Neural correlates of Impulse Control Disorder in Parkinson's Disease:

fMRI evidence from motor, inhibition and semantic domains

Doctoral Thesis by

Teresa Esteban-Peñalba

Supervised by

Dr. Pedro M. Paz-Alonso & **Dr. María Cruz Rodríguez-Oroz**

2022

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Universidad del País Vasco

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bcbl

BASQUE CENTER ON COGNITION, BRAIN AND LANGUAGE

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Mamá,

esto es para ti

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But it is one thing to read about dragons and another to meet them.

Ursula K. Le Guin

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Abstract

Parkinson's disease (PD) is the second most common neurodegenerative disorder associated with aging. Approximately 40% of the PD patients treated with dopaminergic medication will develop Impulse Control Disorder (ICD). PD patients with ICD engage in pathological behaviors akin to behavioral addictions, as a result of a malfunction of their reward system due to chronic exposure to dopaminergic medication. Cognitive neuroscience research has investigated cognitive impulsivity and reward mechanisms in PD patients with ICD. However, functional and molecular imaging evidence indicates abnormalities in regions and networks that are not associated with cognitive impulsivity, but with domains such as movement, inhibitory control, and semantic processing. These domains have either not been previously investigated in this population, or previous literature shows mixed results. This doctoral dissertation aims at examining the neural correlates of three different domains in a group of patients with PD and ICD, a group of patients with PD and no ICD, and a group of healthy control participants using functional magnetic resonance imaging (fMRI). The three domains examined in each Experiment are motor function through a sequential finger-tapping task (Experiment I), inhibitory control through measures of response inhibition (Experiment II), and semantic processing via an auditory processing task (Experiment III). We were particularly interested in group differences in the functional networks and regions implicated in these tasks. Our results revealed that, across the three examined domains (i.e., motor, response inhibition, semantic processing), PD patients with ICD showed differential functional coupling among regions relative to their control counterparts, which remarks the importance of neural networks in cognitive neuroscience. Although the domains examined here had not received special attention in PD patients with ICD, we show that these patients exhibit functional differences beyond the reward system circuitry.

Resumen en castellano

La mejora en condiciones de vida y en el acceso a la sanidad ha supuesto un aumento en la esperanza de vida en países desarrollados. Sin embargo, al aumentar la esperanza de vida, también lo ha hecho la prevalencia de enfermedades neurodegenerativas. La enfermedad de Parkinson (Parkinson's Disease, PD) es la segunda enfermedad neurodegenerativa más prevalente y se espera un aumento en su incidencia en los próximos 30 años (Bach et al., 2011). La PD es un trastorno del movimiento, y las manifestaciones, tanto motoras como no motoras, se asocian a la denervación dopaminérgica y la agregación de α-sinucleína, afectando en primer lugar al estriado motor. En la ausencia de una cura, el tratamiento se centra en tratar las manifestaciones de la enfermedad a través de medicación dopaminérgica. Pese al impacto positivo de la medicación, su administración crónica se asocia a diversos efectos secundarios. Uno de ellos es el trastorno de control de impulsos (Impulse Control Disorder, ICD).

En la PD, el ICD es una complicación compleja asociada al efecto prolongado de la estimulación dopaminergica sobre el circuito límbico de los ganglios basales, afectando particularmente al estriado ventral (ventral striatum, VS) (Aracil-Bolaños & Strafella, 2016). La dopamina exógena altera el funcionamiento del VS, que se torna hipersensible a las recompensas e insensible a los castigos (Zhang et al., 2021). Estos cambios suponen el caldo de cultivo perfecto para desarrollar conductas patológicas. Al sentirse irrevocablemente atraídos hacia refuerzos positivos, y ser incapaces de ajustar su conducta en función de los refuerzos negativos, estos pacientes desarrollan principalmente conductas de hipersexualidad patológica, juego patológico, ingesta compulsiva y/o compra compulsiva, entre otras alteraciones de la conducta (Voon et al., 2006). Sin embargo, estudios de imagen molecular indican que los pacientes con PD e ICD también presentan alteraciones en el estriado dorsal (Premi et al., 2016), regiones frontales (Joutsa et al., 2012; Lee et al., 2014) y temporales (Verger et al., 2018). Asimismo, estos estudios previos (Premi et al., 2016; Verger

et al., 2018) junto con un estudio de resonancia magnética funcional (functional Magnetic Resonce Imaging, fMRI) (Carriere et al., 2015) muestran una conectividad funcional cortico-estriatal reducida. Por tanto, la evidencia previa sugiere que hay cambios a nivel estructural y funcional en pacientes con PD e ICD que van más allá del estriado ventral.

Teniendo en cuenta que la impulsividad, y por tanto, los problemas inhibitorios, son una de las características principales del ICD en la PD, la inhibición, sobre todo sus aspectos más cognitivos, se han estudiado desde diferentes ángulos en pacientes con PD e ICD. Sin embargo, debido a las numerosas alteraciones cerebrales observadas en estos pacientes, y al amplio espectro de funciones que atiende el sistema dopaminérgico, es esperable que otros dominios estén afectados también en esta población. En particular, esta tesis doctoral se centra en investigar tres posibles dominios que podrían estar afectados, pero que o bien no han sido estudiados previamente en pacientes con PD e ICD, o para los que la evidencia previa es contradictoria. En definitiva, en este trabajo se explora el movimiento secuencial, la inhibición de respuesta y el procesamiento semántico en pacientes con PD e ICD, pacientes con PD sin ICD y controles sanos. Debido a las diferencias funcionales y estructurales identificadas en pacientes con PD e ICD, esperamos que estos pacientes muestren diferencias de activación y co-activación en las tareas incluidas en esta tesis, en comparación con los grupos control de pacientes con PD sin ICD y controles sanos. Sin embargo, la escasa evidencia previa disponible no permite predecir de manera inequívoca si estos posibles cambios se asocian con mecanismos compensatorios o con desequilibrios asociados con el ICD. Para estudiar el funcionamiento de estos tres dominios en el contexto del ICD en la PD en humanos, seleccionamos la técnica de imagen de resonancia magnética (Magnetic Resonance Imaging, MRI). Empleando la fMRI, examinamos la activación regional y la conectividad funcional mientras los participantes realizaban las diferentes tareas.

En el Expermiento 1 examinamos el funcionamiento de la red motora a través de una tarea secuencial manual. En el escáner, los participantes debían tocar con el pulgar cada uno de los otros dedos de la mano, alternando el toque de una mano y otra con un periodo de descanso. Analizamos la activación funcional de los núcleos principales del tracto dentato-talamo-cortical, involucrado en la ejecución del movimiento, así como del núcleo de los ganglios basales responsable del control motor, el putamen. Es importante destacar que el

putamen es una de las estructuras más afectadas por la denervación dopaminérgica en la PD. La activación ipsilateral y contralateral de todos los participantes fue la esperada. Además, encontramos que, pese a no haber activación diferencial de estas regiones entre los grupos, al mover la mano izquierda, los pacientes con PD e ICD mostraron una asociación positiva entre la activación del nucleo ventrolateral posterior del tálamo (Posterior ventral lateral nucleus of the thalamus, VLp) derecho y putamen bilateral tanto con la duración de la PD como con la cantidad de levodopa diaria. Esta asociación no existía en el caso de los pacientes con PD sin ICD. El patrón de estas asociaciones indica que el VLp derecho y el putamen son particularmente sensibles a la exposición prolongada a la medicación en pacientes con PD e ICD, de manera similar a la afectación bien documentada del VS. Es más, posteriores análisis de mediación mostraron que, únicamente en pacientes con PD e ICD, cuanta más cantidad de levodopa diaria tomen, mayor es la activación tanto del VLp derecho como del putamen, y estas asociaciones están mediadas por la duración de la PD. Finalmente, realizamos análisis de conectividad funcional (Functional connectivity, FC) entre el VLp derecho y el putamen, y observamos que, durante la realización de la tarea con la mano izquierda, los pacientes con PD e ICD mostraban una co-activación inferior que los pacientes con PD sin ICD y los controles sanos. Sumado al patrón anormal de asociaciones encontrado en pacientes con PD e ICD, los resultados de la FC muestran que los pacientes con PD e ICD reclutan la red motora de manera diferente a los otros dos grupos. Específicamente, la tendencia a una mayor activación del VLp derecho y el putamen a medida que se incrementa la duración de la PD y la cantidad de medicación dopaminergica, y la menor co-activación entre dichas regiones podría indicar una facilitación motora en pacientes con PD e ICD. Por tanto, concluimos que el ICD en pacientes con PD tiene un efecto adicional en la red motora, no estudiado hasta ahora, que altera la FC de los componentes subcorticales y que se asocia a elevadas dosis de estimulación dopaminérgica durante un período de tiempo continuado.

En el Experimento 2 examinamos la inhibición motora, particularmente la inhibición de respuesta, un dominio cognitivo que ha recibido cierta atención en relación con el ICD en PD. Sin embargo, diferentes estudios han encontrado resultados contradictorios respecto a la capacidad de inhibición motora en estos pacientes (Claassen et al., 2015; Filip et al., 2018; Meyer et al., 2020). A nivel funcional, el estudio de Filip y colaboradores (2018) encuentra

alteraciones en regiones subcorticales tras realizar un análisis a nivel de todo el cerebro. Nosotros nos centramos en las regiones de la red de inhibición, las principales responsables en la ejecución y preparación inhibitoria: el giro frontal inferior (Inferior frontal gyrus, IFG), el área motora presuplementaria (preSupplementary Motor Area, preSMA), y el núcleo subtalámico (Subthalamic nucleus, STN) (Aron et al., 2007). Típicamente, esta red se encuentra lateralizada en el hemisferio derecho. A tal fin, los participantes completaron una tarea de inhibición de respuesta altamente demandante en el escáner. En esta tarea, los participantes debían detener una acción iniciada previamente (en este caso, apretar un botón), o continuar finalizando el movimiento. Examinamos dos aspectos de la inhibición de respuesta: inhibición proactiva, es decir, inhibición preparada de antemano; e inhibición contenida, es decir, inhibición del impulso inhibitorio. A pesar de no observar diferencias conductuales entre los tres grupos, los mecanismos empleados por el grupo de PD e ICD para completar cada tipo de inhibición fue diferente al de los empleados por los dos grupos controles. Para realizar la inhibición proactiva, los pacientes con PD e ICD hiperactivaron el IFG y el preSMA bilateralmente en mayor medida que el resto de los grupos, mientras que no encontramos diferencias a nivel de FC. Por tanto, las alteraciones asociadas a la inhibición proactiva indican que los pacientes con PD e ICD reclutan una red más extensa para realizar la misma tarea, probablemente compensando su elevada impulsividad. Para realizar la inhibición contenida, los pacientes con PD e ICD activaron el IFG izquierdo y co-activaron el IFG con regiones atencionales en mayor medida que los pacientes con PD sin ICD, mostrando asimismo menor co-activación entre el SMA derecho y el putamen derecho, y entre el STN derecho y el precuneus. Por tanto, las alteraciones asociadas a la inhibición contenida sugieren que, a la hora de inhibir el impulso inhibitorio, y volver a concentrarse en la tarea de apretar el botón, los pacientes con PD e ICD requirieron de componentes atencionales. Esto probablemente se debió a que lidiar con el elemento distractor y con la reorientación de la atención fue un aspecto particularmente exigente para ellos. Así pues, en este experimento observamos como los aspectos inhibitorios estudiados, la inhibición proactiva y contenida, supusieron retos específicos para los pacientes con PD e ICD, que se reflejaron en los diferentes correlatos funcionales indicados.

En el Experimento 3 examinamos el impacto del ICD sobre el procesamiento semántico centrándonos en las diferencias de procesamiento entre palabras asociadas al ICD

y palabras no asociadas al ICD. Escasos estudios conductuales en pacientes con PD e ICD han examinado tareas lingüísticas. Aquellos que lo han hecho, han investigado la fluencia verbal, llegando a resultados contradictorios (Leroi et al., 2013; Santangelo et al., 2009; Siri et al., 2010). A pesar de que el procesamiento semántico se ve afectado con la disfunción de sistemas cortico-estriatales, como es el caso de la PD (Angwin et al., 2006), ningún estudio hasta la fecha ha examinado el procesamiento semántico en pacientes con PD e ICD. Es más, la reducción de la conectividad cortico-striatal observada en pacientes con PD e ICD en comparación con pacientes con PD sin ICD (Carriere et al., 2015; Premi et al., 2016; Verger et al., 2018) sugiere que el ICD en PD podría presentarse con una mayor deficiencia en el procesamiento semántico. Con el fin de observar los correlatos funcionales de la red semántica, los participantes realizaron una tarea auditiva en la que debían detectar nombres de marcas comerciales, para asegurar que procesaban semánticamente todas las palabras. Incluimos palabras asociadas al ICD y palabras control, y observamos que, en todos los participantes, tres regiones respondían diferencialmente a palabras asociadas al ICD: el giro temporal medio anterior (anterior middle temporal gyrus, aMTG) izquierdo, el giro angular (angular gyrus, AG) izquierdo, y la corteza prefrontal medial (medial prefrontal cortex, mPFC). Dos de estas regiones, el aMTG y AG izquierdos, son considerados nodos semánticos (Fedorenko et al., 2011), mientras que el mPFC podría activar más recursos atencionales, al tratarse de palabras más salientes. Pese a la similar activación en los tres grupos, comparados a los otros dos grupos, los pacientes con PD e ICD mostraron una reducción en la co-activación entre los nodos semánticos, aMTG y AG izquierdos, durante el procesamiento de palabras asociadas con el ICD versus el procesamiento de palabras control. La reducida co-activación entre el aMTG y AG izquierdos podría afectar al procesamiento de las palabras, evocando un mapa semántico menos integrado, y por tanto, reduciendo las asociaciones semánticas entre conceptos y protegiendo a los pacientes del impacto de las palabras asociadas al ICD. Esto sugiere que los pacientes con PD e ICD procesarían las palabras asociadas al ICD en menor medida que los pacientes con PD sin ICD y los controles sanos. Por tanto, a pesar de que gran parte de los estudios que evalúan el efecto del ICD en pacientes con PD se centran en funciones cognitivas ligadas a la impulsividad, como la inhibición y la recompensa, este estudio sugiere una alteración del procesamiento semántico en estos pacientes.

Para concluir, los tres estudios incluidos en esta tesis doctoral han examinado el ICD en PD desde el ángulo de la neurociencia cognitiva con el objetivo de observar el alcance de alteraciones asociadas con el ICD en la PD más allá de la inhibición cognitiva y la recompensa. Para ello, nos hemos centrado en tres dominios diferentes: movimiento secuencial, inhibición motora y procesamiento semántico. En los tres casos, hemos encontrado alteraciones funcionales en las principales redes involucradas en la realización de estas tareas. Estas alteraciones se han reflejado principalmente en FC alterada, que puede interpretarse como un mecanismo compensatorio para mantener un control motor e inhibitorio óptimo, así como para controlar el efecto de posibles detonantes del ICD. Sin embargo, este trabajo es insuficiente para explicar el efecto del ICD en la PD de manera global, y simplemente presenta dominios concretos, más allá de la impulsividad e inhibición cognitiva, que muestran alteraciones funcionales en pacientes con PD e ICD. Se necesitan más estudios, primero para replicar nuestros resultados, y segundo para expandirlos, examinando la relación entre el comportamiento y los correlatos funcionales de estos pacientes en mayor detalle.

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List of acronyms

AG	Angular gyrus
aMTG	Anterior middle temporal gyrus
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
ATP	Anterior temporal pole
BCBL	Basque Center on Cognition, Brain and Language
BG	Basal ganglia
BIS-11	Barratt Impulsiveness Scale
BOLD	Blood-oxigen-level-dependent
CT	Cortical thickness
DAT	Dopamine transporter
deoxyHb	Deoxygenated hemoglobin
DMN	Default mode network
DN	Dentate nucleus of the cerebellum
DTCT	Dentato-thalamo-cortical tract
FA	Flip angle
FAB	Frontal assessment battery
FC	Functional connectivity
FDR	False discovery rate
fMRI	Functional magnetic resonance imaging
FoV	Field of view

FWE	Family-wise error
FWHM	Full width at half maximum
GLM	General linear model
HADS	Hospital anxiety and depression scale
HC	Healthy control
HRF	Hemodynamic response function
HY	Hoehn and Yahr
ICD	Impulse control disorder
IFG	Inferior frontal gyrus
IPC	Inferior parietal cortexl
$LEDD_{L\text{-}DOPA}$	Daily levodopa equivalent dose
M1	Primary motor cortex
MCI	Mild cognitive impairment
mPFC	Medial prefrontal cortex
MRI	Magnetic resonance imaging
MoCA	Montreal cognitive assessment
MTG	Middle temporal gyrus
Mthal	Motor thalamus
OFC	Orbitofrontal cortex
oxyHb	Oxygenated hemoglobin
PD	Parkinson's disease
PD-ICD	Parkinson's disease with impulse control disorder
PD-noICD	Parkinson's disease without impulse control disorder
PET	Positron emission tomography
PFC	Prefrontal cortex
PMC	Premotor cortex
preSMA	Presupplementary motor area

QUIP-RS	Questionnaire for impulsive-compulsive disorders in Parkinson's disease - Rating scale
RF	Radiofrequency
ROI	Region of interest
RT	Response times
SMA	Supplementary motor area
SMG	Supramarginal gyrus
SNpc	Substantia nigra *pars compacta*
SNpr	Substantia nigra *pars reticulata*
SSRI	Selective serotonin reuptake inhibitors
SST	Stop signal task
STN	Subthalamic nucleus
TE	Echo time
TMT-A	Trail making test part A
TMT-B	Trail making test part B
TR	Repetition time
UPDRS	Unified Parkinson's disease rating scale
VA	Ventral anterior nucleus of the thalamus
VIm	Ventral intermediate nucleus of the thalamus
VL	Ventral lateral nucleus of the thalamus
VLa	Anterior ventral lateral nucleus of the thalamus
VLp	Posterior ventral lateral nucleus of the thalamus
VS	Ventral striatum
VTA	Ventral tegmental area
WAIS-III	Wechsler adult intelligence scale version III

Overview

The primary research goal of the current doctoral dissertation is to identify the extent of impulse control disorder (ICD) in Parkinson's disease (PD) by investigating various critical domains and their functional correlates. ICD in PD patients is a complication typically associated with impulsivity. Yet, other functions have not been examined in detail which, together with the scarce functional neuroimaging studies in these patients, limits our knowledge on the multifactorial effects of ICD in PD. The implications of functional and structural alterations identified in PD patients with ICD (PD-ICD) and the impact they could have on motor and cognitive functions beyond impulsivity have been overlooked. This work does not aim at exploring all the affected domains, but centers around three (i.e., movement, response inhibition and semantic processing) in an attempt to investigate the scope of ICD on the functioning of the brain, and to have a better understanding of the effects it can have on patients' quality of life.

Chapter 1 provides the necessary theoretical background to understand PD, going over its neuropathology, the impact over motor and cognitive systems, the role of dopamine and dopaminergic medication. Chapter 2 presents ICDs in PD, including the neuropathology of the complication, and the effect on impulsivity and other less studied domains. Chapter 3 describes the main structural and functional Magnetic Resonance Imaging (MRI) measures employed in the present work to examine the neural correlates of ICD in PD. To conclude the introductory section, Chapter 4 describes the goal of the current dissertation and general hypotheses. Following that, the empirical section (Chapters 5 to 9) presents the main experimental work conducted in the current doctoral dissertation. Chapter 5 characterizes the common methods applied to the sample, followed by Chapter 6, where all common results are detailed. Chapter 7 illustrates Experiment 1, where movement and the motor network are assessed. Chapter 8 focuses on Experiment 2, examining response inhibition and the stopping network. Chapter 9 depicts Experiment 3, semantic processing. Chapters 7

to 9 include a brief rationale, detailed methods and results and the specific discussion corresponding to the experiment presented in the chapter. Finally, Chapter 10 provides a general discussion integrating the findings described and reviewed through the current work.

Introduction

Over the last centuries, medical, sanitary, and scientific advances have rapidly extended the life span of millions of people. First world countries are facing the most direct consequence of longer life spans: taking care of their seniors, while ensuring the best possible quality of life. Longer life spans come with an increase on the number of people suffering neurodegenerative diseases, which constitute one of the major impacts to quality of life, well-being, and survival of elderly populations. Those who suffer from neurodegenerative diseases, as well as their families, experience daily losses as the disease progresses, and new adjustments are necessary constantly. The degenerative aspect of these diseases makes adapting to and living with the disease especially challenging. PD is the second most common neurodegenerative disease, only preceded by Alzheimer's disease. Patients with PD belong to a heterogeneous community, but most face difficulties in maintaining their day-to-day life like they were used to before the disease onset. As PD progresses, patients must restrict the physical, mental, and social activities they can take part in, they require more time to complete any action, simple or complex, and they have to keep on adapting. PD patients endure many changes and challenges to their quality of life, but for some, it even gets tougher. 13.6 to 40% of PD patients treated with dopaminergic medication to alleviate motor symptoms experience ICD as a side-effect of the medication. Similar to other addictions, ICDs can affect the economic, professional, social and affective life of patients and further deteriorate their quality of life. Yet, little is known about how ICD affects motor and cognitive systems in addition to the changes brought by PD. Indeed, examining the influence of ICD in the motor and cognitive functions of PD patients constitutes the main goal of the present doctoral dissertation.

Chapter 1: Parkinson's Disease

In 1817 James Parkinson first described the case of six patients suffering from an unknown debilitating disease in his "Essay on the Shaking Palsy". Fast forward two hundred years, PD is the most rapidly growing neurological condition (Dorsey et al., 2018) with an incidence of 8 to 18 new patients per 100,000 person-year (A. Lee & Gilbert, 2016). PD is typically a late-onset disorder, with age being the greatest risk factor (Poewe et al., 2017). Most patients start experiencing symptoms in their late fifties and onwards. There is no cure yet, and treatment is focused on managing the clinical manifestations. Therefore, the progressive degeneration will lead to losses in the quality of life and increased costs to the community (Andlin-Sobocki et al., 2005). One of the most fatal characteristics of PD is the unstoppable neural degeneration that forces patients to continuously adjust to the impairments they experience. Initial impairments will aggravate, new impairments will emerge, and coping strategies for today's disability degree may not suffice six months or a year later.

Most patients receiving the PD diagnosis suffer from idiopathic PD, not linked to any know genetic risk factor or environmental cause (Sellbach et al., 2006). Known genetic factors only explain 5 to 10% of the risk of suffering PD in the general population (Del Rey et al., 2018), and family history of PD associates with early-onset disease (Marder et al., 2003), this is, below the age of 45. PD's etiology is complex and not fully understood yet, but it is believed that genetic, environmental and lifestyle factors interact (Rocca, 2005).

In the next sections I will introduce the neuropathology and pathophysiology associated with PD and the motor and non-motor clinical manifestations caused by it, along with an overview on current pharmacological treatments. I will elaborate in detail about the functioning and alterations of sequential movements, response inhibition and semantic processing in these patients, due to their relevance in the current dissertation.

1. Neuropathology of Parkinson's disease

The neural degeneration observed in PD is complex, affecting multiple regions and creating a broad spectrum of clinical symptoms. There are two main anatomopathological characteristics associated with degeneration in PD: the progressive loss of dopaminergic neurons and the intracellular inclusion of α-synuclein aggregations in neural populations (see Figure 1). As disease progresses, the widespread pathology and the consequent broad spectrum of motor and non-motor symptoms make PD a multisystemic degenerative disease. Its multisystemic and multicausal nature has broad implications on treatment.

