aprendizaje y con la degeneración frontotemporal subyacente.

- Los pacientes con EP mostraron una reducción de la conectividad funcional, del volumen de sustancia gris y de la sustancia blanca dentro de las áreas de la DMN. La alteración de la conectividad funcional de la DMN se asoció con una disminución del rendimiento cognitivo en la memoria y las capacidades visuales, un menor volumen de sustancia gris y una menor sustancia blanca en la EP. Este estudio destaca que la disrupción de la conectividad funcional entre las áreas posteriores y temporales de la DMN está acompañada de déficits de memoria y habilidades visuales incluso después de controlar la atrofia cerebral de la sustancia gris.

- Los pacientes con EP con altos síntomas de apatía mostraron alteraciones de la conectividad funcional frontoestriatal y fronto-límbica, mientras que los pacientes con bajos síntomas de apatía mostraron alteraciones de la conectividad funcional fronto-límbica pero hiperconectividad frontoestriatal. Los hallazgos sugieren que el aumento del patrón de conectividad acompañado de una menor

sintomatología apática, podría ser la manifestación inicial de mecanismos compensatorios para la disfunción de la vía límbica.

- Los análisis de clustering mostraron tres grupos de pacientes con enfermedad de cuerpos de Lewy clasificados independientemente de la duración de la enfermedad. Los resultados actuales sugieren que el cuadro clínico de las enfermedades por cuerpos de Lewy severas, incluidos los pacientes con demencia por cuerpo de Lewy, los portadores de E46K-SNCA y la mayoría de los pacientes con EP más afectados, se caracteriza por un deterioro cognitivo de rápida evolución que se inicia en la fase inicial del desarrollo de los síntomas motores de la EP.

- El grupo de enfermedad por cuerpos de Lewy severa compuesto por pacientes con demencia por cuerpo de Lewy, los portadores de E46K-SNCA y la mayoría de los pacientes con EP más afectados, mostró alteraciones estructurales en el volumen de sustancia gris de las áreas temporales y frontales, y en la sustancia blanca, principalmente en la radiación talámica anterior en comparación con los pacientes de enfermedad por cuerpos de Lewy moderada y leve. Además, los pacientes con enfermedad por cuerpos de Lewy severa también mostraron una conectividad funcional reducida entre las redes de lenguaje y dorsal-atencional, y entre las redes de lenguaje y saliencia.

VIII. References

8. References

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