1.1. Neurodegeneration of nigrostriatal dopaminergic system

The initial characteristic degeneration observed in PD consists in the selective and progressive loss of dopaminergic neurons in the substantia nigra *pars compacta* (SNpc) (see Figure 1*A*), particularly affecting striatal terminals (Cheng et al., 2010). This pathological hallmark is initially limited to the dopaminergic neurons of the ventrolateral and caudal SNpc, that project their axons to the striatum (Björklund & Dunnett, 2007; Dickson et al., 2009). Therefore, the main structure to suffer the consequences of dopaminergic depletion is the striatum. Specifically, the putamen is the most affected motor area. Thus, the impact of dopaminergic degeneration is responsible for early motor manifestations (Obeso et al., 2008). Nigrostriatal degeneration will continue at a rate of 10-12% terminal loss per year

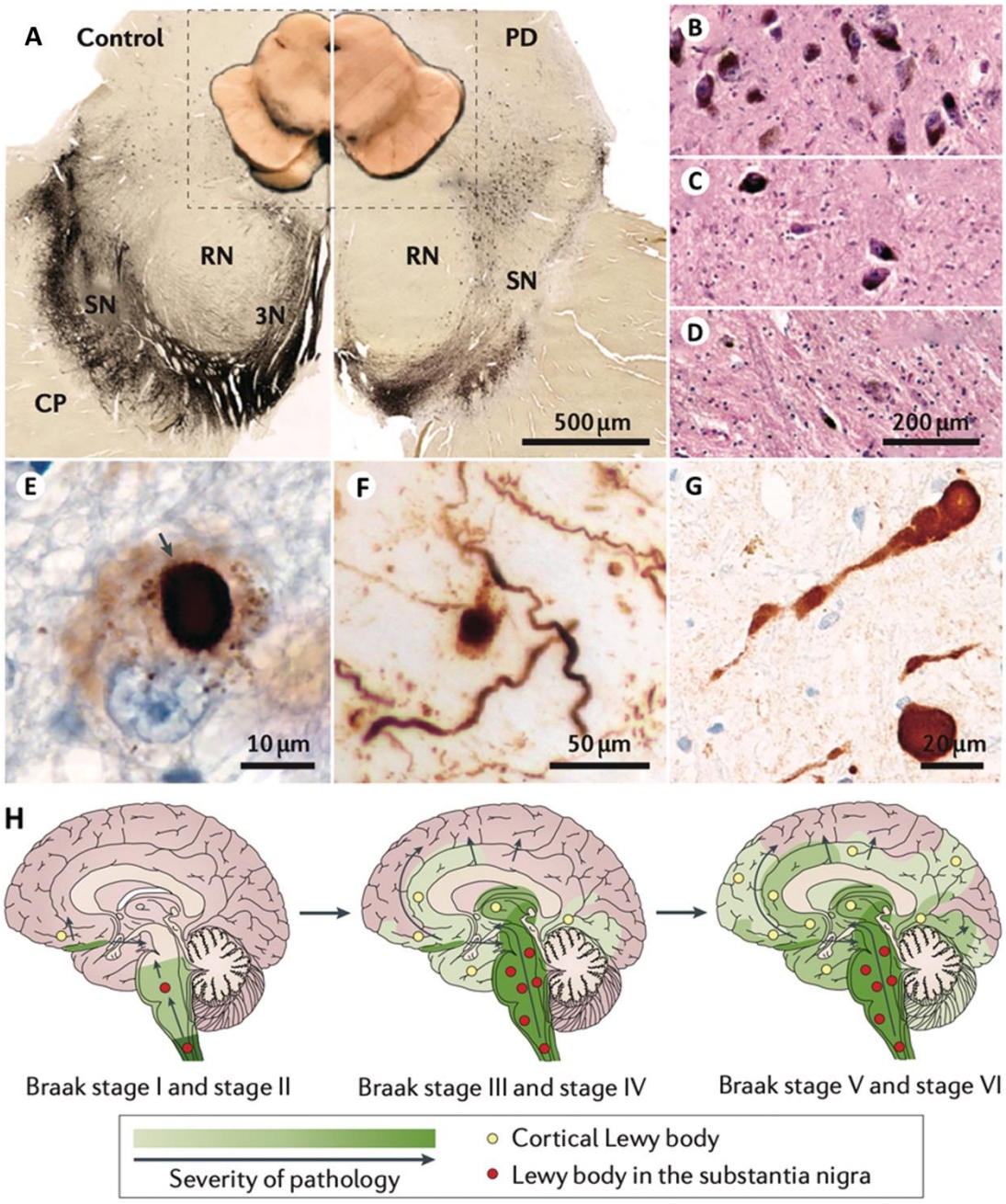

Figure 1. The main neuropathology features in PD. (A) Characteristic loss of dopaminergic neurons in the SN in PD patients (right panel) compared to healthy controls (left panel). Initial selective loss of ventrolateral sections of the SN is observable in the histological section. (B-D) Staining of dopaminergic neurons in ventrolateral sections of the SN in healthy (B), moderate PD (C), and severe PD (D). (E-G) α-synuclein staining showing round and intracytoplasmatic Lewy body (arrow in E), diffuse and granular α-synuclein deposits (E and F), deposits in neuronal cell processes and extracellular α-synuclein structures (F), and α-synuclein spheroids in axons (G). (H) The proposed progression α-synuclein aggregations divided by Braak stages. Adapted from Poewe and colleagues (2017).

(Marek et al., 2001; Morrish et al., 1996), extending along the SNpc (Damier et al., 1999) (see Figure 1*B-D*). With PD progression, the impact of dopaminergic denervation will extend beyond motor networks. However, motor regions, and the motor striatum in particular, will remain more severely affected (Kehagia et al., 2012).

1.2. Synuclenopathy

The importance of α-synuclein aggregations in PD characterization and diagnosis has been gaining relevance in the last years. As a matter of fact, the importance of α-synuclein in the features and progression of the disease has influenced the new definition of PD as a synucleopathy (Berg et al., 2014; Postuma et al., 2016). In brief, α-synuclein is a protein than when misfolded aggregates forming Lewy bodies and Lewy neurites (Goedert, 2001) (see Figure 1*E-G*). These aggregations locate intraneuronally, mostly in the axon of specific population of catecholaminergic neurons both in the central and peripheral nervous system (Braak et al., 2004; Surmeier & Sulzer, 2013). Susceptible populations of neurons possess long axons that are typically unmyelinated (Braak et al., 2004). Moreover, affected regions are interconnected, indicating that α-synuclein aggregates spread to other brain regions (Braak & Del Tredici, 2008).

The α-synuclein pathology has been proposed to follow a staging scheme (Braak & Del Tredici, 2008; Braak et al., 2004) (see Figure 1*H*). Stages 1 and 2, the presymptomatic stages situate the pathology in the dorsal motor nucleus of the vagal nerve and the olfactory bulb, from where it ascends towards the raphe nuclei and the locus coeruleus. As the pathology progresses, stages 3 and 4 represent an important timepoint. It is in stages 3 to 4 when α-synuclein aggregates affect the SNpc and where patients meet the criteria for PD diagnosis. The basal forebrain (including the nucleus of Meynert) and medial temporal lobe structures (particularly the entorhinal cortex, the hippocampal formation and the amygdala) also get affected. In the final stages, the pathology spreads to the neocortex, first affecting the prefrontal cortex and sensory association areas, but gradually propagating to the entire cortex.

2. Clinical manifestations and diagnosis

Since Dr. Parkinson's essay, PD has mainly been considered a motor disorder. Typical PD diagnosis is linked to the onset of motor signs. Yet, the diagnosis is often preceded by a prodromal phase characterized by the apparition of specific non-motor symptoms (Berg et al., 2015; Postuma et al., 2012). In keeping with prodromal manifestations, research indicates that neurodegeneration in the SNpc could antecede the appearance of motor signs by 12 to 14 years (Berg et al., 2015; Postuma & Berg, 2019) (see Figure 2). It is believed that when 50 to 60% of the dopaminergic neurons of the SNpc are lost, the striatum experiences a reduction of dopamine of about 80 to 85% and motor signs start manifesting (Wirdefeldt et al., 2011).

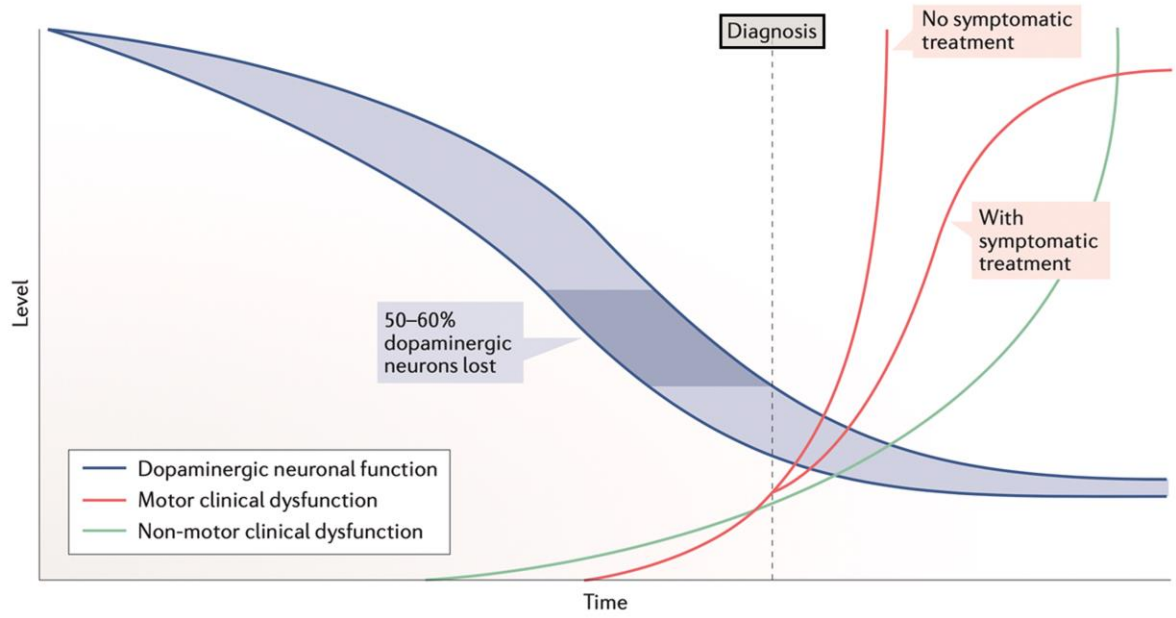

Figure 2. Development and progression of motor and non-motor symptoms in PD, and the decline in dopaminergic neuronal function. Adapted from Schapira et al. (2017).

Idiopathic PD diagnosis follows the UK Brain Bank Criteria (Hughes et al., 2001), and in the absence of a diagnostic biomarker, diagnosis is centered in clinical aspects, based on the motor signs described in the next section (Jankovic et al., 2000; Postuma et al., 2016), along with additional clinical supportive symptoms and the absence of clinical and neurological exclusion symptoms (Hughes et al., 2001). To meet the diagnostic criteria, patients need to present bradykinesia as well as at least rigidity or resting tremor.

2.1. Motor manifestations

Motor signs in PD usually present asymmetrically, initially affecting one limb unilaterally. The cardinal signs of PD are *bradykinesia*, *rigidity*, and *resting tremor*. *Bradykinesia* is universally present in PD diagnosis (Hughes et al., 1992), and it is described as a reduction of speed or amplitude of the movement (Postuma et al., 2016). It commonly presents as reduced arm swing during natural ambulation, impaired repetitive and sequential movement of the hands and hypomimia, or reduced facial expression (Reichmann, 2010). As disease progresses, bradykinesia worsens with some patients experiencing difficulty initiating movement and reduced other automatic and voluntary movements. *Rigidity* is described as permanent increased muscle tone accounting for the phenomenon of "cogwheel" when stretching the agonist or antagonist muscle during passive movement of the joints (Reichmann, 2010), and it can be one of the causes of pain in PD (Ha & Jankovic, 2012). *Resting tremor* typically initiates in one of the upper extremities, distally, affecting the thumb first when it appears in the upper limbs, and it has a frequency of 4 to 6 Hz (Anouti & Koller, 1995; Timmermann et al., 2003). Initially, tremor occurs intermittently at rest but, as disease progresses, postural or kinetic tremor may appear (Reichmann, 2010). Most prominent motor manifestations, such as bradykinesia and rigidity, are associated with nigro-striatal dopaminergic depletion. There are, however, numerous non-dopaminergic motor manifestations, such as treatment-resistant resting tremor, freezing of gait, and postural instability. Although still being researched, non-dopaminergic motor symptoms have been associated with the degeneration of the pedunculopontine nucleus, the centromedian nucleus of the thalamus and the presupplementary motor area (Lang, 2007; Lang & Obeso, 2004).

With disease progression, the neural dopaminergic degeneration along with the α-synuclein pathology spread to other brain areas, aggravating motor symptoms and becoming more disabling. Therefore, unilateral symptoms become bilateral, although the hemibody of symptom onset will remain more severely impaired. It is typically with the bilateral involvement of the disease that postural instability manifests (Bhidayasiri & Tarsy, 2012). On average, this occurs more than 5 years after PD onset (Marttila & Rinne, 2009). Postural instability is characterized as having to take correcting steps after being pulled by

the clinician to restore balance, or as the inability to restore balance (Fahn et al., 1987; Weiner et al., 1984). In addition, gait disturbances, specially freezing of gait, may emerge. Taken together with the worsening of bradykinesia, rigidity and postural instability will lead to possible falls, which become a serious threat to the patient's physical integrity (Koller et al., 1989). In the last stage of the disease, patients will become dependent and unable to stand or move about unaided (Hoehn & Yahr, 1967).

Now I will focus on a particular type of movement, sequential movements. I will briefly present what sequential movements are and how they are impaired in PD to give a background to Experiment 1, involving sequential finger tapping.

2.1.1. Sequential movement impairments

The ability to perform a sequential movement, this is, a complex motor plan composed of a fixed series of movements in succession, is part of some of the most automatic and controlled actions we execute on daily basis, such as walking, speaking or eating. In order to accurately perform a sequential movement, simple motor plans have to be interweaved in a fluid manner. Precisely, the complexity of sequential movements relies on this fluid combination of motor plans that need to be executed as one action.

PD patients experience difficulties controlling sequential and predictive movements (Benecke et al., 1987; Stern et al., 1983). Compared to healthy controls, PD patients seem slower executing a movement and switching from one motor plan to the next (Agostino et al., 1992). Agostino and colleagues (1992) showed that the motor execution slows progressively in PD patients with the last movements requiring more time to complete. This difficulty has been linked to switching problems from one motor plan to another (Benecke et al., 1987). In the case of sequential finger movements, PD patients seem to employ compensatory mechanisms, recruiting in a more extensive motor network (Catalan et al., 1999; Samuel et al., 1997). By doing so, they compensate for the hypoactive striatum and thalamus observed in PD patients OFF medication this is, without the effect of dopaminergic medication, as indicated by functional MRI (fMRI) studies (Mallol et al., 2007; Spraker et al., 2010; Yu et al., 2007). Dopaminergic medication and occupational therapy have shown to

improve motor functioning and co-ordination respectively (Maitra & Dasgupta, 2005; Michely et al., 2015).

2.2. Non-motor manifestations

PD is a complex, far-reaching disease, and although classified as a movement disorder it also curses with multiple non-motor symptoms along the disease. The most common non-motor symptoms are *autonomic dysfunction*, *sleep disorders*, *psychiatric symptoms*, and *cognitive impairment*. *Autonomic dysfunction* include gastrointestinal, urinary, cardiovascular, or respiratory dysfunctions. *Sleep disorders* comprise insomnia, REM behavior disorder or restless leg syndrome. *Psychiatric symptoms* have a significant impact in the quality of life and daily functioning of the patients, account for a poor quality of life in many patients (Tan, 2012). They include anxiety, depression, apathy, or psychosis. Apathy is the most common psychiatric disorder, with over 60% of patients suffering from it (Pedersen et al., 2009), often coexisting with depression or cognitive impairment (Gallagher & Schrag, 2012). *Cognitive impairment* in the form of early dysexecutive syndrome is common at the prodromal and early-PD stages rarely affecting the patients' independence (Kehagia et al., 2012; Schapira et al., 2017).

Non-motor symptoms can appear from the prodromal stage onwards (Jellinger, 2015; Schapira et al., 2017) (see Figure 2). Yet, as disease progresses, existing non-motor symptoms can aggravate and new ones can emerge (Jellinger, 2015). With non-motor symptoms becoming more pervasive, they drastically reduce the quality of life of PD patients, and can become more disabling than motor manifestations (Barone et al., 2009; Hely et al., 2005). In line with this, autonomic failure is considered one of the mortality causes in PD (Hely et al., 2005). Cognitive impairment can progress towards mild cognitive impairment (MCI) and ultimately dementia. Due to the interest on cognition in the current thesis, cognitive impairments in PD will be elaborated in deeper detail in the next subsection.

2.2.1. Cognitive impairments

Cognitive impairment is a pervasive non-motor symptom associated with age, disease duration and disease severity (Litvan et al., 2011), with chances of cognitive decline increasing in patients 65-years-old or older, irrespective of disease duration (Pedersen et al., 2017). Up to 80% of patients with long-term PD develop dementia, and lose their independence (Aarsland et al., 2003; Hely et al., 2008). This means that PD patients face more than twice the risk of dementia than the general population (Aarsland et al., 2003; Hely et al., 2008).

Cognitive impairment has been associated with alterations of different neurotransmitter systems, such as the catecholaminergic systems, including dopamine, and the cholinergic system, along with α-synuclein aggregations, Alzheimer's pathology, and vascular pathologies (Goldman & Sieg, 2020). In addition, the emergence of late-onset cognitive decline has been associated with the bilateral impairment of the limbic circuit linked to the synucleopathy (Braak et al., 2004), indicating that cognitive decline in PD has multifactorial causes. Specifically, cognitive deficits have been linked to the disfunction of the hippocampus, the amygdala, the basal forebrain and the frontal regions (Lang, 2007; Lang & Obeso, 2004).

In addition to the general neurodegeneration associated with PD described in section 1, PD patients who develop MCI or dementia present atrophy in certain regions (González-Redondo et al., 2014). Specifically, González-Redondo and colleagues found that patients with MCI presented atrophy in middle frontal and inferior frontal gyri, angular gyrus (AG), middle occipital gyrus, precentral and supplementary areas. In addition, patients with dementia presented atrophy in previously mentioned areas as well as in medial-superior frontal cortex, hippocampus, and the middle temporal gyri. More recently, Vasconcellos and colleagues (2018) found anatomo-clinical correlations between several cognitive functions (i.e. memory, attention, executive functions, language, and visuospatial functions) and the volume of hippocampus and corpus callosum, which was reduced in PD patients versus healthy control (HC) participants. Remarkably, PD patients in the Vasconcellos and colleagues's (2018) study were cognitively normal which suggests that, even at the sub-clinical stages of cognitive impairment, atrophy associated with PD pathology affects a wide

array of cognitive functions. Atrophy increases steadily, as cognitive impairments worsen. In fact, a recent review highlights frontal and temporal atrophy with the future development of dementia (Martín-Bastida et al., 2021).

Despite the association between cognition and structural integrity of certain areas, cognitive impairment in PD patients is heterogeneous on onset time, speed of progression and affected functions (Biundo et al., 2016; Mak et al., 2015). In fact, as introduced previously, cognitive impairment can take two forms in PD: the common early dysexecutive dysfunction associated with fronto-striatal dopaminergic alterations, and the late-onset cognitive impairment that can lead to dementia, and which seems to be multifactorial. In an attempt to shed light onto the heterogeneity of cognitive impairment in PD, Kehagia and colleagues (2012) proposed the dual syndrome hypothesis. They define two distinct cognitive impairments: i) a fronto-striatal impairment similar to the dysexecutive syndrome that arises from the reduction of dopamine in the fronto-striatal loop, and ii) a posterior and temporal deficit associated with an impaired cholinergic system. The fronto-striatal dysfunction can present impaired attention, working memory and executive functions. These functions are affected by dopaminergic medication and can fluctuate in a similar way to motor symptoms. Contrarily, posterior cholinergic dysfunction is characterized by impaired visuospatial function and semantic deficits, that show no influence of dopaminergic medication. Neuropathology studies have confirmed that there is Lewy body pathology in the brains of PD patients with dementia that account for the disrupted cholinergic system (Biundo et al., 2016; Kotzbauer et al., 2012). In the same line, different genetic factors have been associated with either fronto-striatal dysfunction or with dementia, supporting the different nature of the cognitive profiles addressed by the dual syndrome hypothesis (Huertas et al., 2017; Kehagia et al., 2012). Although the dual syndrome hypothesis attempts to explain the hetegeneous impairments, it only addresses two distinct cognitive profiles. In fact, most patients likely present a combination of fronto-striatal and posterior dysfunction (Goldman & Sieg, 2020).

Dopaminergic medication also impacts cognition, boosting certain domains and impairing others. To address the differential impact of dopaminergic medication as a function of the degree of dopaminergic depletion suffered by fronto-striatal regions Swainson and colleagues (2000) proposed the *dopaminergic overdose theory*. This theory

maintains that dopamine-dependent frontal regions do not need the dopaminergic boost of medication, since they are not depleted in early to mid-stages of PD. Therefore, the exogenous dopamine aimed to treat motor manifestations improves dopaminergic levels in motor striatum, while overdosing frontal regions (see Figure 3). While abilities like planning and working memory can show an improvement when the patient is ON medication, this is, under the effect of dopaminergic medication, abilities sensitive to impulsivity, such as reversal learning, can worsen (Cools et al., 2001, 2003; Gotham et al., 1988; Swainson et al., 2000), representing a dopaminergic overdose on the mesolimbic circuitry.

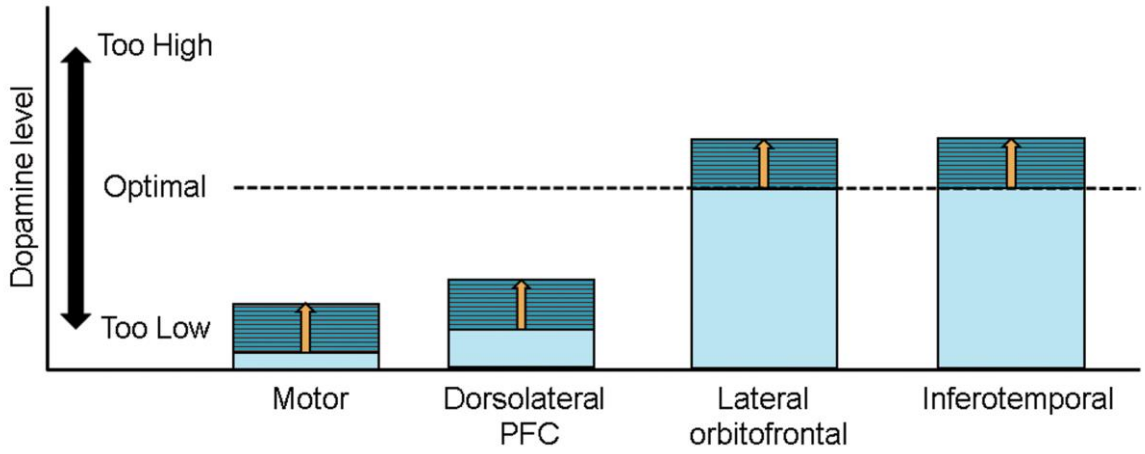

Figure 3. Differential dopaminergic levels within fronto-striatal networks. Darker shaded areas represent dopaminergic increase in response to medication. Adapted from Swainson et al. (2000).

Due to the multicausality of the cognitive impairment, and the progression of the PD pathology, medication has fallen short to maintain or restore cognitive function. Different approaches focusing on cognitive training or physical exercise have been implemented to slow down the degree of cognitive impairment. Evidence suggest that cognitive training can maintain or improve cognitive performance, although results do not show robust outcomes (Glizer & MacDonald, 2016; Orgeta et al., 2020). Similarly, different types of physical exercise have shown maintenance or improvement in cognition (Da Silva et al., 2018; D. K. Murray et al., 2014). However, studies on cognitive or physical training typically do not assess the long-term effect of training, and therefore it is unclear if PD patients should be exposed to cognitive and physical therapy continuously to maintain cognitive benefits. The lack of a clear treatment intensifies the need to understand and properly categorize cognitive impairment in PD.

In the following sections, I will give an overview of the five commonly affected cognitive domains in PD patients. Posteriorly, I will focus on the two cognitive functions investigated in this doctoral dissertation (i.e., inhibitory control and semantic processing). For both cognitive functions, I will first detail what each function entails and then I will conclude explaining how they are affected in PD patients.

2.2.1.1. Affected cognitive domains

Despite the heterogeneity of cognitive impairment in PD patients, five affected cognitive domains have been highlighted by the Movement Disorders Task Force (Emre et al., 2007; Litvan et al., 2011). The affected cognitive domains in PD are attention and working memory, executive functions, language, memory, and visuospatial functions. With the increasing recognition of cognitive impairment in PD, the Movement Disorders Task Force has established the diagnostic criteria for MCI and dementia. To fulfill the criteria for MCI, PD patients have to show impairment in one or several of these domains (Litvan et al., 2012). Studies show single-domain MCI is more common than multiple-domain MCI, with amnesic single-domain MCI being rare (Litvan et al., 2011). To fulfill the criteria for dementia, PD patients must be impaired in two or more of these domains, show impaired global cognition and no longer be independent (Dubois et al., 2007). Impaired performance in attention and working memory, executive functions, language, memory, or visuospatial functions can be expected in PD patients and should be assessed to monitor their cognitive state.

Despite the immense variability in cognitive state, and impaired domains, certain cognitive profiles are more common as PD patients progress to dementia. Studies have shown that PD patients with dementia tend to have a more dysexecutive and less mnemonic profile of impairment as well as a more posterior visuospatial impairment. With the progression of dementia, impaired cognition tends to extend to all domains (Emre et al., 2007). And in fact, poor outcome in semantic fluency and in the ability to copy a figure of two intersecting pentagons is the best predictors of progression to dementia (Williams-Gray et al., 2007), which supports the dual syndrome hypothesis (Kehagia et al., 2012). Understanding the cognitive domains affected in each patient and their association with dopaminergic or cholinergic mechanisms is particularly relevant in early-stage cognitive impairment before atrophy becomes more severe.

In the experiments comprising the current doctoral dissertation, we will be assessing two cognitive functions: inhibitory control and semantic processing. Inhibitory control is a component of executive functions, while semantic processing involves linguistic and memory functions. According to the dual syndrome hypothesis (Kehagia et al., 2012), inhibitory control is sensitive to dopaminergic dysfunction, whereas semantic processing is impaired by cholinergic dysfunction, and therefore not affected by dopaminergic medication. In the following sections, I will elaborate on inhibitory control and semantic processing in more detail.

2.2.1.2. Inhibitory control and response inhibition

The ability to appropriately stop an ongoing motor response or refrain from inhibiting that response enables us to adapt to the environment. Inhibitory control is the cognitive function responsible for those adaptive behaviors, encompassing all forms of behavioral inhibition, from the inhibition of a button-press to higher order cognitive inhibition. Response inhibition refers to the motor form of inhibitory control, and the network recruited while performing response inhibition will be referred to as the *stopping network*. Response inhibition includes measures of reactive inhibition, the ability to stop once instructed, or proactive inhibition, the ability to prepare for inhibition beforehand. Due to its more challenging nature involving preparatory mechanisms, proactive inhibition has been proposed as a more valid measure of response inhibition than reactive inhibition (Aron, 2011; Meyer et al., 2020).

Response inhibition is typically assessed through the Go/No-Go, the antisaccade task or the Stop Signal Task (SST) paradigms (Chikazoe, 2010). Go/No-Go and antisaccade tasks require participants to not perform a movement (i.e., button-press or eye movement respectively), and, since they do not require preparation, measure reactive inhibition. The SST paradigm, on the other hand, is more taxing, requiring participants to stop an already initiated action. In addition, the conditional variation of the SST paradigm includes trials in which participants know beforehand that they may have to inhibit the initiated action, and trials in which they know that they will not have to, therefore measuring proactive inhibition.

2.2.1.2.1. Inhibitory control in Parkinson's Disease

Due to the effect of PD's pathology on motor regions and on movement initiation, multiple studies have examined response inhibition on PD patients. Different aspects of inhibition have been studied, including reactive and proactive inhibition. PD patients show inhibitory deficits in both reactive and proactive inhibition (Gauggel et al., 2004; Mirabella et al., 2017; Obeso et al., 2014). Contrary to what the dual syndrome hypothesis suggests (Kehagia et al., 2012), the inhibitory impairment may not be exclusively related to dopaminergic loss, as medication does not have an effect over the results, with patients showing impaired performance while they are in both ON and OFF states (Obeso et al., 2011). However, the picture is less clear when the effect of the PD pathology is still moderate, contributing to the idea that response inhibition impairment may be associated with later-stage non-dopaminergic deterioration. Early-stage PD patients show heterogeneous impairment, with evidence for impaired (Di Caprio et al., 2020) as well as unimpaired (Vriend et al., 2015) reactive inhibition, and normal proactive inhibition (Di Caprio et al., 2020). The lateralization of the stopping network could also be altered by PD pathology, implicating bilateral structures to a greater extent (Mirabella et al., 2017). Therefore, despite research on the topic, it is still unclear whether the inhibitory deficit is linked to disease progression, and to dopaminergic or α-synuclein-related damage, or to prolonged medication intake. There are also open questions regarding the anatomical and functional substrates producing impaired response inhibition in PD patients.

2.2.1.3. Semantic processing

A key aspect of language, intrinsically related to the memory system, is semantic processing. Semantic processing refers to the act of extracting the knowledge about the world that we have previously learnt and stored in our semantic memory. We resort to our semantic knowledge at all times, from the moment we wake up and need to identify the buzzing alarm and turn it off, to the moment we go back to sleep after remembering that we need to get into our bed for that. Semantic processing is particularly involved in any linguistic act because the relationship between the phonetic or written representation of a word and its meaning are arbitrary, and when we hear each word or when we wish to articulate them, we need the sound and the meaning, the signifier and the signified, to come together. That

coming together is semantic processing. The relevance of semantic processing in our day-to-day is highlighted by patients with semantic impairments, who present linguistic but also non-verbal disabilities (Ralph et al., 2016). Contrary to inhibitory control, semantic processing can be an automatic process, and does not require attentional involvement (Deacon, 2000).

A common imaging task to examine semantic processing consists in the passive exposition to words (i.e., auditorily or visually). Participants must process the words to correctly complete the task, which could be to respond to a type of word, or to differentiate between types of words depending on their meaning, such as differentiating between abstract or concrete words. During the task, words can be presented visually or auditorily.

2.2.1.3.1. Semantic processing in Parkinson's Disease

PD patients can experience an array of difficulties in the linguistic domain, including impairment at the phonetic, lexico-semantic, syntactic, sentence, and prosody levels (Logemann et al., 1978; Paredes Duarte & Espinosa Rosso, 2020). Due to the linguistic impairment associated with PD, multiple studies have studied semantic processing in PD patients. Production studies on PD often assess lexico-semantic processing by means of fluency tasks that prompt patients with a semantic or phonological cue, and ask them to produce as many words as possible associated with that cue. A semantic cue would be a semantic category, such as animals. A phonological cue would be a letter, and patients would have to produce words starting with that letter. Participants are usually asked to produce nouns, but verbs can also be demanded.

When presented with a fluency task, PD patients struggle to produce as many words as their healthy counterparts, showing impaired verbal fluency (Bayles et al., 1993; Flowers et al., 1995). In the same line, PD patients have also been reported to present impaired performance in naming tasks in which participants had to name the object they were seeing, typically from a drawing (Matison et al., 1982), as well as during memory tasks in which semantic cues are given to facilitate recall (Tweedy et al., 1982). When trying to retrieve a name, PD patients show an object naming bias finding verb naming more difficult than object naming (Bertella et al., 2002; Cotelli et al., 2007; Péran et al., 2003), which could be explained on difficulty terms (Colman & Bastiaanse, 2011; Péran et al., 2003). It has been

claimed that most of the linguistic deficits observed in PD, including those at the semantic level, can be attributed to speech difficulties (Illes et al., 1988). However, PD patients' benefit from cues during naming tasks (Matison et al., 1982). PD patients also show differences during fluency tasks associated with task difficulty (Gurd & Ward, 1989), and between verbal and non-verbal fluency tasks (Auriacombe et al., 1993) that cannot be explained only taking into account speech difficulties. Therefore, there are indications suggesting a distinct lexico-semantic cognitive impairment. In fact, a meta-analysis (Henry & Crawford, 2004) focused on verbal fluency in PD observed that semantic fluency was strongly impaired in PD patients. Authors associated the verbal fluency deficit to specific problems with semantic memory, which is also affected by PD. In memory tasks, PD patients show difficulties during recall and recognition, and benefit less than HC participants from semantic cues (Tweedy et al., 1982). A damaged semantic system is in line with Portin and colleagues' (2000) study showing deteriorated semantic knowledge in PD patients with MCI that does not improve with external cues.

Regarding comprehension at the lexico-semantic level, priming studies indicate that PD patients experience difficulties selecting the correct meaning of a word from distractors, whether the target word is primed through isolated words (Copland, 2003) or in a sentence context (Copland et al., 2001). A later semantic priming study (Angwin et al., 2006) evaluated a group of seven PD patients ON and OFF levodopa medication. Angwin and colleagues (2006) found that PD patients ON medication responded similarly to controls, but a different pattern emerged when they were OFF medication. The authors concluded that automatic semantic processing in PD is influenced by dopamine through the optimization of the signal-to-noise ratio in the cortico-striato-cortical loops, allowing the integration of more relevant information. This study contradicts the dual syndrome hypothesis, that proposes that semantic impairments are related with a dysfunction of the cholinergic system, and therefore cannot be regulated with dopaminergic medication (Kehagia et al., 2012). Surprisingly, PD patients can also benefit from semantic priming to a greater extent than matched HC participants (McDonald et al., 1996; Spicer et al., 1994), an effect authors explain as perseverance difficulties whenever task switching is required and not directly related to semantic processing.

Production and comprehension studies similarly point towards semantic deficits that are present before the onset of dementia in PD (e.g., Angwin et al., 2006; Henry & Crawford, 2004; Portin et al., 2000). Semantic deficits have been attributed to the effect of the disease on the cortico-striato-cortical system, mediated by dopamine (Angwin et al., 2006; Copland, 2003), or to the cholinergic dysfunction brought about by the α-synuclein pathology (Kehagia et al., 2012). In the case of comprehension specifically, semantic deficits are also associated with additional task switching difficulties (McDonald et al., 1996; Spicer et al., 1994) and difficulties inhibiting competing alternatives or new contexts (L. L. Murray, 2008), that improve with subthalamic nucleus (STN) stimulation (Castner et al., 2007).

3. Physiopathology of the basal ganglia

The basal ganglia (BG) is a bilateral subcortical group of interconnected grey matter nuclei: globus pallidus, divided in *pars interna* and *pars externa*, striatum, divided in putamen and caudate, substantia nigra (SN), divided in SNpc and *pars reticulata* (SNpr), STN, and ventral tegmental area (VTA). In the next subsections, I will introduce the dopaminergic paths the BG is implicated in and the different BG circuits, with the aim of understanding the disruption suffered by PD patients.

3.1. Dopaminergic regulation of the basal ganglia

The main sources of dopamine in the brain are the SNpc and the VTA. Morphological and connectivity studies indicate that dorsal dopaminergic neurons of the SNpc and VTA project mainly to cortical, limbic, and ventral striatal areas, and to a lesser degree to the dorsal, or motor, striatum. Ventral dopaminergic neurons, on the other hand, mainly project to the striatum (M. Bentivoglio & Morelli, 2005; Björklund & Dunnett, 2007). There are three distinct dopaminergic pathways arising from the SNpc and VTA: *nigrostriatal*, *mesolimbic*, and *mesocortical* pathways (see Figure 4). These pathways are anatomically and functionally segregated. The *nigrostriatal* pathway originates in ventral regions of the SNpc and

innervates de dorsal striatum, especially the putamen. This pathway is the main source of dopaminergic innervation of the motor striatum through which it regulates the activation of the motor circuit of the BG (Gerfen & Surmeier, 2011; J. A. Obeso et al., 2002). Therefore, the nigrostriatal pathway is involved in motor control, and to a lesser extent in associative learning and reward (Haber, 2014; Wise, 2009). The *mesolimbic* pathway projects from dorsal areas of the SNpc and VTA towards limbic regions (i.e., ventral striatum (VS), amygdala, septum, and hippocampus), and mainly regulates reward. Lastly, the *mesocortical* pathway also arises from dopaminergic dorsal areas, and projects to prefrontal, cingulate and perirhinal regions (Aracil-Bolaños & Strafella, 2016). As such, it is involved in cognitive functions like attention control and working memory (Arias-Carrián et al., 2010; Björklund & Dunnett, 2007). Due to their overlap, the last aforementioned pathways are often grouped in the mesocorticolimbic system.

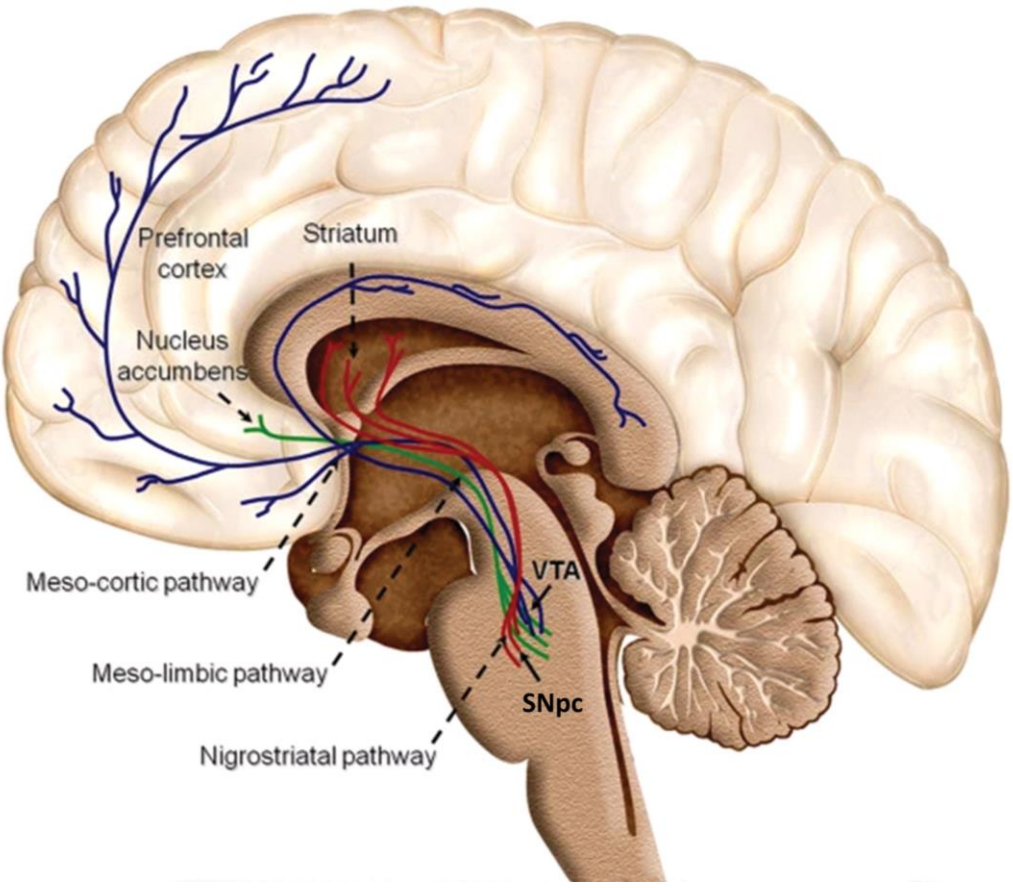

Figure 4. Depiction of the main dopaminergic pathways, and involved regions. Adapted from Arias-Carrián et al. (2010). VTA = ventral segmental area; SNpc = substantia nigra *pars compacta.*

Since the progressive dopaminergic loss in PD initiates in the ventral SNpc, the origin of the nigrostriatal pathway, this pathway is primarily affected, depleting the motor BG of dopamine, and causing the cardinal motor signs. However, the mesocorticolimbic system is affected, albeit to a lesser degree, altering reward-related functions (Kish et al., 1988; Ouchi et al., 1999).

3.2. Basal ganglia loops

Physiological and anatomical studies helped establish the organizational model of the BG (Albin et al., 1989; G. E. Alexander et al., 1986; Crossman, 1987), that allowed the identification of five segregated circuits that connected specific cortical areas with specific

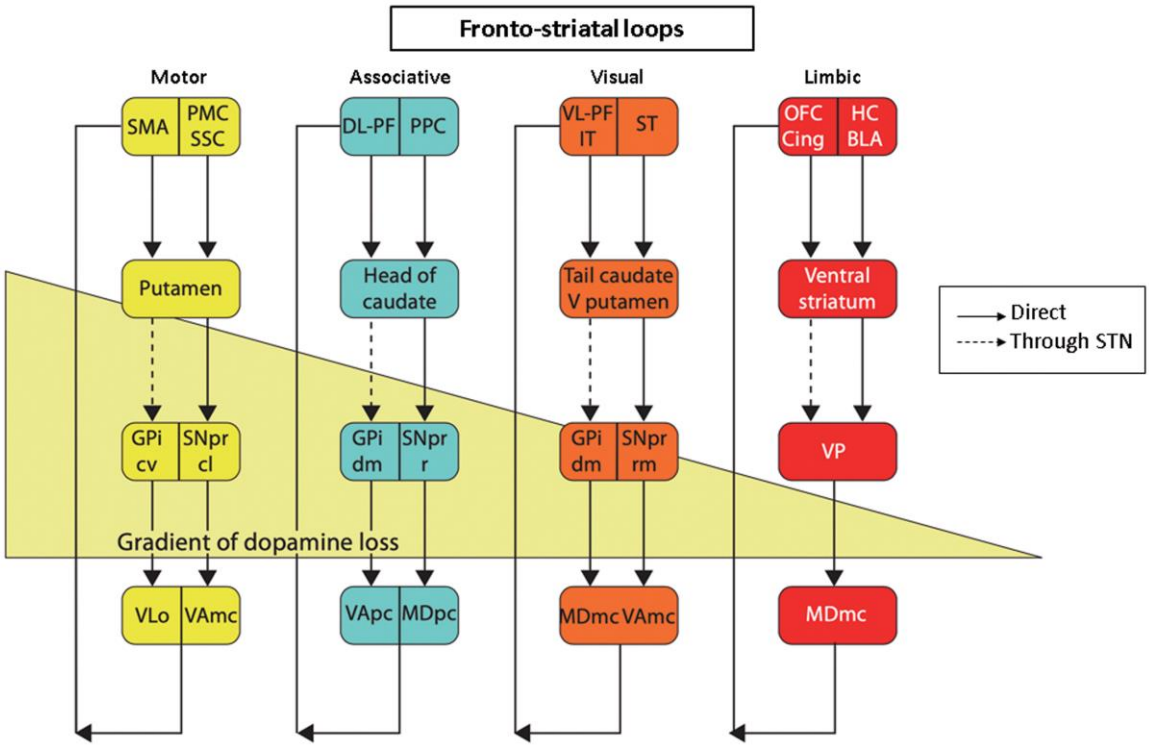

Figure 5. Schematic representation of four fronto-striatal loops. The gradient of dopamine depletion in PD affects dorsal striatum the greatest, and ventral striatum the least. Adapted from Kehagia et al. (2012). SMA = supplementary motor área; SCC = somatosensory cortex; PMC = premotor cortex; PPC = posterior parietal cortex; DL-PF = dorsolateral prefrontal cortex; VL-PF = ventrolateral prefrontal cortex; ST = superior temporal cortex; OFC = orbitofrontal cortex; Cing = cingulate cortex; HC = hippocampus; BLA = basolateral amygdala; V putamen = ventral putamen; GPi = globus pallidus pars interna; VP = ventral pallidum; SNpr = substantia nigra pars reticulata; VLo = ventrolateral thalamus; VA = ventral anterior thalamus; MD = mediodorsal thalamus; STN = subthalamic nucleus; cv = caudoventral; cl = caudolateral; dm = dorsomedial; r = rostral; rm = rostromedial; mc = magnocellular; pc = parvocellular.

BG regions. Interestingly, these circuits are differentially affected by dopaminergic denervation in PD (Kehagia et al., 2012) (see Figure 5). Each of these circuits forms a loop, through cortico-striatal, striato-pallidal and pallido-thalamic projections to finally return to the original cortical region. Importantly, these projections are segregated for each circuit. These circuits were the motor, oculomotor, dorsolateral prefrontal, orbitofrontal, and anterior cingulate circuits (G. E. Alexander et al., 1986; Middleton & Strick, 2000). According to their role, the anatomical circuits are grouped into motor (motor and oculomotor loops), associative (dorsolateral prefrontal and orbitofrontal loops) and limbic (anterior cingulate loop) (see Figure 6). Although movement disorders illustrate the main clinical expression of a faulty BG, the anatomo-functional organization of the BG challenged the traditional conception of the BG as a primary motor structure (J. A. Obeso, Rodríguez-Oroz, et al., 2008). I will describe these circuits below.

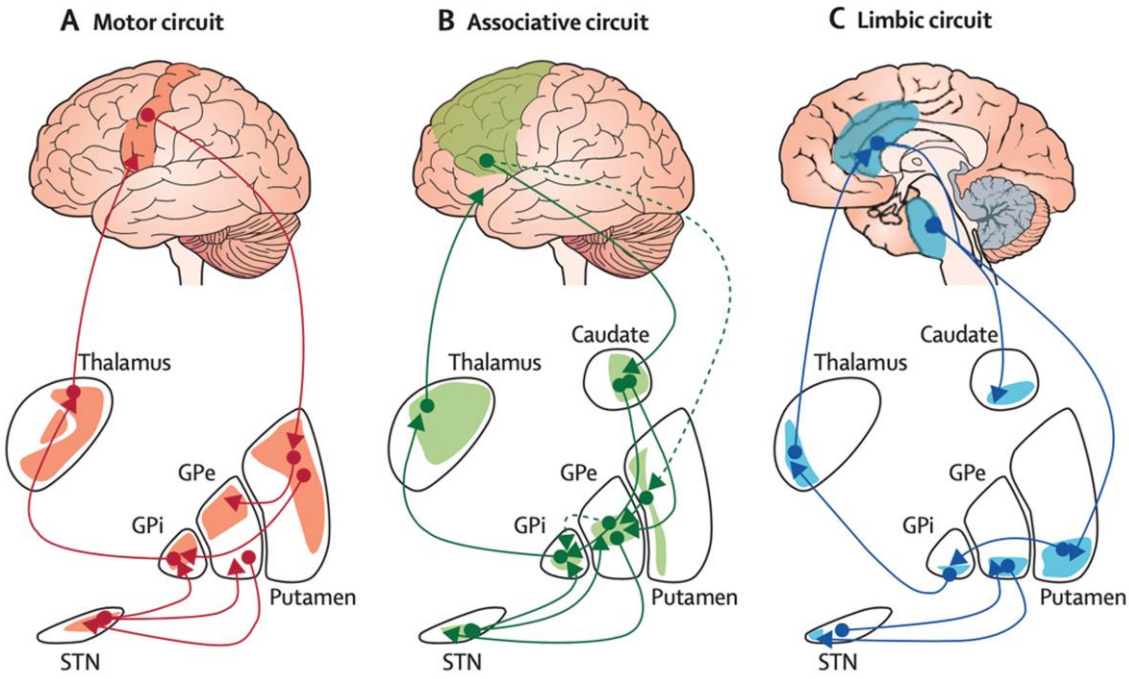

Figure 6. Representation of the functional organization of the basal ganglia, divided into motor (A), associative (B), and limbic (C) circuits. Adapted from Rodriguez-Oroz et al. (2009). GPe = globus pallidus *pars externa*; GPi = globus pallidus *pars interna*; STN = subthalamic nucleus.

3.2.1. Motor circuit

The motor circuit of the BG is involved in the control and planning of voluntary actions (Groenewegen, 2003; Wichmann & Delong, 1996) along with novel action learning and execution (Doyon et al., 2003). This circuit connects the motor cortex, particularly primary motor cortex (M1) and premotor cortex (PMC), with the dorsal striatum, and it is referred to as the cortico-striato-thalamocortical motor circuit (Groenewegen, 2003), which reflects the circuits' circular nature. Motor action is regulated through the *direct* pathway, which is excitatory, and the *indirect* and *hyperdirect* pathways, which have an inhibitory effect on movement (Leisman et al., 2013) (see Figure 7*A*). This circuit connect primary motor and premotor cortical regions with dorsolateral regions of the BG and the thalamus.

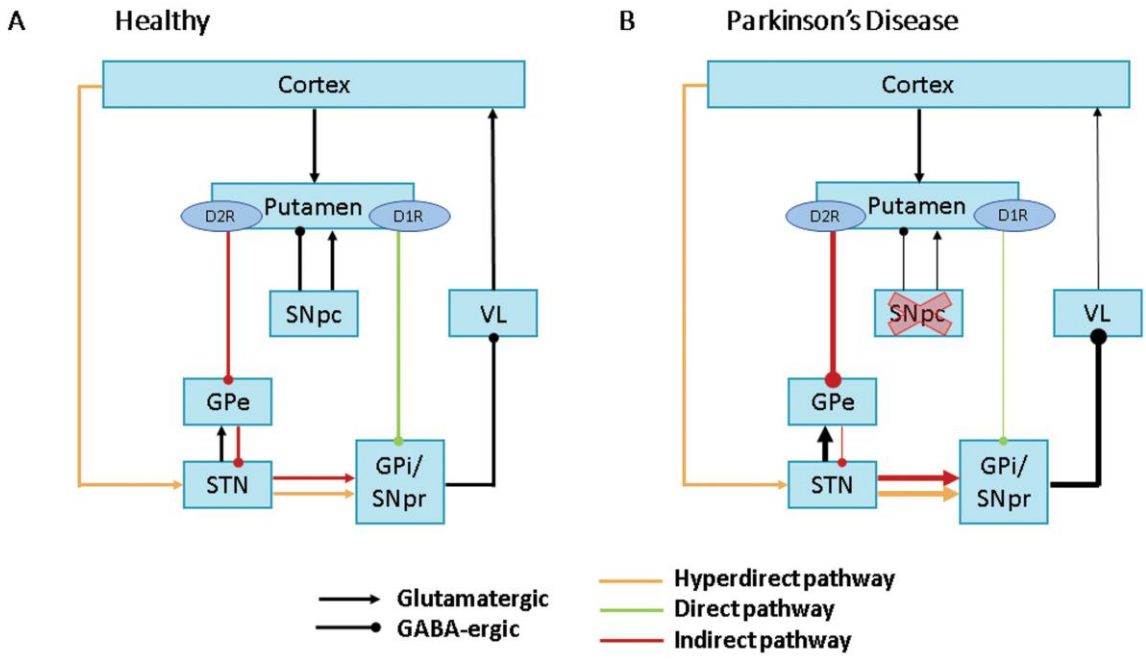

Figure 7. Physiopathological model of the basal ganglia motor circuit in healthy (A) and in Parkinson's disease (B). The cortico-BG-thalamic tracts have been divided into the hyper direct pathway (orange), direct pathway (green), and indirect pathway (red). Pointed arrows represented excitatory glutamatergic input, while oval arrows represent inhibitory GABA-ergic input. Note that in (B), the strength of the input is depicted through the width of the arrow. D2R = D2-like dopaminergic receptors; D1R = D1 dopaminergic receptors; SNpc = substantia nigra pars compacta; GPe = globus pallidus pars externa; STN = subthalamic nucleus; GPi = globus pallidus pars interna; SNpr = substantial nigra pars reticulata; VL = ventrolateral nuclei of the thalamus.

In the direct and indirect pathways, motor cortical regions project in a somatotopically organized manner to the striatum (J. A. Obeso, Rodríguez-Oroz, et al., 2008). Cortico-striatal and thalamo-striatal projections are accomplished through glutamatergic inputs. In addition, the striatum receives dopaminergic inputs mainly from the SNpc (Joel & Weiner, 2000; Lanciego et al., 2012). Therefore, the motor striatum integrates the glutamatergic and dopaminergic projections. The BG motor pathways regulate movement through the interactive effect of glutamatergic (i.e., excitatory) and GABAergic (i.e., inhibitory) inputs. The direct and indirect pathways bifurcate according to two types of GABAergic projection neurons in the striatum: D1 and D2 dopamine receptors (Burke et al., 2017; Gerfen et al., 1990). Regarding the *direct* pathway, striatal neurons mainly expressing D1 dopamine receptors project to the GPi and SNpr. Regarding the *indirect* pathway, striatal neurons mainly expressing D2 dopamine receptors project to the GPe, which in turn sends GABAergic projections to the STN. The *hyperdirect* pathway bypasses the striatum, since the motor cortex projects glutamatergic input straight to the STN. Finally, in both the indirect and hyperdirect pathways the STN projects glutamatergic input to the GPi and SNpr. The ventral lateral nuclei of the thalamus (VL) receive GABAergic projections from the GPi and SNpr, and the motor loop is closed with thalamic glutamatergic projections back to the motor cortex.

The interaction of the different pathways, and their inhibitory and excitatory effects over the thalamus regulate the balance of BG activity. In PD, this equilibrium of inhibition and excitation is disrupted.

3.2.1.1. Motor circuit disruption in Parkinson's Disease

In PD, dopaminergic denervation creates an imbalance in the excitation-inhibition equilibrium of the BG's motor circuit, with a shift towards cortical inhibition (see Figure 7*B*). The dopaminergic loss initially specific to the ventral section of the SNpc translates into a dopaminergic denervation of the nigrostriatal pathway in PD patients. The depletion of dopamine in the striatum affects the direct and indirect pathways of the motor circuit. On one side, it induces a hypoactive state in the *direct* pathway, which, reduces the inhibitory effect on the output nuclei (i.e., GPi and SNpr). On the other side, it potentiates the *indirect* pathway since the neurons that give rise to this pathway become hyperactive (Wichmann et

al., 2011). The alterations in the indirect pathway lead to an increase in glutamatergic input from the STN over the GPi and SNpr. Importantly, both pathways result in an increased inhibitory input from the GPi and SNpr to the thalamus, which in turn reduces the excitation on the motor cortex (Albin et al., 1989; J. A. Obeso et al., 2002). The excitation-inhibition imbalance in the BG motor circuit will signal the appearance of cardinal motor features of the disease (i.e., bradykinesia, rigidity, and resting tremor). In fact, subthalamic stimulation as alleviation of PD-related motor features (Schuepbach et al., 2013; Weaver et al., 2009), has been suggested to modulate the effect of the indirect and hyperdirect pathways (Neumann et al., 2018). This procedure seems to reduce the increased BG inhibition of the thalamus (Trošt et al., 2006; Vitek, 2002), and modulate the sensitivity of the cortico-thalamic and thalamo-cortical connections (Kahan et al., 2012).

As degeneration progresses, the imbalance in the motor circuit exacerbates. In addition, as described in section 1.2, as the synucleopathy progresses, the thalami and motor cortex will be affected. Consequently, previous motor manifestations aggravate and become bilateral, and later stage motor symptoms appear, such as postural imbalance and speech or swallowing difficulties.

3.2.2. Associative and limbic circuits

The *associative* circuit of the BG is involved in cognitive processes, such as executive functions and procedural learning (Jog et al., 1999). It connects the dorsolateral prefrontal cortex (dlPFC) and lateral orbitofrontal cortex (OFC) with the caudate nucleus. In PD patients, executive and working memory deficits have been linked to BG and prefrontal cortex (PFC) dysfunctions (Rodriguez-Oroz et al., 2009), and thus could reflect alterations in the associative circuit linked to the dopaminergic loss in the dorsomedial SNpc and VTA.

The *limbic* circuit of the BG is involved in emotional processing and reward-related processes (Robbins & Everitt, 1996; Schultz, 1997; Wise, 1996), and plays a relevant role in addiction (Koob, 1999; Nestler et al., 1993). It connects the VS with the ventromedial prefrontal cortex (vmPFC) the medial OFC, the anterior cingulate cortex, amygdala and hippocampus (Groenewegen & Uylings, 2010). In PD patients, the limbic circuit plays a crucial role in the development of ICD, and therefore, it will be elaborated in Chapter 2, section 1.

4. Additional motor physiopathology in Parkinson's Disease

Although the BG's motor circuit is necessary for correct and smooth movement, other brain regions and networks are involved as well. In brief, the regions in our brain responsible for articulating our body movements are distributed throughout the cortex, subcortex, and cerebellum. In the cortex, we find the M1, the supplementary motor area (SMA) and the presupplementary motor area (preSMA). Subcortically, we can find the putamen, another nuclei of the BG, and the motor nuclei of the thalamus, and in the cerebellum, we find the dentate nucleus (DN). These areas are functionally and anatomically connected forming motor circuits. Every movement we make is the result of a final impulse sent by the motor cortex to our muscles via the corticospinal tract.

In this section, I will introduce key components of the motor system, and examine the effect of PD over them. I will first focus on individual regions, their functioning, and how they connect to each other. Then, I will describe the dentato-thalamo-cortical tract (DTCT). The aim of this section is to better understand what the effect of the PD pathology in these structures means for the motor manifestations in this disease.

4.1. Regional physiopathology

4.1.1. Motor striatum

The motor striatum, or putamen, as introduced previously, is part of the BG. Its dorsal areas focus on motor functions (Jog et al., 1999). The putamen is relevant because the BG's motor circuit depends on it, and because it receives dopamine and cortical inputs. In addition, it is primarily focused on motor control, with its more anterior section associated with learning, and posterior putamen recruited during automatic movement execution (Balleine &

O'Doherty, 2010; de Wit et al., 2012; Lehéricy et al., 2006). The putamen is also involved in the execution of self-initiated actions (Cunnington et al., 2002; Monchi et al., 2006).

The putamen's loss of dopamine is central to the development of PD motor manifestations. In fact, an indirect measure of dopamine depletion, reduction of [^{123}I]FP-CIT binding to the dopamine transporter in the posterior putamen, correlates inversely with bradykinesia and rigidity (Seibyl et al., 1995). Innervated by the ventrolateral SNpc, it is affected early on by dopaminergic loss. Therefore, the putamen is relevant due to its role in motor control in a motor disease, and because it is directly related to PD's cardinal signs.

4.1.2. Motor thalamus

Until recently, the thalamus has been considered a simple relay. In recent years, the interest on this structure has been growing due to the multidimensionality of information that it hosts, sensory and cognitive, along with thalamus' active role on conveying that information to the cortex (Saalmann & Kastner, 2015). The motor thalamus (Mthal) comprises the thalamic nuclei that connect to motor regions such as the motor, and supplementary motor cortex, PMC, cerebellum, and BG (Hamani et al., 2006). The Mthal corresponds to the ventral thalamus, and it is comprised of the following regions: ventral anterior (VA), and VL further divided into anterior (VLa) and posterior (VLp). Similarly to BG and motor cortex, it is the Mthal contralateral to the body part being moved which will relay the motor information.

PD pathology affects the thalamus as well. The proposed mechanism has been selective non-dopaminergic degeneration associated with α-synuclein depositions (Henderson et al., 2000), along with dopamine depletion affecting the thalamus indirectly by causing a faulty communication with the BG (Blesa et al., 2016). Furthermore, it has been indicated that PD patients show systematic changes in the shape of their thalami compared to HC participants (McKeown et al., 2008). Although animal models indicate that the Mthal is not directly affected by the dopaminergic degeneration associated with PD (Monje et al., 2020; Pifl et al., 2013), it has been shown that PD patients suffering from tremors show increased white matter concentrations in the ventral intermediate nucleus (VIm) (Kassubek et al., 2002). In fact, tremor in PD can be treated surgically by lesioning or stimulating the VIm (Gross et al., 2004). Interventions in the VIm will exclusively improve resting tremor

(Lozano, 2000). Importantly, the VLp encompasses the VIm (Macchi & Jones, 1997; Nowacki et al., 2019).

4.1.3. Motor cortex

Cortical areas responsible for contralateral movement are located anterior to the central sulcus. M1, or Brodmann area 4, sits adjacent to the central sulcus. M1 holds large corticospinal neurons that interact with contralateral spinal motor-neurons to transmit the movement signal to the muscle (Chouinard & Paus, 2006). M1 is particularly relevant for fine movement. After a lesion in M1, gross hand movement, such as opening and closing may recover but the fine movement of individual fingers will not (Gandevia et al., 2012). The PMC, Broadmann area 6, is located anterior to M1, on the lateral surface of the cortex. Although it also contains corticospinal neurons, its greater contribution to motion is to combine sensory information processed in higher order sensory regions to modulate movement through PMC's connections with M1 and the spinal cord (Dum & Strick, 1991). Transcranial stimulation studies have shown that PMC employs visual information to regulate grasp, selects motor responses based on visual or auditory learnt rules, and controls arm movements (Chouinard & Paus, 2010). The supplementary motor cortex is located anterior to M1 and dorsal to PMC, and it extends medially. It is comprised of the SMA and the more anterior preSMA. The SMA evokes movements more easily than the preSMA, since it is part of the corticospinal tract (He et al., 1995). The SMA is active during motor tasks, simple or complex, but its primary role is organizing temporal order of movements (Tanji, 1994). This is necessary to perform any sequential action. The preSMA, on the other hand, may not be directly involved in producing movement, but rather inhibits current movements (Aron et al., 2007), and changes future movements (Matsuzaka & Tanji, 1996).

Within the progression of PD, cortical regions are the last to be affected by the α-synuclein aggregations (Braak et al., 2004). However, mild and moderate PD patients exhibit altered presynaptic inhibition in the motor cortex (Chu et al., 2009) and exaggerated coupling between phase and amplitude, a mechanism for large-scale interactions, specifically in the M1 (De Hemptinne et al., 2013). Despite changes in the motor cortex

reflecting degeneration associated with the synucleopathy, dopamine seems to modulate M1 excitability in PD patients (Ueki et al., 2006).

4.1.4. Dentate nucleus

The dentate nucleus (DN) of the cerebellum is located laterally above the roof of the fourth ventricle (Rhoton, 2000). Unlike previous regions, the DN's activation is related to the movement of the ipsilateral hemibody, this is, when moving the right hand, cerebellar activation is mostly restricted to the right DN and *vice-versa*. It is the largest deep cerebellar nucleus (Akakin et al., 2014) and it is thoroughly connected with the rest of the cerebellum and with the thalamus. In fact, the DN participates in the cerebellar feedback loops, and receives most of the cerebellar cortical efferents. Most of these fibers leave the cerebellar cortex synapsing in the DN before reaching extracerebellar structures (Guell et al., 2020). Similarly to the BG, the DN has been consistently associated with motor as well as non-motor functions, such as visuospatial abilities, language, and executive functions (Dum & Strick, 2003; Küper et al., 2011; Küper et al., 2012). Activation associated with motor tasks are specifically found in the ipsilateral dorso-rostral DN, a region in which limb specific activation is arranged in the rostral-caudal direction. Finger activations, for example, are located caudally to the ipsilateral dorso-rostral DN (Küper et al., 2012). Animal studies indicate that lesioning the DN increases response times (RT) and reduces accuracy (Beaubaton & Trouche, 1982; Tsujimoto et al., 1993).

PD pathology mostly spares cerebellar structures as they are formed of myelinated neural populations that are not sensitive to the synucleinopathy (Braak et al., 2004). Yet, PD patients' DN functions differentially: the ipsilateral DN is hyperactivated probably to compensate for BG malfunction (Yu et al., 2007) and it shows abnormal functional connectivity with the default mode network (Liu et al., 2013). In the case of PD patients with tremor, DN shows an increased functional connectivity (FC) with other regions of the cerebellum. In addition, decreased FC between the DN and the PFC correlates with tremor severity, underlying the role of the DN in the pathogenesis of tremor (Ma et al., 2015).

4.2. Motor circuits

The planning, adjustment, and order to execute motor actions requires of all motor areas discussed above and depends on a smooth communication between them, often requiring multiple feedback loops. During PD not only individual regions are affected, but whole networks are altered as a result. As the normal functioning and PD-related alterations of the BG's motor circuit has already been introduced, I will focus on presenting the DTCT. For clarity, the tracts have been presented separately but, in reality, the motor system requires of the integration of all of the tracts, with the Mthal as a hub.

4.2.1. Dentato-thalamo-cortical tract

The DTCT connects the DN with contralateral motor areas. It is sometimes considered as two different tracts: the dentato-thalamic tract relaying information into the Mthal, and the thalamo-cortical tract, reaching motor cortical areas. The DTCT is the greatest efferent tract originating in the deep cerebellar nuclei that passes through the Mthal. Therefore, the BG is not the only source of motor information and command to the Mthal. Unlike the BG output that modulates motor control, the information relied from the DN is mostly involved in movement coordination and timing, although it is involved in higher order cognitive functions as well (Middleton & Strick, 1998). The DTCT mostly originates in the DN of the ipsilateral cerebellum to the planned movement. From the DN, the tract ascends through the superior cerebellar peduncle forming the wall of the fourth ventricle (Rhoton, 2000). It then decussates to the contralateral red nucleus from where it ascends to the thalamus, specifically to the VLp (Hamani et al., 2006). Traditionally, the tract has been thought to decussate completely to exclusively arrive at the contralateral thalamus. Recent evidence shows a minor portion of the tract reaches the ipsilateral thalamus as well (Meola et al., 2016; Petersen et al., 2018).

Once the Mthal has received the input from BG and cerebellum, the motor plan will reach the cortical areas (Kwon et al., 2011), from where the signal will be sent to the spinal cord to execute the motor plan. Projections from the thalamus to the cortex reach frontal, sensoriomotor and motor regions (Hagmann et al., 2003). This is not a one-way

communication path in which the thalamus relays information, but rather, a complex feedback loop in which the cortex and the thalamus both send and received input from each other (Briggs & Usrey, 2008) aiding sensory processing and movement execution. Animal lesion studies show us that lesioning the Mthal or the thalamo-cortical efferents that reach motor and premotor areas will disrupt limb movement (Sauerbrei et al., 2020). It has been proposed that Mthal would aid in the execution of the motor plan by exciting and inhibiting M1 and PMC areas (Nashef et al., 2021) through thalamocortical neurons.

4.2.1.1. Dentato-thalamo-cortical disruption in Parkinson's Disease

In PD, increased activation of the DTCT has been linked to the disruption of the motor circuit of the BG, via the thalamus (Helmich et al., 2013). Yet, tremor in PD has been associated with alterations of this tract, particularly involving the VLp, and therefore not derived from the BG's inputs the VL receives (Helmich et al., 2013; Ni et al., 2010). In fact, stimulating the M1 and cerebellum may alleviate tremor in PD patients (Ni et al., 2010). In addition, it has been proposed than when lesioning or stimulating the VIm the improvement in tremor can be linked to the suppression of abnormal oscillations transmitted from the DN (K. H. S. Chen & Chen, 2019).

5. Pharmacological treatment

As most motor and some non-motor manifestations are associated with dopaminergic denervation of the SNpc and its impact on fronto-striatal loops, dopamine replacement therapy is one of the main pharmacological approaches to PD treatment. The role of dopamine replacement therapy is precisely to try to restore the dopaminergic depletion via the intake of *dopamine agonists* or *levodopa*. *Dopamine agonists* act on post-synaptic dopamine receptors and mimic the effect of dopamine. On the other hand, *levodopa*, the precursor of dopamine, crosses the blood-brain barrier that dopamine cannot cross, and synthesizes in dopamine that is then stored in axon terminals until it is released into the synaptic cleft (Koller & Rueda, 1998) (see Figure 8). To date, levodopa therapy considered

the gold standard antiparkinsonian drug. The systematic administration of levodopa remains the most efficient pharmacological treatment (Lang & Lozano, 1998), with almost all PD patients benefiting from levodopa treatment eventually (Gray et al., 2014; LeWitt & Fahn, 2016).

Dopaminergic medication, therefore, effectively alleviates motor symptoms, being tremor often not as responsive as the other cardinal manifestations (Hallett, 2012; Mure et al., 2011). Motor improvement upon treatment is associated with the restoration of the equilibrium to the BG's motor circuit. Regarding finger tapping specifically, dopaminergic medication improves speed and amplitude of movement (Michely et al., 2015). However, it does not aid with additional manifestations unrelated to dopaminergic denervation, such as cognitive constrains (Ruitenberg et al., 2015). This means that no therapy exclusively targeting the nigro-striatal dopamine deficiency will manage the myriad of clinical manifestations experienced by PD patients. Non-dopaminergic motor symptoms such as postural instability occurring late in the disease, along with many non-motor symptoms will not benefit from increased levels of dopamine since the degeneration caused by α-synuclein aggregations in non-dopaminergic regions also contributes to their development (Lang & Obeso, 2004; Poewe et

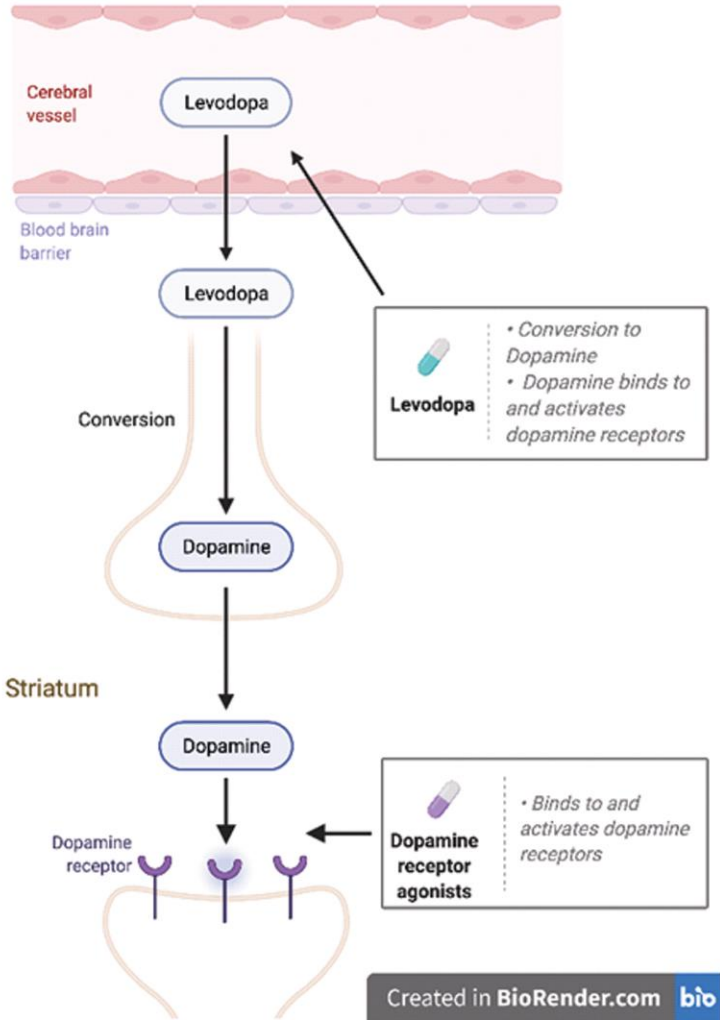

Figure 8. Mechanisms of action of Levodopa and Dopaminergic agonists over the receptors of the post-synaptic cell.

al., 2017). In fact, most levodopa-resistant symptoms can partly or exclusively be attributed to the extension of α-synuclein pathology beyond the SNpc or to the degeneration of other neurotransmission systems such as the cholinergic system. Medication, however, comes with possible side-effects that will be discussed in the next subsection.

5.1. Complications associated with chronic medication intake

Although dopaminergic medication has entailed a great advancement in the treatment of PD, as disease progresses and treatment becomes chronic not only does dopaminergic medication fail to compensate for the increasing dopaminergic loss, but complications associated with PD progression and chronic treatment emerge. Despite levodopa being the gold standard in PD treatment, it needs of the presynaptic neuron to convert into dopamine and release that dopamine. Therefore, as disease progresses and more dopaminergic neurons are lost, the sustained effect of levodopa is affected causing motor complications.

The most common motor complications are *fluctuations*, and the appearance of levodopa-induced *dyskinesias*, especially remarkable in the case of oral levodopa treatment. Up to 80% of patients on levodopa will experience motor fluctuations and dyskenisias after 10 years of treatment (Fabbrini et al., 2007). Contrary to the early stage of PD in which the intake of levodopa provides a stable motor benefit, in later stages patients experience motor *fluctuations*. This is, the benefit of each tablet vanishes after a few hours, and the patient requires to take another tablet to feel the motor benefit. Fluctuations can be simple or complex. Simple fluctuation tend to appear first in the progression of PD. Simple fluctuations are predictable and they manifest in the form of wearing-off effect of the medication. This is, patients experience simple fluctuations as a worsening in motor abilities before the next dose is due. Complex fluctuations tend to appear later on the disease, and they follow an unpredictable pattern (Nyholm, 2007). In addition to motor fluctuations, PD patients are also likely to experience *dyskinesias* (Nyholm, 2007). This is, involuntary, irregular, and unpredictable movements that have no purpose (J. A. Obeso et al., 2000). Dyskinesias are modulated by denervation of the BG in combination with intermittent dopaminergic release (J. A. Obeso, Marin, et al., 2008).

These motor complications reflect the narrowing of the treatment window as the disease progresses, requiring higher and more frequent doses. Several factors lead to the narrowing of the treatment window: i) levodopa is eliminated from the bloodstream quickly (Olanow et al., 2006), ii) degeneration linked to PD progression impairs the optimal exploitation of levodopa (Melamed et al., 1980), and iii) as PD progresses, previous compensatory mechanisms such as dopamine turnover cannot cope with the shortage in dopamine (M. J. Zigmond et al., 1990). The development of dopamine agonists have opened new treatment options since they take longer than levodopa to be eliminated from the bloodstream, extending their effect on time. Combining dopamine agonists and levodopa after the initial years of treatment with levodopa can slow down the narrowing of the treatment window (Jenner, 2015; Münchau & Bhatia, 2000), thus reducing motor fluctuations and particularly dyskinesias in PD patients (Rascol et al., 2012).

A final non-motor complication associated with chronic medication intake, especially of dopaminergic agonists, is the appearance of ICD. Due to the centrality of ICD to this doctoral dissertation, the concept will be further described in Chapter 2.

Chapter 2: Impulse Control Disorders in Parkinson's Disease

ICDs have been clinically defined as the difficulty to withhold a tentation or impulse to compulsively perform a detrimental act to oneself or others (American Psychiatric Association, 2013). This is, ICDs prompt compulsive behaviors whose excessive repetition interferes in vital areas of life functioning (Schreiber et al., 2011). ICDs have been considered as behavioral addictions due to their commonalities with drug addiction (Dagher & Robbins, 2009; Holden, 2001). Both types of addictions share risk factors, clinical and cognitive changes, neurobiological correlates and treatment options (Jiménez-Urbieta et al., 2015; Weintraub et al., 2015).

Dopaminergic medication places PD patients at a higher risk of developing ICD than the general population (Callesen et al., 2013; Voon et al., 2006; Weintraub et al., 2006). Specifically, longitudinal studies centered in PD patients on dopaminergic medication have found a cumulative incidence of 39 - 46% over the course of four to five years (Bastiaens et al., 2013; Corvol et al., 2018). PD patients with ICD compulsively engage in pathological behaviors, experience pleasure when engaged in compulsive behaviors, and show reduced control over these impulsive behaviors (Ceravolo et al., 2009). PD patients who develop ICD

tend to present one or more of the following pathological behaviors: *pathological gambling*, *compulsive shopping*, *pathological hypersexuality* and *binge eating* (Voon et al., 2006). *Pathological gambling* is defined as persistent gambling behavior that is problematic, manifests with increased irritability when non engaged in gambling, involves a constant preoccupation with gambling, and induces lying in patients to cover the extent of the fixation with gambling (Goudriaan et al., 2014). *Compulsive shopping* is defined as excessive buying that cannot be resisted, and that can create financial and psychological difficulties (Dittmar, 2005). *Pathological hypersexuality* is defined as a constant preoccupation with sex accompanied by excessive sexual needs that lead to excessive use of pornography and self-stimulation, as well as seeking sexual services and engaging in exhibitionism (Lim et al., 2008). Finally, *binge eating* is defined as an uncontrollable intake of large quantities of food, leading to weight gain and related health problems (Nirenberg & Waters, 2006).

Additionally, PD patients can experience the following ICD-related disorders: i) punding, or repetitive and purposeless behaviors, ii) hobbyism, or a compulsive preoccupation with specific activities, iii) walk-abouts, or excessive and purposeless wandering, iv) hoarding, and v) dopamine dysregulation syndrome, or inappropriately increasing the dopaminergic medication, similar to a drug-addiction (Weintraub et al., 2015). The severity of the ICD varies, but these behaviors can have disastrous consequences in the financial, work, family, and social realms (Bharmal et al., 2010; Voon et al., 2011). Although it is more common for patients to experience a single pathological behavior, they can also experience multiple ICDs (Garcia-Ruiz et al., 2014; Voon et al., 2011). Similar to other addictive disorders, patients hide the problems from family, friends, and often the clinician as well, in order to maintain their pathological behaviors, which leads to aggravated consequences and treatment difficulties.

In the next sections, I will introduce the neuropathology associated with ICD in PD, and its link to the emergence and treatment of the side-effect. I will then summarize the literature on impulsivity impairments in PD-ICD patients, and briefly present what is known of how ICD in PD affects other domains. I will particularly discuss findings related to motor impulsivity, motor functioning and semantic functioning, due to their relevance in the current doctoral dissertation.

1. Neural Alterations of Impulse Control Disorders in Parkinson's Disease

The development of ICD has been linked to dopaminergic alterations in the mesocorticolimbic system, particularly affecting the limbic circuit of the BG described in Chapter 1, section 3.2.2. In addition, as a behavioral addiction, ICD in PD is characterized by impaired decision making, learning, and motivation (Berke & Hyman, 2000), which are cognitive functions associated with the fronto-striatal associative circuit of the BG (Dagher & Robbins, 2009; Kehagia et al., 2012). These dopaminergic alterations can be traced to the VS and manifest as a hyperdopaminergic state. VS alterations are at the root of FC abnormalities observed in these patients (e.g., Carriere et al., 2015; Paz-Alonso et al., 2020; Petersen et al., 2018; Politis et al., 2013; Rao et al., 2010; Voon et al., 2011). Interestingly, the VS is linked to drug addictions (Robbins & Everitt, 1999), and has shown hyperdopaminergic responses to reward in addiction (Evans et al., 2006).

It is believed that PD pathology facilitates the development of ICD by altering the normal functioning of the mesocorticolimbic system due to the increasingly available dopamine. This hyperdopaminergic state on top of the dopaminergic denervation associated with PD allows rewarding behaviors or substance use to become habitual and pathological (Dagher & Robbins, 2009). Alterations in the mesocorticolimbic system manifest in this population as a reduced binding to dopamine transporters (DAT) in the presynaptic neuron, which can be interpreted as increased fiber degeneration, loss of presynaptic terminals, or functional changes of the DAT (Majuri & Joutsa, 2019). These alterations typically manifests as reduced DAT binding in the VS (Cilia et al., 2010; Navalpotro-Gomez et al., 2019), which correlates with ICD severity (Navalpotro-Gomez et al., 2019). These dopaminergic alterations are associated with increased dopamine release in the VS during rewarding tasks (O'Sullivan et al., 2011; Steeves et al., 2009; Wu et al., 2015), or during rest (Rao et al., 2010).

1.1. Alterations of the reward system

The mesocorticolimbic system, particularly the limbic circuit of the BG, comprises the reward system, necessary to predict and experience reward, and to adapt behavior to maximize reward while avoiding punishment. The relevance of the reward system in shaping behavior makes it a key system for learning. Dopamine regulates learning by indicating differences between expected and received reward, prompting the repetition of behaviors with positive outcomes, and avoiding the repetition of behaviors with negative outcomes (Clark & Dagher, 2014). The consequence of the alteration on the mesocorticolimbic system is that PD-ICD patients become more sensitive to rewarding outcomes, while underestimating adverse outcomes (Piray et al., 2014). Learning from positive outcomes is accomplished through phasic dopamine release from the VTA to the VS, specifically the nucleus accumbens (Schultz et al., 1997). Phasic dopamine release occurs while performing the behavior associated with the reward, and when receiving the reward (Phillips et al., 2003). Therefore, phasic dopamine acts as learning and incentive signal, manifesting as increased reward expectation and bias towards reward-associated behaviors (Dagher & Robbins, 2009). Learning from negative outcomes is accomplished through the pausing of the phasic dopamine (Schultz et al., 1997; van Eimeren et al., 2009). Dopaminergic medication may prevent this pausing (Frank, 2004; Gerlach et al., 2003), impairing negative feedback learning and increasing impulsive tendencies (Muhammed et al., 2016; Van Wouwe et al., 2017). Increased sensitivity to rewards and impaired negative feedback learning provide a powerful mechanism to develop addictions: focus on reward-seeking on one side, impairments on learning from negative consequences on the other (Dagher & Robbins, 2009) (see Figure 9). Although the VS has been associated with the development of ICD, an underactive frontal lobe could be contributing to the complication by impairing the top-down control in the mesocorticolimbic system (Robbins & Everitt, 1999).

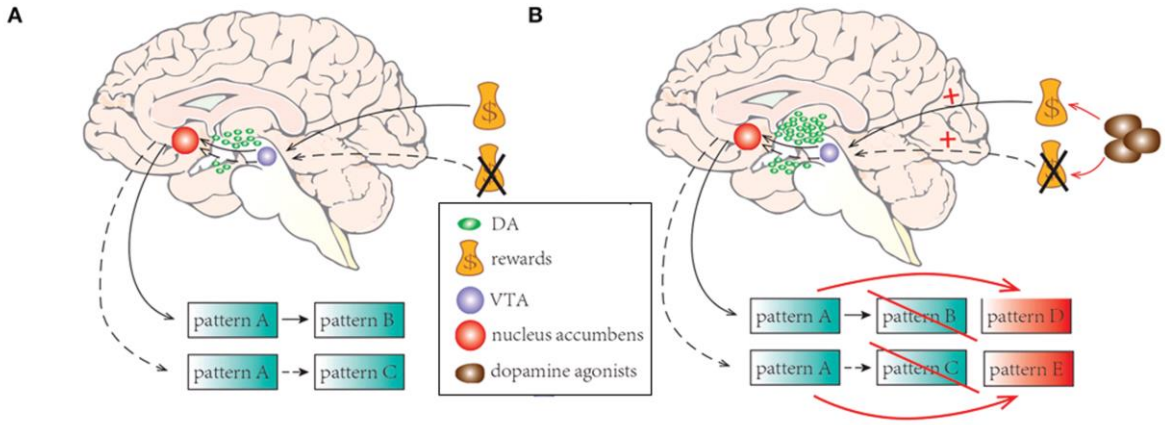

Figure 9. Schematic representation of learning and dopamine transmission. (A) The normal learning process involves phasic release of dopamine with reward, and phasic suppression of dopamine when the expected reward is not received. Learning involves performing behavior pattern A (e.g., entering the kitchen) and being able to choose an adequate pattern of response depending on the positive or negative rewards of the action. For example, when there are positive rewards (e.g., calming hunger), the person can adapt their behavior and perform pattern B (e.g., eat a biscuit). However, when there are negative rewards (e.g., breaking a diet), the individual can adjust their behavior and perform pattern C instead (e.g., reevaluate their hunger levels, or eat a piece of fruit). (B) In PD, dopaminergic medication disrupts normal learning. PD-ICD patients become more sensitive to reward, and less sensitive to absence of reward or negative events. When performing behavior A, PD-ICD patients' inability to process positive and negative rewards impairs them choosing the correct response patterns B or C. Therefore, under a positive reward condition, a patient with a binge eating disorder may experience difficulties performing pattern B, and show an aggravated form of the behavior, performing pattern D instead (e.g., eating the full box of biscuits). Alternatively, under a negative reward condition, the patient may choose pathological pattern E (e.g., eat every sweet sitting by the fruit in the pantry) instead of adaptative pattern C. Adapted from Zhang et al. (2021).

1.2. Alterations beyond the reward system and the ventral striatum

Despite the relevance of reward system alterations in PD-ICD patients, specifically alterations of the VS, metabolic changes are observed beyond the VS, with PD-ICD patients

presenting reduced dopamine transportation in the left putamen (Premi et al., 2016), and the opposite pattern, increased metabolic activity, in the ventromedial PFC (J.-Y. Lee et al., 2014) and medial orbitofrontal cortex (Joutsa et al., 2012) compared to PD patients with no ICD (PD-noICD) patients. PD-ICD patients do not exclusively exhibit with an altered mesocorticolimbic network, since the temporal cortices, loosely connected to the mesocorticolimbic pathway, have been found to be affected in PD-ICD patients too (Verger et al., 2018).

These patients have also shown reduced cortico-striatal connectivity functionally and structurally (Carriere et al., 2015; Premi et al., 2016; Verger et al., 2018). Specifically, Carriere and colleagues (2015) assessed resting-state FC differences of the striatum between PD-ICD and PD-noICD patients. They found that the left anterior putamen showed reduced co-activation with the left inferior temporal gyrus and the left anterior cingulate gyrus. In a follow-up study, (Premi et al., 2016) employed molecular imaging to further study impaired cortico-striatal connectivity in PD-ICD patients, and found reduced connectivity between the left putamen and both right BG and left cingulate cortex. In addition, Verger and colleagues (2018) found a disconnection between the left caudate and contralateral middle and inferior temporal gyri. Altered connectivity at the cortico-striatal level should not come as a surprise since, partly overlapping with the mesocorticolimbic network, it heavily relies on dopamine. Yet optimal cortico-striatal functioning is required in many functions beyond reward-based learning. The BG motor loops along with most cognitive functions involving the frontal lobe will depend on adequate cortico-striatal functioning to some extent (Leisman et al., 2013).

1.3. Alterations beyond the dopaminergic system

Despite the relevance of the dopaminergic system in addiction in general, and ICD associated with PD in particular, the involvement of additional neurotransmitter systems has been suggested as a relevant factor (Vriend, 2018). Serotoninergic and noradrenalinergic systems, which are affected by the PD pathology (Braak et al., 2003), may contribute to the development of ICD. Animal studies have confirmed the relevance of serotonin in inhibitory control since lesioning serotoninergic neurons of the raphe nucleus reduces inhibitory

control (Harrison et al., 1999; Winstanley et al., 2004). In humans, selective serotonin reuptake inhibitors (SSRI), which increase the availability of serotonin in the synaptic cleft, increase the activation of orbitofrontal and right inferior frontal gyrus (IFG) activation during inhibitory control (Del-Ben et al., 2005; Macoveanu et al., 2013) suggesting serotonin's boost in inhibitory control. A study assessing brain activation during a stop-signal task found that, during inhibition, PD patients on SSRI showed increased activation of the right IFG, a region of the stopping network (Ye et al., 2014). The role of noradrenaline improving impulse control has been indicated by animal studies (Baarendse et al., 2013; Robinson et al., 2008). In the same vein, in PD patients with no psychiatric complications, selective noradrenalin reuptake inhibitors increase the activation of the right IFG while inhibiting a motor action (Ye et al., 2015), but also reduce impulsive and risk-taking behaviors (Kehagia et al., 2014). However, it must be considered that the dopaminergic, serotoninergic and noradrenalin systems are interconnected, and a disturbance in one may affect the others (Benarroch, 2009; Boureau & Dayan, 2011). The opioid system has also been linked to ICD, since in substance and behavioral addictions, reducing opioid transmission through opioid receptor antagonists reduces the impulsive symptoms (Piquet-Pessôa & Fontenelle, 2016; Rösner et al., 2010). In PD-ICD patients, opioid receptor antagonists have no effect of ICD severity, although patients report a small improvement compared to placebo (Papay et al., 2014). Yet, more research is needed to fully elucidate the effects of opioid receptor antagonists on ICD.

1.4. Summary

To conclude, although the mechanisms leading to ICD in PD are not clear, imaging studies confirm the involvement of dopamine and the reward system. While performing reward-related tasks PD-ICD patients show increased VS activity during rewarding visual stimuli (Frosini et al., 2010; Paz-Alonso et al., 2020; Politis et al., 2013), but during risk taking PD-ICD patients show reduced VS activation compared to their PD-noICD counterparts (Rao et al., 2010). Even at rest, the FC of the VS with other regions of the mesocorticolimbic network is excessively co-activated in PD-ICD patients (Petersen et al., 2018), supporting the constant reward-seeking behavior in PD-ICD patients. These findings could provide additional support

to the *dopaminergic overdose theory*, and the dopamine imbalance between dorsal and ventral striatum (Kehagia et al., 2012; Swainson et al., 2000).

2. Emergence, detection and treatment

The emergence of ICDs in PD patients has been consistently linked to dopaminergic medication. PD medication may provide excessive dopaminergic doses in certain areas of the brain that are not deprived, thus overdosing them. However, dopaminergic medication could also overdose denervated regions. In addition, dopamine turnover and the stimulatory effect of dopamine agonists over postsynaptic dopamine receptors allow for a disproportionate flow of dopamine that may alter the physiologic response of the network in a similar way to a drug addiction, inducing ICD (Clark & Dagher, 2014; J.-Y. Lee et al., 2009). Although the precise mechanisms giving rise to ICD in PD are not well understood, three mechanisms have been proposed to alter the functioning of the mesocorticolimbic system in these patients (see Figure 10). *Dopamine overdosing of the VS* states that levodopa, while supplementing the loss of dopamine in the deteriorated dorsal striatum, overdoses the VS (Voon, Mehta, et al., 2011; Vriend, 2018). Support for this mechanism arises from studies indicating that the dopaminergic denervation of the striatum progresses from caudal (i.e., posterior putamen) to rostral (i.e., VS) areas (Damier et al., 1999; Hsiao et al., 2014). The relevance of this mechanism is that patients with PD-noICD can also experience impulsivity as a result of dopaminergic overdose in unimpaired frontal regions (Swainson et al., 2000). Another proposed mechanism contributing to the development of addiction in PD is the *supersensitization of the VS* (Evans et al., 2006; Prieto et al., 2011; Vriend et al., 2014). According to this mechanism, the VS of patients with PD-ICD would be affected by dopaminergic denervation, which, upon repeated administration of levodopa, would produce increasing amounts of dopamine with each dose. Supporting the concept of sensitization, Evans and colleagues (2006) found that PD patients with dopamine dysregulation syndrome show increased dopamine release in the VS after a dose of levodopa, in comparison with PD patients without the disorder. Similarly to substance abuse,

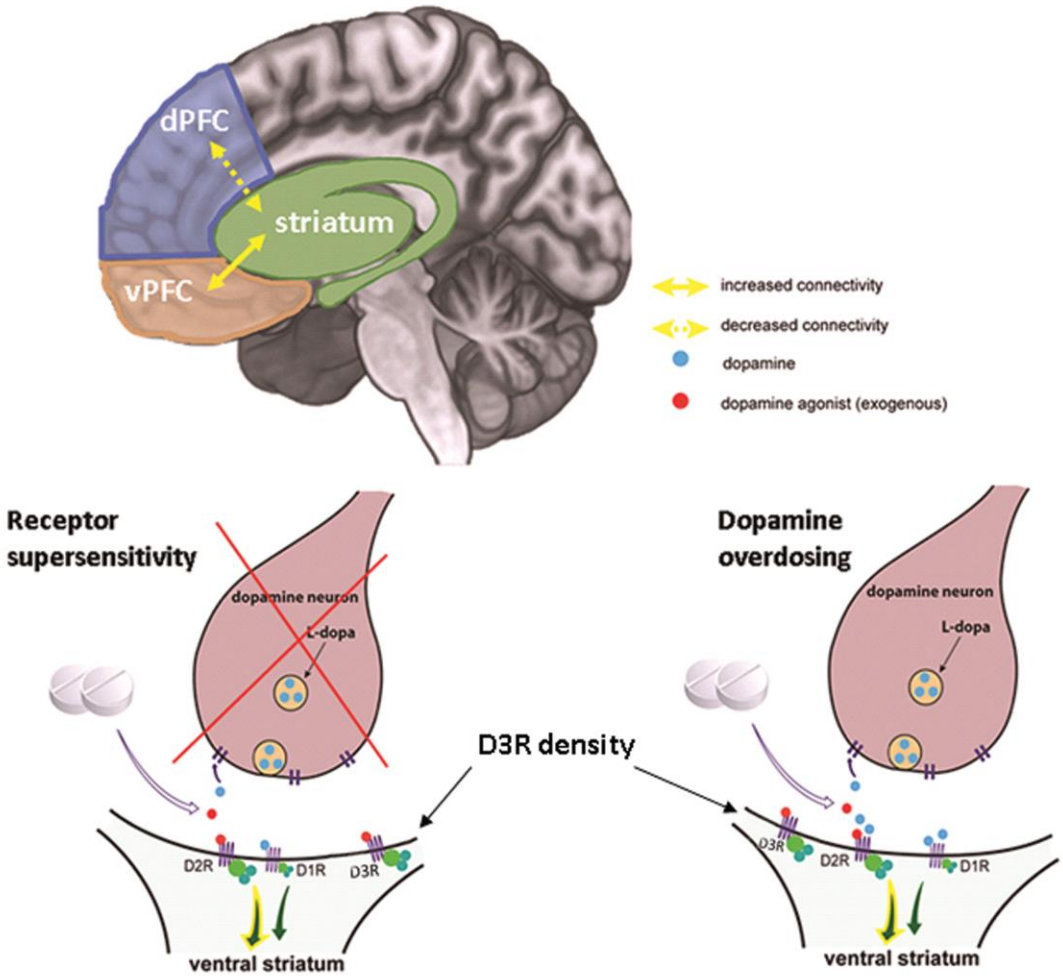

Figure 10. Schematic summary of the three possible mechanisms leading to a VS imbalance in PD-ICD patients: Receptor supersensitization, reduced D3R density, dopamine overdosing. Adapted from Vriend (2018). dPFC = dorsal prefrontal cortex; vPFC = ventral prefrontal cortex.D2R = D2 dopamine receptor; D1R = D1 dopamine receptor; D3R = D3 dopamine receptor.

PD-ICD patients also show increased dopamine release in the VS when engaged in pathological behaviors (Voon et al., 2011). *D3 dopamine receptors* are likely to play a role in this overstimulation of the VS. D3 receptors are mainly located in the VS (Boileau et al., 2013) and are associated with mood, motivation and reward (Aracil-Bolaños & Strafella, 2016). As dopaminergic agonists selectively prefer D2-like (i.e., D2 and D3) dopamine receptors, it has been suggested that the continuous stimulation of D3 receptors of the VS may have a stronger effect than in regions with fewer D3 receptors. Either due to genetical factors sensitizing D3 receptors in some patients, or due to VS deterioration leading to upregulation of D3 receptors, the continuous stimulation of these receptors may lead to increased

impulsivity, and eventually the development of ICD (Ahlskog, 2011; Napier et al., 2020; Voon & Dalley, 2011). The specificity and effect of dopaminergic agonists over D3 receptors was indicated by Payer and colleagues (2015), through a PET study with a radiotracer with preference for D3 receptors. They showed that PD-ICD patients presented reduced binding of the radiotracer in the VS compared to PD-noICD patients, which indicated a higher dopaminergic tone in the VS of patients with impulsivity. Therefore, dopamine overdose, sensitization, and the involvement of D3 receptors in the VS seem to be associated with behavioral addictions in PD (Aracil-Bolaños & Strafella, 2016). Whether by overdose, sensitization or continued interaction with D3 receptors, exaggerated dopamine levels lead to a prolonged overstimulation of postsynaptic receptors in the VS, which affects the dopaminergic mesocorticolimbic system, specifically affecting the limbic and associative circuits of the BG (Cools, 2006; Voon et al., 2011).

Dopaminergic agonists have been strongly associated with ICD, due to their preference for D2-like receptors (Napier et al., 2020). Although being on dopaminergic agonist is one of the primary risk factors for developing ICD, the disorder can also be triggered by levodopa (Molina et al., 2000; Weintraub et al., 2010). As previously mentioned, dopamine agonist and levodopa treatment are often combined to reduce motor complications associated with levodopa. This specific combination of dopamine agonists and levodopa is reported to increase the probability of developing an ICD by around 50% (Weintraub et al., 2010). In addition, levodopa seems to have a direct link with ICD development as higher dosage of levodopa is linked to ICD development (Voon et al., 2009). Furthermore, patients on levodopa experience ICDs more frequently and severely than patients not taking levodopa (Simoni et al., 2020). Yet, the emergence of ICD on PD is not exclusively explained by one type of medication or the other, that would preferentially act through one of the mechanisms, but probably a combination of them is at play differentially in each patient depending upon numerous neurobiological, environmental, and genetic factors that may increase their vulnerability to dopamine-induced impulsivity (Giladi et al., 2007; Weintraub et al., 2010). Briefly, disease duration, male gender, duration of dopamine agonist treatment, a personal or familiar history of addiction, and impulsive or novelty seeking personality traits are risk factors of developing ICD.

ICD can be a debilitating factor on the strained quality of life of PD patients and their caretakers. However, due to the addictive nature of the behaviors patients engage in, they can lie to family and clinicians either out of shame or in order to preserve the pathological behavior, hindering early detection. It is also possible that patients fail to realize they have a pathological behavior. When suspecting the appearance of ICD, movement disorders specialists employ semi-structured diagnostic interviews and screening questionnaires, such as the Questionnaire for Impulsive-Compulsive Disorder in Parkinson's Disease-Rating Scale (QUIP-RS) (Weintraub et al., 2012). The QUIP-RS was employed to assess the severity of the ICD on the participants of the current work, and therefore it will be discussed in Chapter 5, section 2.3. In addition, different diagnostic criteria are also available for each specific ICD (i.e., pathologic gambling, compulsive shopping, pathologic hypersexuality and binge eating) (e.g., American Psychiatric Association, 2013; Lejoyeaux et al., 1997; Voon et al., 2006).

Given the link between ICD in PD and dopaminergic medication, the first step to try to resolve the ICD involves an adjustment of the medication. The adjustment can be challenging and needs to be individualized (Gatto & Aldinio, 2019). Typically, PD patients developing ICD are under oral dopaminergic agonists exclusively or in combination with levodopa (Corvol et al., 2018; Garcia-Ruiz et al., 2014). Reducing the dosage of dopaminergic agonist or stopping them has been shown to make the ICD disappear in one to twelve months in most cases (Corvol et al., 2018; Dagher & Robbins, 2009). Yet, although effective, adjusting medication may be a challenging process. First, some patients may suffer from dopamine agonist withdrawal syndrome, experiencing elevated levels of anxiety, fatigue, insomnia or depressive mood (Pondal et al., 2013). Second, compensating the reduction in dopamine agonist with an increase in levodopa can, in the long term, produce the motor complications associated with levodopa, explained above in Chapter 1, section 5.1 (i.e., motor fluctuations and levodopa-induced dyskinesias). Third, patients may experience worsening of motor symptoms until the necessary medication adjustments are found. Finally, patients may resist the medication change to preserve their pathological behaviors. Deep brain stimulation in the STN has been used to treat motor symptoms, therefore allowing the reduction of dopaminergic medication (Schuepbach et al., 2013; Weaver et al., 2009). Yet its effects on ICDs are mixed, with some patients showing improvements while

for others their ICD increases in severity (Samuel et al., 2015). These mixed results are associated with the STN's involvement in impulse and inhibitory control (Lopez et al., 2017; Voon et al., 2017). The difficulties associated with preventing, detecting and treating ICD highlights the need of understanding its implications in aspects of daily living, and recognizing PD-ICD as an entity more complex than the comorbidity of PD and ICD.

3. Impulsivity alterations

In most cases, the effect of dopaminergic medication on the reward system interacts with previous predispositions in life to develop an ICD. Due to the implication on pathological behaviors of alterations at the level of reward and impulsivity, most cognitive neuroscience research in PD-ICD patients has focused on impulsivity-related functioning. Impulsivity here is understood as a behavioral tendency towards disinhibited, rapid, ill-considered decision. Thus, when addressing impulsivity, I am also referring to faulty inhibition. Typically, inhibition encompasses cognitive and motor aspects (Voon et al., 2017).

3.1. Cognitive inhibition

Cognitive inhibition is associated with high cognitive functions and include *delay discounting*, *negative prediction errors* in learning, *reflection impulsivity*, *risk taking* and *response conflict*. *Delay discounting* refers to a tendency to choose small immediate rewards over larger delayed rewards. PD-ICD patients have been shown to present greater delayed discounting behaviors compared to PD-noICD patients (Housden et al., 2010; Leroi et al., 2013; Voon et al., 2010; Voon et al., 2011). Enhanced delayed discounting in PD-ICD patients has been associated with increased dopamine release in the anterior putamen (Joutsa et al., 2015). Animal models (Tedford et al., 2015) and a clinical study with a PD-noICD sample and healthy controls (Al-Khaled et al., 2015) has suggested that PD pathology and dopaminergic agonists have an independent effect in intensifying delayed discounting.

Regarding *negative prediction errors*, there is ample evidence showing this learning pattern in PD-ICD patients. As previously mentioned, dopaminergic medications are thought to increase sensitivity to reward (i.e., positive prediction error), while impairing negative feedback learning (i.e., negative prediction error). The combined effect of increased reward sensitivity and impaired learning from negative feedback increase impulsivity (Collins & Frank, 2014). Studies on PD-ICD patients have validated this hypothesis. Voon and colleagues (2010) found that PD-ICD patients on dopaminergic medication showed enhanced reward learning, compared to PD-noICD patients, and impaired negative feedback learning compared to healthy controls. Furthermore, enhanced reward learning was associated with increased VS activation. Likewise, Piray and colleagues (2014) found that PD-ICD patients' reward learning pattern was associated to the values of stimuli, while PD-noICD patient's learning pattern was linked to the evaluation of the values of potential actions. Finally, Paz-Alonso and colleagues (2020) found that during the initial period of trials in which PD-ICD, PD-noICD and HC participants were presented with negative feedback, PD-ICD patients showed increased activation in bilateral insula and right VS. PD-ICD patients also showed an association between ICD severity and the activation of right frontostriatal regions. The associations between ICD severity and right insula and right IFG, specifically, were mediated by their FC with the right VS, highlighting the relevance of the VS during learning, and its involvement in ICD.

Reflection impulsivity refers to decision making with little reflection or time. Djamshidian and colleagues (2012) found that PD-ICD patients on medication had similar reflection impulsivity to people with drug misuse disorders, and higher reflection impulsivity than PD-noICD patients. This study strengthens the claims to consider ICD as a behavioral addiction, due to its similarities with other addictions.

Risk taking is typically studied through gambling-like tasks. An electrophysiological study examining the local field potentials of the STN showed that PD-ICD patients tended towards a risky strategy, which was associated with lower frequency STN activity in trials that could involve risk taking (Rosa et al., 2013). The authors interpreted the findings as indicating that PD-ICD patients present a higher sensitivity to risky situations, due to STN malfunction.

Response conflict refers to increased interference by competing responses leading to increased error rates and slowdown of RT. PD-ICD patients ON medication have not shown increased response conflict compared to their PD-noICD counterparts (Djamshidian et al., 2011; Wylie et al., 2012). However, response conflict may vary from one pathological behavior to another, as Vitale and colleagues (2011) found that PD-ICD patients with pathologic hypersexuality and binge eating experience more difficulties processing interference than PD-ICD patients with pathological gambling.

As presented above, cognitive inhibition has been studied thoroughly in PD-ICD patients, and it is believed that pathological behaviors associated with this disorder can be in part explained by addictive-like mechanisms. Different aspects of cognitive inhibition (i.e., delay discounting, negative prediction errors in learning, reflection impulsivity, and risk taking) are impaired in PD-ICD patients, and are associated with different functional correlates.

3.2. Motor inhibition

Altered motor inhibition is associated with less elaborated decisions on motor responses such as response inhibition. Although not as extensively studied as cognitive inhibition, several studies have assessed response inhibition as a measure of motor inhibition in PD-ICD patients. Inhibitory control and response inhibition were elaborated in Chapter 1, section 2.2.1.2, and therefore, here I will focus on discussing findings related to ICD in PD.

Behaviorally, studies with PD-ICD patients have shown mixed results. It has been reported that PD-ICD patients i) stop initiated movements faster than matched PD-noICD and HC participants (Claassen et al., 2015); ii) behave like their control counterparts (Filip et al., 2018); and iii) respond more impulsively than PD-noICD controls (Meyer et al., 2020). Meyer and colleagues (2020) also found abnormal beta activity in the SMA and precuneus during proactive inhibition in their PD-ICD group.

To the best of our knowledge, only one fMRI study to date has examined response inhibition in PD-ICD (Filip et al., 2018). Filip and colleaguese (2018) found no behavioral

differences in reactive inhibition between PD-ICD and PD-noICD groups ON dopaminergic medication. However, PD-ICD patients showed hypoactivation in frontal areas and the left caudate compared to PD-noICD and HC groups. Furthermore, compared to the other groups, the PD-ICD group showed reduced FC between the caudate nuclei and both the superior parietal lobe and insula. These alterations of co-activation strengthened the authors' claim that changes associated with PD-ICD go beyond the stopping network, since they found no alterations in the main regions associated with response inhibition. Remarkably, this study did not show functional activation or connectivity differences in areas of the stopping network. This could be due to their choice of paradigm, a task assessing reactive inhibition, that may not have been sufficiently challenging to detect changes in this population.

Although scarce and contradictory, most evidence leans towards a lack of behavioral impairment in PD-ICD compared to PD-noICD individuals in response inhibition (Claassen et al., 2015; Filip et al., 2018). Preserved behavior on the face of functional and structural cortico-striatal alterations (Carriere et al., 2015; Premi et al., 2016) would suggest compensatory mechanisms in PD-ICD patients.

4. Impact of Impulse Control Disorders across other domains

Most cognitive neuroscience research on PD-ICD has revolved around impulsivity and reward, since it has been assumed that most neurological and cognitive changes brought by the ICD are associated with the altered dopamine-driven reward system and the pathological behaviors the patients engage in.

Some studies have assessed general cognitive functions, finding mixed results. One of the studies with a greater sample size, the ICARUS study, reported no impaired cognition in PD-ICD patients, as measured by two screening instruments and the Frontal Assessment

Battery (FAB) (Antonini et al., 2017). However, previous studies with smaller samples found either a trend towards impaired performance on the FAB (A. R. Bentivoglio et al., 2013) or actual significant impairments on this same battery (Santangelo et al., 2009). Interestingly, a longitudinal study on PD-ICD and PD-noICD patients observed reduced impairment on frontal tests in PD-ICD patients overtime, although both groups showed no differential cognitive performance at baseline (Siri et al., 2015). Siri and colleagues (2015) suggested that the impaired impulsivity characteristic of PD-ICD patients could be associated with the effect of medication over a spared prefrontal region. This claim resembles the *dopaminergic overdose theory* (Swainson et al., 2000). Yet, studies assessing frontal lobe functioning or general cognitive performance are exclusively behavioral, limiting their neural-related interpretation.

Studies assessing specific cognitive functions have also shown mixed results. PD-ICD patients have been found to perform better, similarly or worse than their counterparts in verbal fluency tasks (Leroi et al., 2013; Santangelo et al., 2009; Siri et al., 2010) and attention task (Leroi et al., 2013; Siri et al., 2010; Vitale et al., 2011); to perform better during auditory memory tasks (Siri et al., 2010), and worse during spatial planning (Vitale et al., 2011) and spatial working memory (Santangelo et al., 2009).

To date no studies have assessed the integrity of the motor system in this population. In addition, studies comparing PD-ICD and PD-noICD patients match the groups based on motor state, among other factors, thus preventing between-groups motor differences examination. Yet, increased fiber degeneration in striatal and frontal regions (Aracil-Bolaños & Strafella, 2016; Joutsa et al., 2012; J.-Y. Lee et al., 2014) and reduced cortico-striatal connectivity in PD-ICD patients compared to their PD-noICD counterparts (Carriere et al., 2015; Premi et al., 2016) could suggest abnormal motor functioning: by altering the motor loop of the BG, the output to other motor regions could be affected.

Mixed results along with lack of neuroimaging studies examining performance and structural or functional neural correlates difficult the understanding of the neuropathological impact of ICD in PD on the cognitive profile of these patients. Available research also allows the perpetuation of the intuition that PD-ICD patients are only impaired in cognitive domains associated with cognitive impulsivity and reward-based processing. Yet, the extent of the

neurobiological changes associated with PD-ICD, including i) the involvement of multiple neurotransmitter systems (Vriend, 2018), ii) increased dopaminergic degeneration in addition to the deterioration associated with PD pathology (Aracil-Bolaños & Strafella, 2016; J.-Y. Lee et al., 2014), and iii) disrupted cortico-striatal connectivity (Carriere et al., 2015; Premi et al., 2016) indicates the possibility of additional behavioral alterations associated with this complication.

5. Summary

ICD in PD is a complex side-effect brought by the effect of dopaminergic treatment on the limbic loop of the BG. The exogenous dopamine alters the functioning of the VS, which becomes hypersensitive to rewards and unresponsive to negative feedback. The limbic alteration is associated with the pathological behaviors that patients engage it, since they become drawn to positive feedback, and unable to adjust their behavior in response to corrective feedback. The dopaminergic alterations in PD-ICD patients seem focused on the VS, yet, as metabolic and MRI studies presented above suggest, these alterations are not limited to the limbic system.

Considering that impulsivity, and therefore faulty inhibition, is one of the main characteristics of ICD in PD, inhibition, particularly at the cognitive level, has received ample attention in this sample. Yet, as seen in Chapter 1, section 3.1, the dopaminergic nigrostriatal and mesocorticolimbic pathways are implicated in a wide range of domains. Therefore, it can be assumed that other non-impulsivity related domains may be affected in PD-ICD patients, particularly, the ones investigated in this doctoral dissertation: sequential motor movements, response inhibition, and semantic processing. To study the functioning of these domains on the context of ICD in PD in humans, MRI has been selected as an optimal technique, and with this aim, it will be described in the next chapter.

Chapter 3: Magnetic Resonance Imaging

The interest for the human brain is not new. The development of neuroscience has required centuries, evolving from the initial efforts of renaissance physicians already speculating with the mental properties of the brain, and phrenologists trying to localize brain functions and personal characteristics based on the shape of the skull (Wickens, 2014). Currently, neuroscience is a well-established discipline that has undergone a drastic growth in the last three decades. The birth of cognitive neuroscience is estimated in 1988, enabled by the previous introduction of positron emission tomography (PET), MRI and contrast and analysis development to measure brain function (Raichle, 2009). Cognitive neuroscience is interested in understanding the workings of the brain and how its functioning allows us to go about our daily lives (Poldrack, 2006). Neuroimaging tools have become a window into the living brain and its functioning, granting us to better understand the relationship between behavior, anatomy, and function. It is partly due to the development of different neuroimaging tools that the discipline has been able to grow to the current extent.

Different functional brain scanning techniques allow for the measuring of *in vivo* brain activation. To measure electrical activity, electroencephalography and magnetoencephalography record either voltage or magnetic fields from the scalp. PET is slightly more invasive as it measures the gamma-rays of a positron-emitting tracer

introduced in the participants blood stream. Finally, MRI that measures the magnetic changes in the tissue by applying magnetic fields and radiofrequency (RF) pulses.

Unlike the other methods mentioned, MRI allows the combination of structural and functional neuroimaging. Another advantage of this tool is that MRI techniques provide high spatial resolution, allowing the localization of the functional information in voxels, typically of one to three cubic millimeters. MRI capitalizes on the magnetization properties of protons, mostly of hydrogen atoms. Hydrogen atoms in water molecules are normally randomly oriented. Placing a body into an external magnetic field causes protons to align. By delivering RF pulses, the alignment is disturbed. After each pulse stops, protons start aligning back with the external magnetic field, and release RF energy in the process (Plewes & Kucharczyk, 2012). Coils along the MR machine capture the released energy from each location and the computer converts it from frequency into intensity through the inverse Fourier transformation. Different MRI sequences can be programmed by varying the time between RF pulses and the time at which the released RF energy is captured (Huettel et al., 2008). MRI was the technique selected to carry out the experiments included in this doctoral dissertation. Therefore, in this chapter I will present the neuroimaging methods employed in the current work.

1. Structural MRI

Structural MRI provides information about the structures of the brain: their size, shape, and the segmentation and integrity of gray and white matter. Since MRI is obtaining its signal from hydrogen atoms, the signal contrasts vary between different tissues, as gray matter contains a high proliferation of cell bodies and white matter is mostly composed of nerve fibers. As previously mentioned, MRI provides a combination of structural and functional neuroimaging, with functional imaging being mapped on the higher resolution structural image. That structural image is typically T1-weighted, in which the contrast and brightness are mainly determined by the rate at which the protons align back to the external magnetic

field. Therefore T1-weighted images emphasize the difference between gray and white matter.

T1-weighted images can be processed to extract volumetric features, such as cortical thickness (CT). CT is used to estimate the thickness of gray matter in different regions, which varies from 1 to 4.5 mm (Fischl & Dale, 2000). CT is a relevant structural measure when studying neurodegenerative diseases (e.g., Dickerson et al., 2009; Frisoni et al., 2011), which tend to affect the functioning of the brain along with its anatomical properties. To extract CT measures, voxels comprising the brain in T1-weighted images are segmented into gray matter, white matter, and cerebrospinal fluid, which delineates de boundaries between gray matter with white matter medially, and with the pial matter externally (Cardinale et al., 2014; Fischl & Dale, 2000). In the current doctoral dissertation, CT of each participant was calculated and between groups comparisons were executed to discard the possibility of anatomical differences that could be biasing the functional results.

2. Functional MRI

fMRI is used to measure activation across the brain while participants perform tasks, or rest, inside the scanner (Bandettini, 2012). In the current doctoral dissertation, only task fMRI will be employed, and therefore I will focus on fMRI employed to determine the location of cognitive changes associated with task performance. fMRI sequences measure the blood-oxigen-level-dependent (BOLD) response, which is the ratio of deoxygenated (deoxyHb) and oxygenated hemoglobin (oxyHb) molecules in blood vessels (Ogawa et al., 1990). fMRI functioning capitalizes on the differential magnetic properties of hemoglobin: while oxyHb has no effect on the local magnetic field, deoxyHb is paramagnetic, and therefore, disturbs the homogeneity of the magnetic field. When the brain is engaged in a demanding task (i.e., a motor or cognitive task), the regions involved in the task will require increased blood supply, resulting in BOLD signal changes. Specifically, when a certain brain region is recruited, its oxygen consumption increases (i.e., increase in deoxyHb), and after two seconds, oxygen consumption is compensated with an increase in localized cerebral blood

flow (i.e., increase in oxyHb). Therefore, a region recruited for a task will show increased oxyHb and, consequently, decreased deoxyHb levels. The changes in BOLD signal make it possible to map changes in activation related to different tasks (Raichle, 2009). fMRI experiments aim to measure to what extent specific task manipulations produce BOLD signal changes.

There are two main types of experimental fMRI designs: block and event-related designs (Buckner et al., 1996; Dale & Buckner, 1997). Block designs present consecutive stimuli of the same condition for a fixed period that typically lasts at least 10-12 seconds and that are referred to as block. Activation blocks will consist of multiple stimuli of the same condition, typically be followed by rest blocks that are used as baseline activation. The advantages of block designs is that presenting the same condition for a relatively long period of time (e.g., 10 to 20 seconds) will create a relatively sustained BOLD signal change compared to rest blocks (Buxton et al., 1998). Block designs typically have the advantage of providing superior statistical power relative to event-related designs (Friston et al., 1999). Therefore, block designs are a good option to detect sustained activation and functional differences between conditions. However, they cannot be employed when it is important that the task is not predictable for the participant, since all the stimuli in a given block will belong to the same condition (e.g., an oddball task), or when conditions depend on participants' behavior (e.g., correct > incorrect responses in a memory retrieval task where participants must identified words as remembered or as new) and can be in general less engaging for participants. Event-related designs consist of a series of short stimuli, in which conditions and stimuli presentation are randomized or pseudorandomized. Advantages of event-related designs is that they are useful to reduce expectancy effect (D'Esposito et al., 1999), can detect transient changes in the BOLD signal, and allow the analysis of participants' responses for single trials (Schacter et al., 1997).

In the experiments that conform the present doctoral dissertation, we employed both block and event-related designs. Experiment 1 focuses on a finger tapping task designed in a block design: left-hand blocks, right-hand blocks, and rest blocks. Experiment 2 and 3, on the other hand, had an event-related design. The paradigm in Experiment 2 consists in an inhibitory task in which participants don't know when the inhibitory trial will be presented.

In Experiment 3 participants heard words belonging to different conditions, that were presented pseudorandomized per condition.

2.1. Data preprocessing

The main challenge in fMRI analysis is to compare images or groups of images in a statistically sound way. Before performing any analysis, however, it is necessary to perform the following preprocessing steps: *slice-timing correction*, *realignment*, *coregistration*, *normalization*, and *smoothing* (see Figure 11). *Slice-timing correction*, or temporal interpolation, compensates for slice acquisition delays. A full volume of brain slices cannot be acquired at the same time, but this step compensates the small time differences. *Realignment*, or spatial interpolation, helps to correct motion artifacts by aligning the functional images with each other by moving or rotating them. This step deals to some extent with the minimal movement of participants during scanning, which can result in

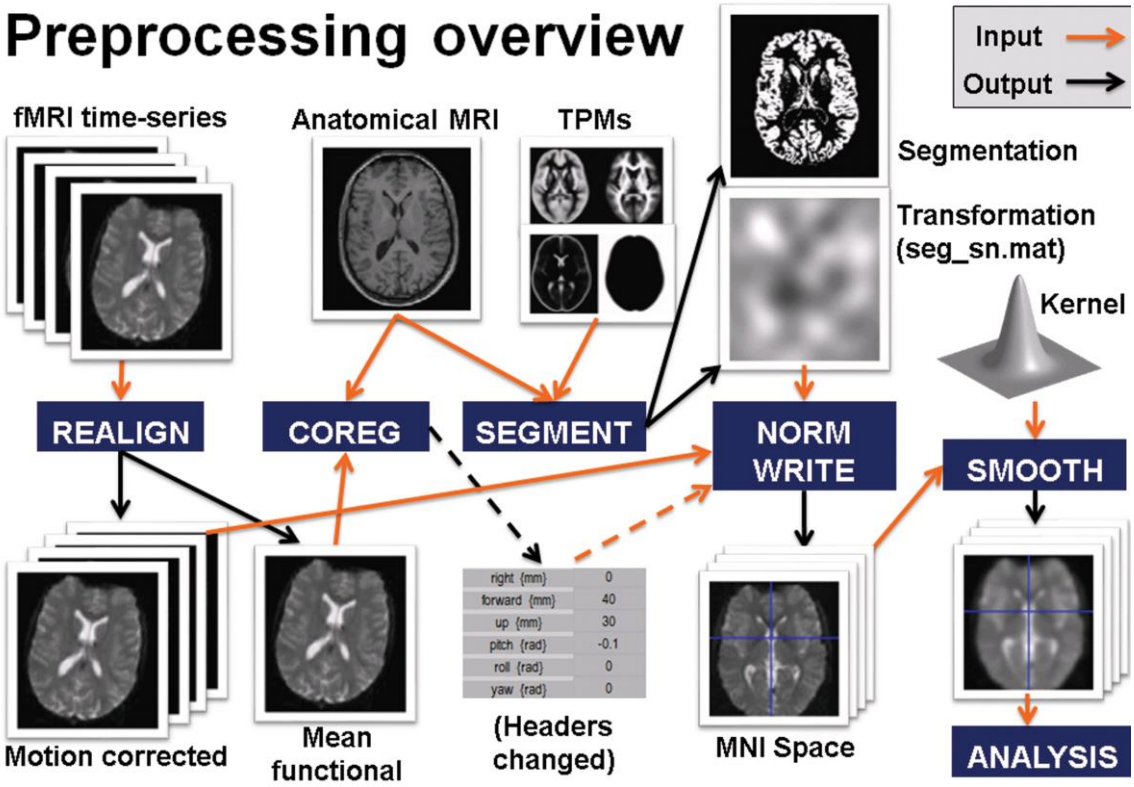

Figure 11. Overview of fMRI data preprocessing. Adapted from SPM preprocessing, available on: https://www.fil.ion.ucl.ac.uk/spm/course/.

varying the location of each voxel between scans. *Coregistration* improves the spatial resolution of functional images by mapping low-resolution functional images into higher resolution T1 or T2-weighted structural images. During *normalization*, participants' brain images are warped into a standardized stereotaxic space. By using landmarks, this step adjusts position, orientation and size of each participants' brain scans to the reference brain template. The most common reference templates employ MNI space, considered the international standard for normalization (Brett et al., 2002). MNI space is based on the Talairach space, which introduced a 3-dimensional coordinate system to identify specific locations in the brain, a system to transform and scale brains to match one another, and a brain atlas with corresponding anatomical and cytoarchitectonic labels (Talairach & Tournoux, 1988). The normalization process reduces inter-human variability, by allowing data averaging across participants. In addition, the use of a common space across studies and laboratories allows for comparability and reproducibility across the scientific community. Normalization is relevant for fMRI studies interested in group-analysis. *Smoothing* involves the averaging of voxels with their neighbors. Smoothing each voxel will improve signal-to-noise ratio since BOLD signal values will not present sudden changes, and the changes in the BOLD response in a limited region will be limited, since it is dependent on blood flow.

In the experiments conducted in the present doctoral dissertation, we applied all these preprocessing steps, except for Experiment 1. There, we also analyzed participants' functional data in the native space, without using normalization, to localize subcortical and cortical regions more precisely. Also, considering that PD patients tend to move more than healthy participants, we applied additional motion correction algorithms in all our experiments. All the specific preprocessing details for each of the experiments here conducted will be further specify below in empirical chapters 5, 6, 7, 8, and 9.

2.2. Data analysis

After preprocessing, fMRI images can undergo statistical analyses. The most widely used tool to fit and detect changes in BOLD response is the general linear model (GLM) (Friston

et al., 1995). The GLM can be used to perform multiple types of analyses such as correlations, one sample t-tests, two sample t-tests, analyses of variance (ANOVA), analyses of covariance (ANCOVA), as well as multiple or single regression among other possible analyses. Specifically, fMRI analyses are carried out in several stages. For example, for a two-sample t-test, first-level analysis involves modeling the data for each subject separately and estimating subject-specific differences depending on the experimental paradigm and its conditions. Second-level analysis gets fed the subject-specific parameters and variance estimates from first-level analysis, and models it. Posteriorly, within-subject variance is estimated in the first-level, and between-subject variance in the second-level. Lastly, the model estimates each group's mean, and the contrast of interest to compare between groups (Poldrack, 2011).

The common objectives in fMRI analysis are to localize brain regions activated by a specific task or condition, to compare activation of a region known to be involved between different groups or conditions, and to determine the brain networks involved in specific functions. *Voxel-wise* analysis is an approach to examine the activation across the whole brain. For an image composed of N voxels, there are two ways to assess if there are variations in the BOLD response: voxel-level, this is, by testing each voxel in the brain; and cluster-level, this is, examining clustered activation encompassing several voxels. When carrying out whole-brain analyses it is necessary to avoid "multiple testing problems", such as Type I error, this is, considering the activation of one voxel or cluster as statistically significant when really it is not. Different methods have been created to avoid this problem at the voxel and cluster-level: the False Discovery Rate (FDR, only recommended for cluster-level corrections) or the Family-Wise Error (FWE, recommended for voxel-level as well as for cluster-level corrections). When performing these statistical corrections with voxel-wise analysis, the statistical power will usually be small due to the multiple comparisons corrections that need to be performed over thousands of voxels.

A similar approach to examine activations in brain regions is the *Region of interest (ROI)* analysis. When a study is focused on specific regions due to prior evidence suggesting the involvement of specific regions in a certain function and the study's hypotheses, ROI analysis can be used, limiting the search of differences in activation to a certain number of ROIs (Poldrack, 2007; Saxe et al., 2006). This approach involves the extraction of signal (i.e.,

parameter estimates) from each selected ROI. ROIs can be delimited depending on anatomical bases, previous studies, and task-related activation. Employing ROI analysis is interesting for the following reasons. First, in complex designs with multiple levels discerning the pattern of activation from a voxel-wise map across conditions may be challenging, whereas ROI analyses may depict the pattern more clearly. Second, by limiting the number of statistical tests to certain ROIs, one reduces the magnitude of corrections needed for a large number of voxels, one can better control for Type I errors, and one can increase statistical power (Poldrack, 2007; Saxe et al., 2006).

Determining the brain networks involved in specific functions has become more and more relevant as the cognitive neuroscience community is moving from a region-centered approach towards the idea that most functions are supported by the coordinated action between different distant regions (Catani et al., 2003). This idea has led to the implementation of analyses to understand the interaction between different brain regions. One approach to examine these interactions is *FC*, which refers to the co-activation between voxels in different brain regions. This approach typically computes correlations between ROIs, this is, pairwise FC, or between a "seed" region and the rest of the voxels in the brain, this is, whole-brain FC. This type of analysis allows to discover patterns about regions that work together in time, and to compare those patterns between different functional networks, between groups, and between conditions (Friston, 2011). There are different methods to estimate FC, such as the beta-series correlation developed by Rissman (Rissman et al., 2004), psychophysiological interactions, or dynamic causal models. However, elaborating on multiple methods is outside the scope of this dissertation, as we employed the beta-series correlation method in the experiments. It is a method that capitalizes on trial-to-trial variability to characterize dynamic inter-regional interactions. This method assumes that if two brain regions are functionally interacting with each other during a specific task or condition, then the amount of activity presented in both regions should be correlated across trials. Therefore, this method provides information about how different regions co-activate and allows examining FC differences at the whole-brain and the pairwise level. The beta-series correlation method has been widely used in fMRI studies (e.g., Chadick & Gazzaley, 2011; Paz-Alonso et al., 2013). FC analysis was employed in Experiments 1 to 3 to examine differences between groups.

Chapter 4: Aim of the current dissertation

1. Hypotheses

In an attempt to examine the neural underpinnings of PD-ICD patients in non-reward-related tasks, the three experiments in this doctoral dissertation will investigate the following hypotheses:

1.1. ICD beyond reward

As introduced in Chapter 2, section 1, the extent of changes associated with PD-ICD indicates that neural alterations are unlikely limited to the reward system in these patients. ICD in PD is understood as a result of hyperstimulation of the VS, which should spare other fronto-striatal or posterior regions. However, PD-ICD patients show unique alterations (Aracil-Bolaños & Strafella, 2016; Zhang et al., 2021) that are not confined to the reward system (e.g., Carriere et al., 2015; J.-Y. Lee et al., 2014; Vriend, 2018), suggesting that the complication should be associated with alterations in domains beyond reward and cognitive inhibition. In fact, some studies also show different dopaminergic activity in the putamen

(Premi et al., 2016), and frontal regions (Joutsa et al., 2012; J.-Y. Lee et al., 2014) between ICD and non-ICD PD patients suggesting further motor and cognitive functions in ICD patients.

Despite the extent of these alterations, mixed results in the study of motor inhibition and scarce investigation on domains that are not associated with reward have not allowed to demarcate the limits of functional changes associated with PD-ICD. We hypothesize that the influence of ICD in PD will be present in the motor and cognitive domains here investigated (i.e. sequential movement, response inhibition, and semantic processing), and that PD-ICD participants will employ different neural mechanisms to execute the tasks associated with each domain. Differential neural correlates in PD-ICD patients across tasks would indicate that PD-ICD is an overarching complication that not only has an effect on the observed pathological behaviors that these patients suffer.

1.2. Compensation or deterioration?

If PD-ICD patients present functional alterations in the examined domains as expected, these changes could reflect compensatory correlates or, alternatively, changes associated with the negative impact of ICD over the brain. Compensatory alterations could be indicated by increased or widespread recruitment to perform the same task, while pathological alterations could be reflected by hypoactivation of regions necessary to perform the task and disrupted co-activation between relevant regions.

The existence of both compensatory or deterioration correlates are possible. Yet, there are two indications suggesting compensatory mechanisms that lead to spared behavior in the studied domains: i) literature examining response inhibition behaviorally indicate spared performance (Claassen et al., 2015; Filip et al., 2018) ii) motor and semantic functioning have not been previously examined in PD-ICD patients suggesting no visible interference with daily functioning that would attract the clinician's attention. Although behavior will only be directly examined in Experiment 2, the level of manual proficiency will be controlled for in Experiment 1, and participants' through neuropsychological examination will include several tasks requiring semantic processing, assessed functionally in Experiment

3. Thus, depending on the observed performance and the specific neural alterations related to each experiment, if they exist in PD-ICD patients, we will be able to determine if neural changes relate to compensatory mechanisms or dysfunctional alterations.

2. Objective

To date most research on PD with ICD has focused on identifying risk factors and biological mechanisms associated with impulsivity-related cognitive factors and a faulty reward system. This doctoral dissertation aims to employ fMRI to examine the functional correlates of PD-ICD on three different domains: sequential movement, response inhibition, and semantic processing to investigate functional changes associated with ICD in PD. By examining these domains in a common sample of patients with PD-ICD, patients with PD-noICD, and HC participants, we seek to expand the interest on ICD-related mechanics beyond the reward system, and to shed light on the cognitive and motor profile of PD-ICD patients.

3. Methods

. Specifically, I will be examining the following domains:

- Sequential movement: A central focus of PD, movement and the motor system has not received substantial attention in the context of PD and ICD. In Experiment 1 we examine the functional correlates of the motor network, focusing on the putamen due to its relevance on motor control, and the dopaminergic denervation suffered in PD, as well as on the main components of the DTCT pathway (i.e., DN, Mthal, M1). To do so, we employed a sequential finger tapping task demanding fine motor control and coordination.

- Response inhibition: Response inhibition has received more attention, with a special emphasis in measures of motor impulsivity. Yet, behavioral studies have shown mixed results (Claassen et al., 2015; Meyer et al., 2020; Voon et al., 2017). In addition, the only fMRI study conducted to date has found hypoactive fronto-striatal regions and reduced co-activation between the caudate and both insula and parietal cortex, but no differences on regions of the stopping network (Filip et al., 2018). In Experiment 2 we employ a demanding response inhibition task, the SST, to examine different aspects of inhibition. We do so with a focus on the main components of the stopping network (i.e., IFG, preSMA and STN), which is responsible for inhibiting motor actions (Aron et al., 2007; Aron, 2011).
- Semantic processing: Few behavioral studies on PD-ICD patients assessing a wide range of cognitive domains have included linguistic tasks. Among them, the majority have used verbal fluency that that have showed mixed results (Leroi et al., 2013; Santangelo et al., 2009; Siri et al., 2010). None of these studies have specifically examined semantic processing in PD-ICD patients. Semantic processing is impaired when cortico-striatal systems malfunction, as in the case of PD (Angwin et al., 2006). The reduced cortico-striatal connectivity observed in PD-ICD patients compared to their PD-noICD counterparts (Carriere et al., 2015; Premi et al., 2016; Verger et al., 2018) suggests a greater impairment at the semantic processing level in PD-ICD patients. To assess the impact of ICD over the semantic system, in Experiment 3 we investigate the functional correlates of semantic processing in PD-ICD patients focusing on differences in the processing of ICD-laden and ICD-free words.

By examining motor, response inhibition, and semantic processes, I hope to bring light on domains not specifically investigated before in this population, or where the behavioral evidence is contradictory. We will be employing fMRI to capture expected task-related group differences at the whole-brain, region-of-interest, and FC levels. For Experiment 1 and Experiment 2, we will be looking at the motor and stopping network respectively, through an ROI approach, whereas for Experiment 3, due to the lack of previous literature, we decided to follow a legitimate whole-brain approach. We will focus on the networks responsible for executing these processes, and the regions recruited by the networks, that will be described below.

3.1. Motor network

Movement is ontogenetically one of our earliest skills. As infants and later as children we refine those skills when we learn to walk, handle objects, and importantly, talk. We usually take our free range of motion for granted, until we start experiencing problems to articulate our movements. Due to the motor manifestations of PD, I have talked about the impact of PD over the BG (see Chapter 1, section 3) and additional key motor regions (see Chapter 1, section 4), and therefore, I here will focus on the involvement of the all previously introduced

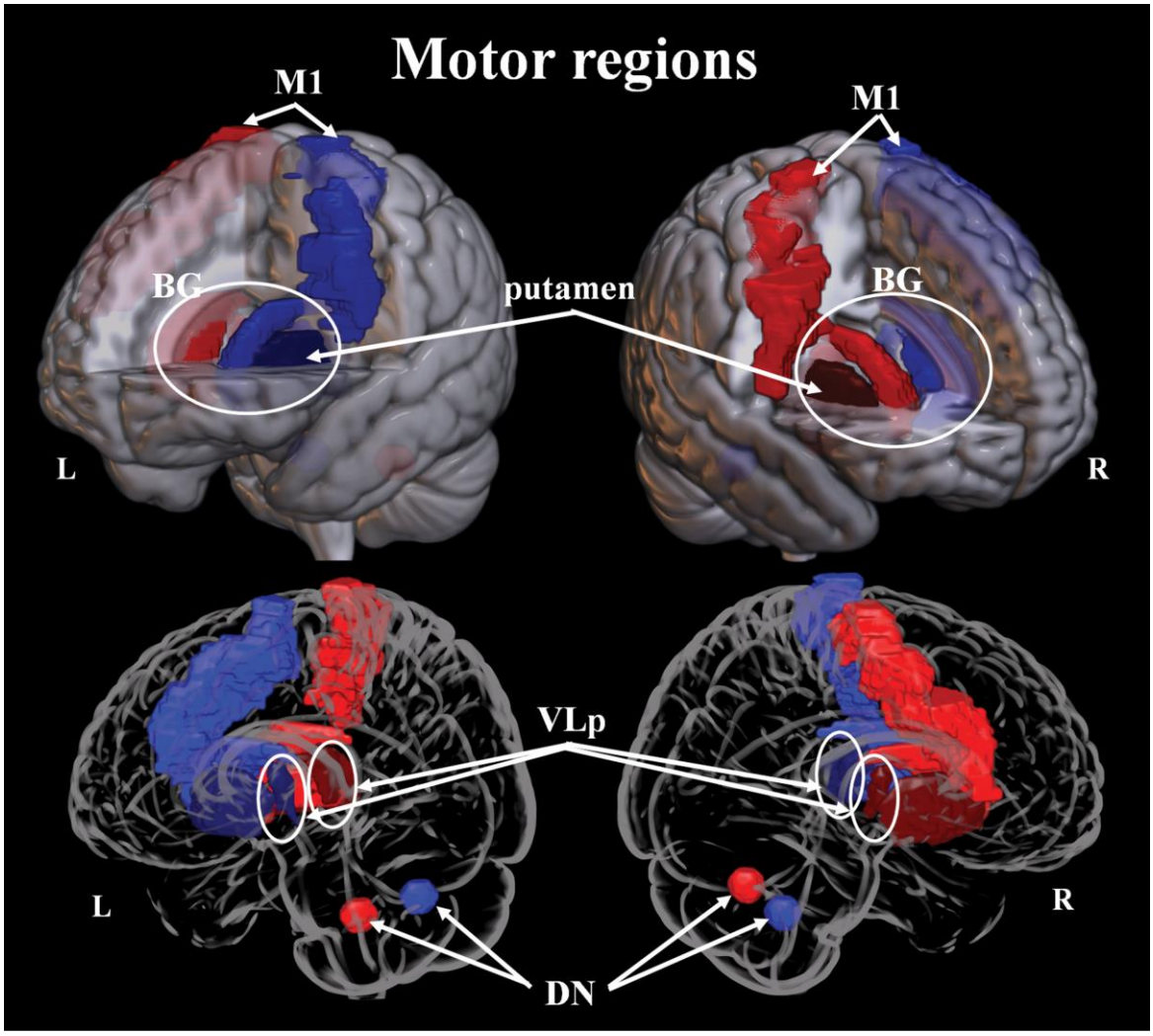

Figure 12. Representation of relevant motor regions. Regions colored in red are recruited by movements of the left hemibody, regions colored in blue by movements of the right hemibody. BG = basal ganglia, VLp = posterior ventral lateral nucleus of the thalamus, M1 = primary motor cortex, DN = dentate nucleus.

motor regions on sequential movement (see Figure 12). Although the BG and the DTCT have been presented separately, it is the proper functioning of the whole motor network that will allow us to move fluidly. Specifically, to perform sequential tasks mainly involves contralateral M1 and SMA (Richter et al., 1997; Ueno et al., 2010). Yet, the full network seems more extent including bilateral sensoriomotor cortex and PMC, bilateral BG, cerebellum and inferior parietal and contralateral VL (Mallol et al., 2007).

3.2. Stopping network

The stopping network is responsible for executing motor inhibition, specifically, response inhibition. The neural underpinnings of response inhibition are a right-lateralized network consisting of the anatomically connected (Aron et al., 2007) preSMA, IFG, and STN (Aron, 2011) (see Figure 13). Despite the right-lateralization of the stopping network, some left hemisphere recruitment, particularly of the left IFG, is typically observed (Aron et al., 2014; Criaud & Boulinguez, 2013; Swick et al., 2008, 2011). Yet, to correctly complete a response inhibition task, participants need to recruit not only inhibitory mechanisms, but also error monitoring and attentional resources to maintain the focus and to reorient attention. In fact, attentional resources are often confounded with inhibitory components, as studies aimed at

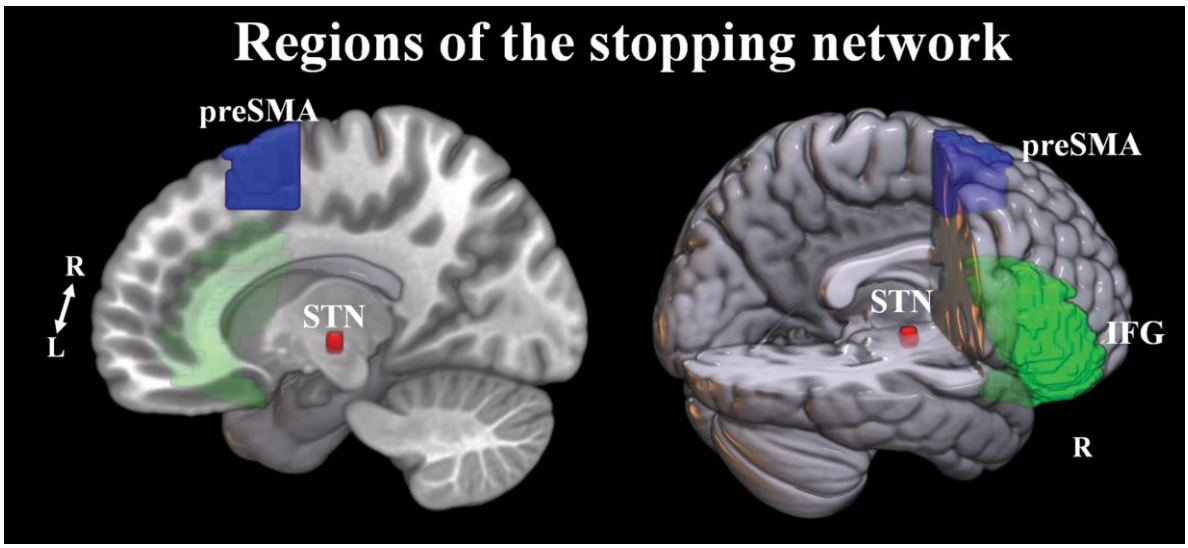

Figure 13. Representation of regions of the right-lateralized stopping network. preSMA = presupplementary motor area, STN = subthalamic nucleus, IFG = inferior frontal gyrus.

segregating the effects of response inhibition and attention have showed (Criaud & Boulinguez, 2013; Hampshire et al., 2010; Meffert et al., 2016). Therefore, alongside the stopping network, attentional mechanisms managed by the dorsal and ventral networks ensure that participants are able to complete the task without distractions. The dorsal network, comprising mostly bilateral areas, such as dorsal fronto-parietal regions (Corbetta et al., 2008), is responsible for maintaining alertness, through the top-down allocation of attention. The ventral network, comprising right-lateralized frontoparietal areas, such as the IFG (Cabeza et al., 2008; Corbetta et al., 2008), is responsible for shifting attention to reorient from one stimulus to another (Fan et al., 2005). Although segregated, both attentional networks interact to meet task demands. This flexible collaboration is orchestrated by the IFG and the middle frontal gyrus (Vossel et al., 2014).

3.3. Semantic network

There are multiple brain regions involved in semantic processing, comprising the IFG, the dorsomedial PFC, the ventromedial PFC, the cingulate gyrus, the inferior parietal lobe and the anterior and middle temporal gyrus (MTG) (Binder et al., 2009; Xu et al., 2016) (see Figure 14). Patients with semantic aphasia commonly have lesions in the left posterior lateral

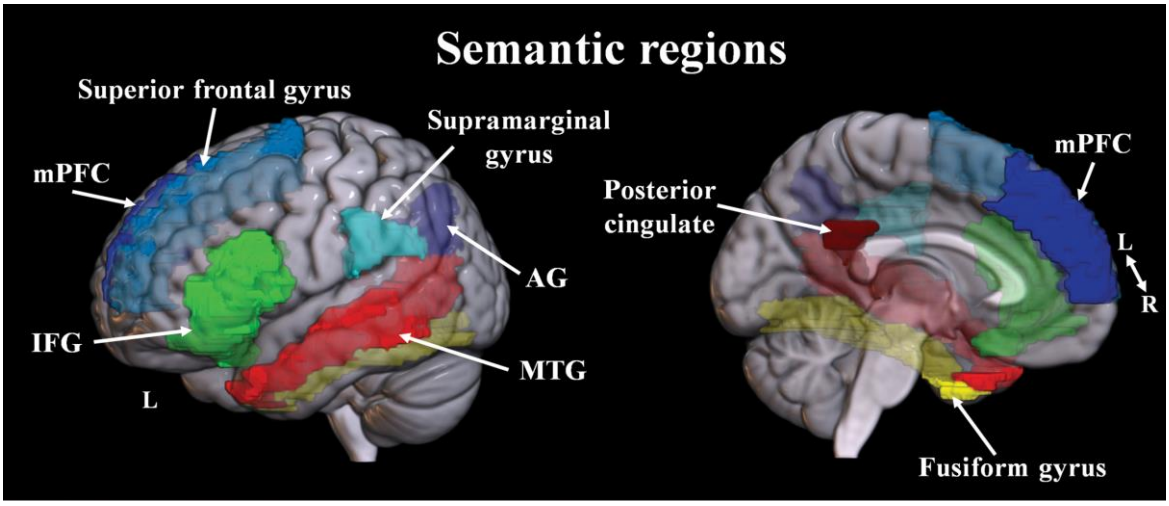

Figure 14. Representation of regions reliably involved in semantic processing, as presented in Binder and colleagues (2009)'s metanalysis. mPFC = medial prefrontal cortex, IFG = inferior frontal gyrus, AG = angular gyrus, MTG = middle temporal gyrus.

temporal cortex and AG, suggesting both regions are necessary for semantic processing. Additionally, stimulating left AG facilitates semantic integration (Price et al., 2016). Semantic regions are widely distributed across the brain with a predominance of the left hemisphere but not exclusively (Binder et al., 2009). These regions form the semantic network, which is anatomically interconnected through white matter pathways. Semantic tasks typically reveal activation in the nodes conforming this network, as well as significant co-activation among these nodes. (Fang et al., 2015; Xu et al., 2016).

The recruitment of the semantic system is mostly independent of the modality in which stimuli is presented (i.e., auditorily or visually). However, presenting words auditorily seems to activate the left MTG, left fusiform gyrus and right cerebellum more strongly than during visual presentation (Chee et al., 1997). The type of word, on the other hand, differentially engages the semantic system. For example, there is a vast literature on the processing of emotional vs. neutral words. Behaviorally, emotional words, particularly positive words, seem to be processed faster than neutral words (P. Chen et al., 2015). At the imaging level, Kuchinke and colleagues (2005) showed that emotional words activate left orbitofrontal gyrus and bilateral IFG to a greater extent than neutral words. Furthermore, the contrast Positive > Negative words revealed activation in frontal and temporal regions such as the superior frontal gyrus and the MTG.

4. Relevance

Due to the difficulty in detecting and treating an emerging ICD in PD patients, along with the devastating consequences it can have on these patients who already have a deteriorated quality of life, to understanding the mechanisms and consequences of ICD is vital. In the current doctoral dissertation, I investigate the neural correlates of the three domains described above (i.e., movement, response inhibition, and semantic processing) not with the aim of offering a complete understanding of ICD in PD, but to raise the interest of the cognitive neuroscience community in regard to this complication and the overarching consequences that seem to extend to multiple domains. This work is just a step forward,

examining three of numerous domains that can be altered in PD-ICD patients. Understanding the implications that ICD in PD has on patient's motor and cognitive domains, beyond the altered reward system, can help introduce additional therapeutic strategies to treat and rehabilitate these patients.

Empirical section

Chapter 5: General Methods

The three experiments presented in this thesis were collected in the same sample. Participants were included under the same selection criteria, they underwent the same motor and neuropsychological assessments, imaging took place in the same MRI scanner and the structural sequence used across experiments was the same. Therefore, to avoid repetition in the experimental chapters, all methodological commonalities will be described below.

1. Participants

A total of 59 participants took part in the experiments. Participants from three groups were selected: 21 PD-ICD patients, 18 PD-noICD patients and 20 HC participants. Not all participants described here have been included in the final sample of the three experiments. The reasons are several: a few participants did not complete the three tasks, some showed too much movement during one task but not necessarily during another, some performed poorly on a specific task. Although the characteristics of the sample will not vary greatly from what has been described here, the experimental chapters will detail information about the final sample analyzed in each experiment.

All PD patients were diagnosed according to the UK Parkinson's Disease Society Brain Bank criteria (Hughes et al., 1992). They were recruited from the Movement Disorders Unit of the Hospital Universitario Donostia, Spain. Exclusion criteria for all PD patients were dementia (Emre et al., 2007) and MCI according to the Movement Disorders Society Task Force criteria (Level II) (Litvan et al., 2012), presence of dyskinesias, brain surgery, or previous diagnosis of PD-ICD that had been resolved at recruitment. Additional inclusion criteria for the PD-ICD group included at least one ICD not present either at the time of PD diagnosis or before the initiation of dopamine replacement therapy. The ICD diagnosis was confirmed by a neurologist and a psychiatrist based on the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 2013) criteria and the Questionnaire for Impulsive-Compulsive Disorders in PD (Weintraub et al., 2009). Every PD-ICD patient scored above the cutoff for their ICD subtype in the Questionnaire for Impulsive-Compulsive Disorders in PD Rating Scale (QUIP-RS) (Weintraub et al., 2012). See more information on the QUIP-RS in section 2.3 below. HC participants were recruited from the Basque Center on Cognition, Brain and Language (BCBL)'s participants' pool. Exclusion criteria for HC participants was the presence of any neurological condition or any type of cognitive impairment. Details on the sample can be found in Table 1. The three groups underwent a comprehensive neuropsychological assessment to ensure they were cognitively healthy (see Table 2). The neuropsychological battery will be described below. This study was approved by the Gipuzkoa Clinical Research Ethics Committee. All participants were right-handed and had normal or corrected-to-normal vision. All participants provided written informed consent before joining the experiment.

Table 1. Demographic and clinical characteristics of the sample.

	Complete sample				*Experiment 1*				*Experiment 2*				*Experiment 3*			
	PD-ICD n = 21	**PD-noICD n = 18**	**HC n = 20**	**q**	**PD-ICD n = 17**	**PD-noICD n = 17**	**HC n = 20**	**q**	**PD-ICD n = 18**	**PD-noICD n = 17**	**HC n = 15**	**q**	**PD-ICD n = 18**	**PD-noICD n = 15**	**HC n = 19**	**q**
Age	62.24 (8.12)	61.67 (8.94)	62.35 (9.33)	0.978[a]	60.59 (7.1)	61.23 (9.02)	62.35 (9.33)	0.890[a]	63.33 (8.24)	61.65 (9.21)	61.87 (9.77)	0.837[a]	61.67 (7.74)	61.4 (8.28)	62.42 (9.58)	0.971[a]
Sex, male (%)	17 (85.71%)	15 (83.33%)	17 (85%)	0.978[b]	15 (88.24%)	14 (82.35%)	17 (85%)	0.890[b]	16 (88.89%)	14 (82.35%)	14 (93.33%)	0.837[b]	17 (94.44%)	13 (86.67%)	16 (84.21%)	0.731[b]
Education (years)	14 [7-20]	11.5 [7-20]	17.5 [5-20]	0.447[c]	16 [7-20]	12 [7-20]	17.5 [5-20]	0.575[c]	12.5 [7-20]	11 [7-20]	20 [5-20]	0.232[c]	15 [7-20]	12 [7-20]	20 [5-20]	0.385[c]
Premorbid IQ (WAIS-III Vocabulary)	44.29 (10.04)	45.17 (9.98)	49.9 (8.01)	0.300[a]	45.94 (9.28)	45.94 (9.72)	49.9 (8.01)	0.575[a]	42.94 (10.13)	44.82 (10.18)	50.2 (7.46)	0.203[a]	47 [21-58]	49 [24-55]	52 [31-62]	0.280[c]
Disease duration (years)	6 [1.7-16.4]	6 [2-19]	-	0.838[d]	7.26 (4.01)	7.56 (4.52)	-	0.890[e]	7.136 (3.96)	7.56 (4.52)	-	0.837[e]	7.476 (4.00)	6.836 (3.64)	-	0.731[e]
UPDRS-III	22 [8-46]	17.5 [10-30]	-	0.479[d]	22 [8-46]	17 [10-30]	-	0.539[d]	21.5 [10-46]	18 [11-30]	-	0.837[d]	22.94 (10.35)	17.6 (6.16)	-	0.203[e]
H&Y stage	2 [1.5-3]	2 [1-3]	-	0.447[b]	2 [1.5-3]	2 [1-3]	-	0.575[b]	2 [1.5-3]	2 [1-3]	-	0.837[b]	2 [1.5-3]	2 [1-2.5]	-	0.298[b]
$LEDD_{TOTAL}$ (mg)	1210 [450-2660]	771 [250-1664]	-	0.447[d]	1090 [450-1730]	792 [250-1664]	-	0.821[d]	970 [450-2660]	792 [250-1664]	-	0.837[d]	1168.75 [450-2660]	792 [250-1664]	-	0.513[d]
$LEDD_{L\text{-}DOPA}$ (mg)	801.38 (465.51)	566.86 (372.43)	-	0.251[e]	686.41 (341.22)	579.62 (379.81)	-	0.575[e]	750 [150-2080]	532 [150-1147.5]	-	0.702[d]	803.58 (504.37)	580.23 (372.91)	-	0.3293[e]
$LEDD_{DA}$ (mg)	240 [0-600]	270 [0-480]	-	0.978[d]	150 [0-600]	300 [0-480]	-	0.768[d]	194.83 (165.99)	211.76 (144.88)	-	0.837[e]	195 [0-600]	300 [0-480]	-	0.971[d]
HADS score	8 [1-25]	4.5 [1-10]	5 [0-16]	0.088[c]	7 [1-25]	4 [1-10]	5 [0-16]	0.148[c]	6.5 [1-25]	4 [1-10]	6 [1-16]	0.108[c]	7.5 [1-25]	5 [1-10]	5 [0-16]	0.128[c]
BIS_{TOTAL}	44.14 (18.34)	31.06 (8.16)	38.5 (13.76)	0.115[a]	44.94 (20.04)	30.59 (8.16)	38.5 (13.76)	0.148[a]	45 (18.1)	30.41 (7.92)	38.13 (14.12)	0.108[a]	46.56 (18.38)	30.67 (8.64)	38.63 (14.12)	0.096[a]
$BIS_{COGNITION}$	13.24 (6.07)	10.33 (3.73)	13.1 (4.96)	0.300[a]	13.76 (6.64)	10.06 (3.65)	13.1 (4.96)	0.301[a]	13.5 (5.85)	10.23 (3.82)	13.67 (4.79)	0.203[a]	14.11 (5.93)	9.73 (3.77)	13.21 (5.07)	0.141[a]
BIS_{MOTOR}	15.29 (6.78)	10.39 (4.68)	14.15 (5.95)	0.115[a]	15.59 (7.18)	10.29 (4.81)	14.15 (5.95)	0.148[a]	15 (6.48)	10 (4.51)	13.33 (6.25)	0.144[a]	16.17 (6.88)	10.93 (4.67)	13.95 (6.04)	0.144[a]
$BIS_{NONPLANNING}$	15.62 (8.89)	10.33 (3.51)	11.25 (6.28)	0.115[a]	11 [5-34]	9 [4-17]	9.5 [2-23]	0.575[c]	16.5 (9.18)	10.18 (3.56)	11.13 (6.67)	0.108[a]	16.28 (9.26)	10 (3.27)	11.47 (6.37)	0.128[a]
QUIP-RS score	17 [7-46]	0 [0-0]	0 [0-0]	<0.001[c]	17 [8-30]	0 [0-0]	0 [0-0]	<0.001[c]	16.5 [7-46]	0 [0-0]	0 [0-0]	<0.001[c]	17.5 [8-46]	0 [0-0]	0 [0-0]	<0.001[c]

Note: Values expressed in Mean (SD) for normally distributed variables, in Median [Range] for other variables.

[a] One factor ANOVA; [b] Chi-Square Likelihood Ratio; [c] Kruskall-Wallis; [d] U Mann Whitney; [e] Two-sample T-test.

Abbreviations: IQ = Intelligence Quotient; WAIS-III = Wechsler Adult Intelligence Scale-III; UPDRS = Unified Parkinson's Disease Rating Scale; H&Y = Hoehn and Yahr scale; $LEDD_{TOTAL}$ = Total levodopa equivalent daily dose was calculated according to the formula described by Tomlinson et al. (2010); $LEDD_{L\text{-}DOPA}$ = Levodopa equivalent daily dose was calculated using the same formula; $LEDD_{DA}$ = Levodopa-equivalent daily dose of dopamine agonist calculated with the previous formula; HADS = Hospital Anxiety and Depression Scale; BIS = Barratt Impulsiveness Scale; QUIP-RS = Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale.

Table 2. Neuropsychological information of the sample.

	Complete sample				***Experiment 1***				***Experiment 2***				***Experiment 3***			
	PD-ICD n = 21	**PD-noICD n = 18**	**HC n = 20**	**q**	**PD-ICD n = 17**	**PD-noICD n = 17**	**HC n = 20**	**q**	**PD-ICD n = 18**	**PD-noICD n = 17**	**HC n = 15**	**q**	**PD-ICD n = 18**	**PD-noICD n = 15**	**HC n = 19**	**q**
MoCA	26 [16-29]	25.5 [19-30]	27 [23-30]	0.449[a]	26.41 (1.77)	25.71 (2.84)	26.65 (1.90)	0.572[b]	26 [16-29]	26 [19-30]	27 [24-30]	0.363[a]	26.17 (1.89)	25.93 (2.55)	26.63 (1.95)	0.711[b]
Digit span *forwards*	6 [4-8]	5.5 [4-7]	6.5 [4-9]	0.064[a]	6 [4-8]	5 [4-7]	6.5 [4-9]	0.125[a]	6 [4-7]	6 [4-7]	7 [4-9]	0.070[a]	6 [4-8]	5 [4-7]	7 [4-9]	0.065[a]
Digit span *backwards*	4 [2-7]	4 [2-14]	5 [3-8]	0.045[a]	4 [4-7]	4 [2-14]	5 [3-8]	0.125[a]	4 [2-5]	4 [2-14]	5 [3-7]	0.070[a]	4 [3-7]	4 [2-14]	5 [3-8]	0.065[a]
LNS	11 [6-13]	9.5 [3-13]	12 [6-15]	0.064[a]	11 [6-13]	10 [6-13]	12 [6-15]	0.125[a]	11 [6-13]	9 [3-13]	12 [6-15]	0.075[a]	11 [6-13]	10 [6-13]	12 [6-15]	0.065[a]
TMT-A (s)	43 [15-86]	31 [19-77]	36 [21-75]	0.384[a]	40 [15-81]	30 [19-67]	36 [21-75]	0.572[a]	42.5 [15-86]	30 [19-77]	37 [21-75]	0.363[a]	40.5 [15-86]	30 [19-67]	35 [21-75]	0.591[a]
TMT-B (s)	91 [49-212]	82 [48-731]	71 [49-250]	0.304[a]	80 [49-145]	82 [48-509]	71 [49-250]	0.572[a]	97.5 [49-212]	82 [48-731]	67 [50-250]	0.277[a]	86 [49-190]	82 [48-509]	71 [49-250]	0.490[a]
Stroop test (words-colors)	32.9 (11.91)	36.72 (10.90)	41.5 (11.33)	0.165[b]	34.35 (11.58)	37.82 (10.15)	41.5 -11.33	0.334[b]	31.65 (12.33)	37 (11.17)	41.93 (12.07)	0.147[b]	36.67 (11.63)	36.47 (10.02)	41.42 (11.63)	0.386[b]
RAVLT total recall	44.9 (7.94)	42.61 (13.29)	51.85 (8.65)	0.064[b]	46.59 (7.80)	44.06 (12.15)	51.85 (8.65)	0.156[b]	45.28 (9.03)	41.88 (13.32)	52.8 (9.03)	0.070[b]	45.78 (8.26)	43.8 (12.96)	51.84 (8.89)	0.210[b]
RAVLT delayed recall	9.38 (2.94)	8.06 (4.53)	10.15 (3.00)	0.304[b]	9.88 (3.02)	8.53 (4.18)	10.15 (3.00)	0.543[b]	9.33 (2.99)	8 (4.66)	10.33 (3.06)	0.318[b]	6 [3-15]	9.5 [3-13]	11 [5-15]	0.663[a]
RAVLT recognition	14 [4-15]	12 [3-15]	14 [6-15]	0.304[a]	14 [4-15]	12 [10-15]	14 [6-15]	0.506[a]	14 [4-15]	12 [3-15]	14 [6-15]	0.604[a]	14 [4-15]	12 [10-15]	14 [6-15]	0.446[a]
Phonemic fluency	15.67 (5.38)	13.83 (1.16)	18.05 (5.74)	0.147[b]	17.06 (4.92)	14 (4.23)	18.05 (5.74)	0.156[b]	14.94 (5.08)	14.12 (4.11)	18.53 (5.10)	0.090[b]	16.11 (4.86)	13.73 (4.18)	17.84 (5.82)	0.219[b]
Semantic fluency	20.62 (5.93)	20.61 (6.38)	23.15 (5.09)	0.384[b]	22.47 (4.94)	21.29 (5.86)	23.15 (5.09)	0.572[b]	20.78 (5.88)	20.88 (6.47)	23.53 (4.39)	0.363[b]	21.44 (5.86)	20.87 (5.62)	22.89 (5.10)	0.674[b]
Boston naming test	13 [6-15]	13 [7-15]	13.5 [8-15]	0.449[a]	13 [9-15]	13 [8-15]	13.5 [8-15]	0.572[a]	12.5 [6-15]	13 [7-15]	14 [8-15]	0.318[a]	13 [9-15]	13 [8-15]	13 [8-15]	0.711[a]
VOSP object decision	17 [11-19]	16.5 [11-20]	16 [11-20]	0.240[a]	16.76 (2.08)	16.76 (2.56)	15.5 (2.04)	0.334[b]	17 [12-19]	16 [11-20]	16 [12-18]	0.231[a]	17 [11-19]	17 [11-20]	16 [11-20]	0.300[a]
VOSP number location	10 [7-10]	10 [5-10]	10 [8-10]	0.792[a]	10 [8-10]	10 [5-10]	10 [8-10]	0.572[a]	10 [7-10]	10 [5-10]	10 [8-10]	0.920[a]	10 [7-10]	10 [5-10]	10 [8-10]	0.756[a]

Note: Values expressed in Mean (SD) for normally distributed variables, in Median [Range] for other variables.

[a] Kruskall-Wallis; [b] One factor ANOVA.

Abbreviations: MoCA = Montreal Cognitive Assessment; LNS = Letter-Number Sequencing; TMT = Trail Making Test; RAVLT = Rey Auditory Verbal Learning Test; VOSP = Visual Object and Space Perception Battery.

2. Batteries

2.1. Motor testing

Given the importance of a good characterization of participants with PD, they underwent an in-depth assessment to allow us to match the PD-ICD and PD-noICD groups in their PD stage at time of assessment, their current motor state, and the amount and effect of medication. A neurologist assessed the participants with the two most important PD scales: the Hoehn and Yahr scale (HY) and the Unified Parkinson's Disease Rating Scale (UPDRS). The UPDRS score was obtained under the effect of the dopaminergic drugs.

The **HY scale** (Hoehn & Yahr, 1967) defines five broad stages of PD disease progression, with stage 1 being the milder, when a person just meets the criteria for diagnosis, to stage 5, where the person is no longer independent. Specifically, patients in stage 1 present motor impairment exclusively in one side of the body, with minimal or no functional involvement. In stage 2, the motor impairment is bilateral, but balance is preserved. In stage 3, motor impairment is more severe, postural reflexes are affected and patients may be restricted in some activities, although they maintains their independence. In stage 4, patients are incapacitated by the motor impairments although they can stand or walk without help. In stage 5, patients are no longer able to move unassisted, and are confined to bed or a wheelchair when there is no help. As described, progression on the scale is associated with motor deterioration (Bhidayasiri & Tarsy, 2012). The scale was designed to classify how the motor symptoms of PD progress (Hoehn & Yahr, 1967), and its broadly defined stages do not aim to capture all the complexity of the symptoms experienced at a specific timepoint for a patient with PD. It is however commonly used for its simplicity and it gives a general idea of the state of the patient. Patients included in the study ranged from stage 1 to stage 3. Therefore, the included patients with milder PD presented motor symptoms restricted to one side of the body (stage 1) that interfered minimally or not at all in their daily living; while the patients with more severe PD presented motor symptoms bilaterally, started showing impaired postural reflexes (stage 3), and their daily living may

have been mildly restricted while maintaining independence. The reasons for patient selection being skewed towards the initial stages are that patients needed to be cognitively unimpaired to avoid functional alterations related to cognitive dysfunction and ensure adequate task performance. In addition, to successfully undergo the imaging acquisition, patients needed to be able to stay still inside the scanner for a prolonged period, which excludes patients with severe motor impairments.

The second PD evaluation tool used, the **UPDRS** (Fahn et al., 1987). It is the most used scale in clinical research and practice (Movement Disorder Society Task Force on Rating Scales for Parkinson's Disease, 2003) assessing the degree of disability and impairment in PD (Martínez-Martín et al., 1994). It is comprised of four parts, assessing different aspects of the disease. Part I assesses non-motor aspects experienced daily such as the cognitive and mental state. Part II assesses motor activities of daily living, such as eating, walking or talking. Part III is the most commonly used section of the UPDRS (Movement Disorder Society Task Force on Rating Scales for Parkinson's Disease, 2003), as it comprises the motor exploration. Unlike in Part II where the patients were asked how they handled certain activities on day-to-day basis, in Part III the clinicians assess the impairment of different motor aspects after exploring the patients and asking them to perform certain actions. Specifically, speech, facial expression, hand tremor, rigidity, bradiquinesia, postural reflexes, gait, and the quality of the movement of extremities are evaluated in this part. Finally, Part IV assesses complications linked to treatment. In order to match the PD-ICD and the PD-noICD group, we focused on Part III to have a more detailed understanding of the current motor state of the patient than what is possible with only the HY scale. The patients included in the current thesis showed a mean score of 19.72/108, confirming the mildness of the disease of the included patients as indicated by the HY scale.

2.2. Neuropsychological testing

In order to assess if participants were cognitively unimpaired, they completed an extensive neuropsychological battery to ensure they did not have MCI according to the Movement Disorders Society Task Force criteria (Level II) (Litvan et al., 2012) nor dementia (Emre et al.,

2007). Participants completed a test to evaluate global cognition and at least two tests in each cognitive domain assessed: attention and working memory, executive functions, language, memory, and visuospatial functions. Impairment in each test was operationalized as a performance 1.5 standard deviations below that of a sample of 34 age matched healthy controls. Following Litvan and colleagues' (2012) guidelines, patients with impaired scores in two tests were considered to have a cognitive impairment at least amounting to MCI, and therefore excluded. The neuropsychological battery, divided by domains, is the following:

- **Global cognition:** The **Montreal Cognitive Assessment (MoCA)** (Nasreddine et al., 2005) is a ten minute cognitive screening tool. It is widely used to detect MCI and dementia in patients with PD (Dalrymple-Alford et al., 2010; Hoops et al., 2009). We used the MoCA as a tool to evaluate global severe impairments, but no patient was excluded based on their MoCA scores exclusively. In order to follow the Movement Disorders Society Task Force Level II criteria to assess cognitive impairment, any global cognition test needs to be complemented with two specific assessments per cognitive domain below.
- **Attention and working memory:** Participants were assessed on the **Digit Span test** in both Forward and Backward modalities. This test is a subtest of the Wechsler Adult Intelligence Scale version III (WAIS-III) (Wechsler, 1997). Participants were asked to repeat number strings that increased in length as they responded correctly. In the *Forward modality*, participants had to repeat the numbers as they heard them, engaging attention and maintenance. In the *Backward modality* participants had to retain and manipulate the order of the numbers in the string to repeat them from last to first number heard, therefore recruiting both components of working memory: maintenance and manipulation (Baddeley & Hitch, 1974). We also administered the **Letter Number Sequencing Task,** another subtest from the WAIS-III (Wechsler, 1997), as an additional measure of working memory, although visuospatial working memory and processing speed have also been shown to explain task performance (Crowe, 2000). In this task participants heard a random sequence of words and letters, and they had to repeat the sequence in a certain order: starting with numbers from lower to higher, and then repeating the letters in alphabetical order. Participants also completed the **Trail Making Test part A (TMT-A)**, adapted from

Partington's pathway test (Partington & Leiter, 1949), measuring attention and processing speed. Participants had to connect 25 numbered circles in ascending order as quickly as possible.

- **Executive functions:** Participants completed three tests targeting executive functions. Following TMT-A, they completed the **TMT part B** (**TMT-B)** in which participants were presented with 25 circles that this time include a letter or a number inside each circle. They had to connect the circles alternating between number and letter, the numbers in increasing order, the letters in alphabetical order, in the following manner: 1, A, 2, B and so on. They were asked to do it as quickly as possible. To perform the test, participants needed to flexibly switch between number and letter, always keeping track of which element of both categories they connected last. Another test assessing executive functioning is the **phonemic fluency task**, in which participants were asked to produce as many words as possible starting with the letter 'p' in one minute. Although a linguistic task, it is often regarded as measuring executive functions (Lezak et al., 2012) since, in order to produce multiple exemplars, participants should devise a word retrieval and recall system, that needs to get more refined as time passes to avoid repeating items while accessing new ones, along with inhibiting competitors that do not meet the criteria (i.e., proper names, verbs) (Henry & Crawford, 2004). The last measure of executive functions was the **Stroop test** (Golden, 1978). In this test, participants went through three stages: First, they were given a sheet with a list of words that represent colors (i.e., blue, yellow, green, red) and were asked to read them aloud as quickly as possible. Second, they received a sheet with colored 'X's in the same four colors they read before and were asked to name the colors they saw as quickly as possible. Finally, they saw a sheet with a list of words that represent colors, as in the first stage, but this time the words were colored, as in stage two. They were asked to name the colors they saw as quickly as possible, neglecting the written word. This last stage evaluates divided attention and interference resistance (Peña-Casanova et al., 2004).
- **Language:** Participants were assessed in two language tasks: semantic fluency and the Boston Naming Test. For **semantic fluency**, participants had one minute to name as many animals as possible. In a similar way as phonemic fluency, this task includes other components in addition to semantic retrieval which are not purely linguistic.

However, it was selected as a language measuring task since its reduced difficulty compared to phonemic fluency reduced the executive load of the task. The other linguistic task, the **Boston Naming Test** (Kaplan et al., 2001), required participants to name the objects upon seeing their drawing, with word frequency decreasing to modulate difficulty.

- **Memory:** The **Rey Auditory Verbal Learning Test** (Schmidt, 1996) was used to assess auditory memory through the test's three components: immediate recall, delayed recall and recognition. Participants were initially presented auditorily with a list of 15 words. The list was repeated five times, and after each repetition participants were prompted to repeat as many words as they can remember. The sum of all the words repeated during the five attempts constituted the *immediate recall* score. Participants were then tested on other domains for 20 minutes, to avoid rehearsal, after which they were asked to recall as many words as possible, which constituted the *delayed recall* part of the task. Finally, *recognition* was assessed by reading to participants a list that included words they have memorized and new words, and they had to identify which words they had heard before and which they had not.
- **Visuospatial function:** Participants completed two subtests of the Visual Object and Space Perception Battery (Peña-Casanova et al., 2009; Warrington & James, 1991). For the **Object Decision test** participants saw twenty matrices of four shapes and they had to identify the real shape in each matrix. For the **Number Location test**, participants went through ten trials of randomly distributed numbers in a square. For each square, participants were presented with a same-sized square that only contained a dot. The dot represented the position of a number in each trial, a number that participants had to identify.

2.3. Impulsivity scales

Given the relevance for this work of impulsivity and on ICD developed as a complication in PD patients, correcting assessing impulsive behaviors and ICD typology was necessary. To do so, participants completed the QUIP-RS (Weintraub et al., 2012) and the Barratt Impulsiveness Scale (BIS-11) (Patton et al., 1995).

The QUIP-RS has been specifically designed to measure the severity of ICD and related disorders occurring in PD patients (Weintraub et al., 2012). The QUIP-RS allows the assessment of pathological behaviors associated with gambling, buying, sexual conducts, and eating. It also evaluates ICD-related disorders hobbysim, punding and compulsive medication use. Different cutoff scores have been established for each ICD providing a sensitivity and specificity greater than 80%: pathological gambling ≥ 6, compulsive shopping ≥ 8, pathological hypersexuality 8 ≥ and binge eating ≥ 7. Finally, the composite score represents the severity of the patient's ICD. The QUIP-RS can also help evaluating if the patient is experiencing single or multiple pathological behaviors. The QUIP-RS has become a useful tool in clinical and research practice, and has been translated and validated in multiple languages (e.g., Marques et al., 2019; Martinez-Martin et al., 2018; Probst et al., 2014).

In the current sample, the characteristics and severity of the ICD on PD-ICD patients was confirmed by the QUIP-RS. Regarding the different pathological behaviors, one participant met the cutoff for pathological gambling, six for compulsive shopping, 9 for pathological hypersexuality, and 9 for binge eating. Out of the 21 patients with PD-ICD, 11 of suffered combined ICDs, while 10 suffered single ICDs.

The other scale used, the BIS-11, is a 30-item questionnaire that measures trait impulsivity. It is the most common self-reported measure of impulsivity and it is heavily used in research (Ireland & Archer, 2008; Stanford et al., 2009). Specifically, analyses carried by the authors suggested it measures attentional impulsivity (i.e., the easiness to lose focus across different tasks), motor impulsivity (i.e., acting on impulse), and nonplanning impulsivity (i.e., lack of planning) (Patton et al., 1995). Yet, the different factors measured by the BIS-11 have been considered instable (Reise et al., 2013; Vasconcelos et al., 2012). In this work we considered the BIS-11 total and derived scores as measures of trait impulsivity, as opposed to the pathological and more complex implications of ICD. A total score of 74 or higher is considered to designate individuals with high impulsivity (Patton et al., 1995), although a more conservative cutoff of 72 has been proposed more recently (Stanford et al., 2009).

The BIS-11 has been employed in multiple clinical settings, including PD patients with and without ICD (Stanford et al., 2009). Despite PD patients presenting higher scores than HC in this scale (Nombela et al., 2014), the BIS-11 score has been associated with the severity of the ICD in PD-ICD patients but not with ICD prevalence (Marín-Lahoz et al., 2018). In the current sample, participants of all groups scored well below the cutoff score of 74, which can be interpreted as participants manifesting controlled personality traits, opposed to impulsive traits, despite being PD-ICD, PD-noICD or HC participants. Overall, PD-ICD patients scored higher, despite group differences being not statistically significant (see Table 1).

3. Statistical analyses

Statistical analyses on demographic, neuropsychological, behavioral variables as well as ROI and pairwise FC analyses were performed on JASP Version 0.13.1. Outlier removal for ROI and FC values was performed discarding values three standard deviations above or below the mean. We checked the normality of the distributions through the Shapiro-Wilk test, and when necessary, homogeneity of variances was checked via Levene's test. Demographic and neuropsychological between-group differences were examined in the following way: differences between the three groups were tested with one-way ANOVA test if the variable was normally distributed, and with Kruskal-Wallis test if it was not normally distributed. Differences between two groups, when variables were only applicable to PD-ICD and PD-noICD participants, were tested with 2-tailed Student T-test if the variable was normally distributed; or with U-Mann Whitney test if it was not normally distributed. Nominal (i.e., sex) and ordinal (i.e., Hoehn and Yahr scale) variables were analyzed using Chi-square tests. FDR-corrected p-values, this is q-values, were applied when multiple analyses were executed, unless otherwise indicated.

4. MRI acquisition

Imaging data were obtained at the BCBL 3T Siemens Magnetom TIM Trio MRI scanner (Siemens Medical Solutions, Erlangen, Germany) using a 32-channel head coil. All PD patients were under the effects of their usual dopaminergic medication during MRI scanning. Ear plugs and snug-fitting headphones (MR Confon, Madgeburg, Germany) were used to dampen scanner noise as well as to allow communication with experimenters while participants were in the scanner. Head movement was limited by adding padded foam to the area between the participants' head and the coil. In addition, participants were asked to remain as still as possible.

Participants underwent the same scanning routine, including functional and structural sequences. Structural T1-weighted images were acquired with a MPRAGE sequence with repetition time (TR) = 2530 ms, echo time (TE) = 2.97 ms, inversion time = 1100 ms, flip angle (FA) = 7 º, field of view (FoV) = 256 x 256 mm, 176 slices, and voxel size = 1 mm^3. Details for the three functional sequences included in this thesis will be described in their corresponding chapter, since they vary as a function of each of the used functional tasks.

5. MRI data analysis

SPM8 (Wellcome Centre for Human Neuroimaging, London) was used to perform standard preprocessing routines and analyses. Slice-timing correction was conducted and images were realigned to the first volume by means of rigid-body transformation. Next, for processing normalized data in the experiments, spatial smoothing, motion correction, co-registration, and normalization were implemented. First, spatial smoothing was applied with a 4-mm full width at half maximum (FWHM) isotropic Gaussian kernel. After smoothing, motion parameters obtained at the realignment step were used for a volume repair procedure (ArtRepair; Stanford Psychiatric Neuroimaging Laboratory) that detects bad volumes depending on within-scanner movement and signal fluctuations, then corrects

them via interpolation. Volume-by-volume correction was applied with a motion and signal fluctuation threshold different for each experiment. We adapted the threshold to the sample in each experiment. We increased the motion threshold to up to a 1mm in two of the tasks. The clinical nature of the sample prompted us to be more liberal with the thresholds than we would have been with healthy participants, while still ensuring the quality of the data. Threshold details of each experiment will be provided in its corresponding chapter.

Once outlier volumes had been corrected, structural and functional volumes were co-registered and spatially normalized to the T1-weighted and echo-planar imaging templates, respectively. The normalization algorithm used a 12-parameter affine transformation together with a non-linear transformation involving cosine basis functions. During normalization, the volumes were sampled to 3 mm cubic voxels. Templates were based on the MNI305 stereotaxic space. Then, a second spatial smoothing using a 7 mm FWHM isotropic Gaussian kernel was applied. Lastly, a 128 sec high-pass filter was used to eliminate noise coming from slow drifts or signals. This concluded the standard preprocessing carried out in the three experiments for normalized data. Please note that in Experiment 1 we also analyzed the data in the individual space, with a different smoothing and resampling to the one described above, and with no normalization performed. The detailed explanation will be found below in Chapter 7, section 2.4.

After preprocessing, statistical analyses were performed on individual participant's data applying the GLM. The fMRI time series data were modeled by a series of events convolved with a canonical hemodynamic response function. The relevant conditions for each experiment were modelled, and the produced functions were entered as covariates in a GLM, together with the motion parameters for translation (x, y, and z) and rotation (yaw, pitch, and roll), which were entered as covariates of no interest.

6. Structural group comparison analyses

With the aim of examining gray matter differences as a factor of group, the T1-weighted images of all participants were processed with the standard Freesurfer 6.0.0 recon-all pipeline. Then, data was resampled in common space, concatenated in a single file and spatially smoothed through the mris_preproc command. Finally, the program mri_glmfit was executed to perform GLM analysis on all the corticography measures available in Freesurfer (i.e., surface, thickness, and volume) to test differences as a function of group.

Chapter 6: General Results

1. Demographic and clinical results

There were no statistically significant differences between groups on age, years of schooling, and premorbid intelligence, as measured by the Vocabulary subtest of the WAIS-III. The three groups also showed no statistically significant differences in their anxiety and depression scores, as measured by the Hospital Anxiety and Depression Scale (HADS) (Herrero et al., 2003; A. S. Zigmond & Snaith, 1983), or in their impulsivity scores, measured by the BIS-11 (Patton et al., 1995). PD-ICD participants showed higher scores in the QUIP-RS, the scale to measure ICD in PD (Weintraub et al., 2012). Within the PD-ICD group, the distribution of ICD subtypes was heterogeneous. Eleven PD-ICD participants (52%) showed a single ICD, while the rest showed combined ICDs. The most common ICD was binge eating, experienced by 9 patients (43%), followed by pathological hypersexuality and hobbysm, both experienced by 8 (38%) (see Supplementary Table 1 in Appendix for more details). PD-ICD and PD-noICD groups showed no differences in the motor stage of the disease, measured by the HY and UPDRS-III scales, nor in disease duration or levodopa daily dose (see Table 1 for more details).

Regarding neuropsychological testing, groups only differed in their score in the Backward modality of the Digit Span (q = .45), one of the tasks assessing working memory. Post-hoc U-Mann Whitney tests showed the HC group had performed better at the task than the PD-ICD (q = 0.003) and PD-noICD (q = 0.021) participants, while there was no difference between PD-ICD and PD-noICD groups (q = 0.855). This group difference has no implications for the experiments performed by the sample for two reasons. First, as the Movement Disorders Society Task Force states in its Level II criteria for cognitive impairment, one test per domain is not enough to consider cognitive impairment, requiring two impaired tests to consider a patient has cognitive impairment (Litvan et al., 2012). Yet, there were no between group differences in the Letter Number Sequencing task, which assesses working memory in a similar fashion, suggesting HC participants do not generally show better working memory skills than PD participants. And second, while the group difference in the Digit Span Backwards holds for the whole sample, it is not significant in the specific samples included in any of the three experiments. No other neuropsychological group differences were found (see Table 2 more details).

2. Structural imaging results

After analyzing the T1-weighted images of all participants, we found no between-group differences in surface area, cortical thickness, and cortical volume, with a cluster forming correction of $p < .05$ per vertex. The absence of structural group differences is probably due to recruited PD patients being in the initial stages of the disease (Sarasso et al., 2021).

Chapter 7: Experiment 1

1. Introduction

In Experiment 1, we aimed to investigate a central element of PD that has barely received attention in association with PD-ICD. There are strong suggestions that the motor network may be differentially affected in PD-ICD patients beyond the impact of PD. As presented in Chapter 2, section 1.1, PD-ICD patients have been characterized as showing abnormal VS functioning, with increased dopamine release and reduced DAT binding in the VS (Aracil-Bolaños & Strafella, 2016; O'Sullivan et al., 2011; Rao et al., 2010; Steeves et al., 2009). However, metabolic changes seem to extend beyond the VS into the putamen (Premi et al., 2016) and frontal regions (Joutsa et al., 2012; J.-Y. Lee et al., 2014). Building on the abnormal dopaminergic functioning specific to PD-ICD patients, a resting-state fMRI study has shown reduced FC between anterior putamen and frontal areas, as well as a tendency towards functional disconnection between posterior putamen and premotor areas in these patients (Carriere et al., 2015). Premi and colleagues (2016) confirmed the disconnection of the frontostriatal network in patients with PD-ICD, proposing the left putamen at the center of the disconnection. Therefore, on top of the major alterations of the BG and Mthal present in PD patients, PD-ICD patients present altered functioning of the putamen, a central node of

the BG, and reduced connectivity with frontal regions compared to their PD-noICD counterparts. The differential functioning of the putamen in PD-ICD patients prompts the question of the effect of PD-ICD specific abnormalities on the motor system at the activation and FC levels.

To examine the functioning of the motor network, we utilized a sequential finger-tapping task that would require the putamen to perform its role on motor control, engaging with the DTCT pathway in a feedback loop by receiving afferents from M1 and projecting to the Mthal. We selected all ROIs in the individual-subject level space and performed all ROI and FC analyses at the individual level to maximize our chances of observing a differential functioning of the motor network as a function of group, if such effect was indeed present. In addition to suffering from abnormal impulsivity, it has been suggested that PD-ICD patients may need a greater dosage of levodopa to maintain a similar motor functioning level than PD-noICD patients (Voon et al., 2014). Therefore, we were also interested in investigating if the amount of levodopa and other severity-related factors linked to PD (i.e., disease duration and motor score in the UPDRS-III) were associated with the functioning of the motor network in PD-ICD patients, despite PD severity-related factors not being different between both PD groups.

In this experiment, we investigated the differential neural correlates of sequential finger-tapping for patients with PD-ICD, and two control groups: patients with PD-noICD and HCs. We did so by examining the activation of key motor nodes along the DTCT (i.e., the DN, the VLp of the Mthal, and the M1 region) as well as the putamen. We examined the activation and FC of these regions bilaterally during sequential finger-tapping of the left and of the right hand.

2. Methods

2.1. Participants

The final sample consisted of fifty-four participants, divided in three groups as follows: 17 PD-ICD patients (Mean Age = 60.58 years, Mean Disease Duration = 7.2 years, 3 Female), 17 PD-noICD patients (Mean Age = 61.2 years, Mean Disease Duration = 7.5 years, 1 Female), and 20 HC participants (Mean Age = 62.35 years, 2 Female). Out of the initial sample of 59 participants three participants did not complete the task (two PD-ICD and one PD-noICD), and two additional PD-ICD participants were excluded for excessive head motion during fMRI scanning (see section 2.4 for more details).

2.2. fMRI data acquisition

Functional images were acquired in one functional run using a gradient-echo echo-planar pulse sequence with the following acquisition parameters: TR = 3000 ms, TE = 28 ms, 41 contiguous 3 mm^3 axial slices, 10% inter-slice gap, FA = 90º, FoV = 192 x 192 mm. 79 volumes of interest were collected in a single run. The first 4 volumes of each run were discarded to allow for T1 equilibration effects.

2.3. fMRI paradigm: Sequential finger-tapping

Inside the scanner, participants completed a block design finger-tapping task. Participants completed finger-tapping blocks corresponding to the left or to the right hand, separated by a 16 s rest period (see Figure 15). A total of four blocks per hand were scanned per participant, alternating left- and right-hand blocks. During each block of 12 s, participants saw arrows pointing to the left or right, indicating which hand they had to use. Whenever they saw an arrow, they were asked to sequentially tap the tip of the thumb with the tip of the other four fingers of the same hand until the arrow disappeared. Before performing the in-scanner task,

participants completed a practice version outside the MR scanner to ensure the task had been understood correctly as well as participants' capability to perform the task.

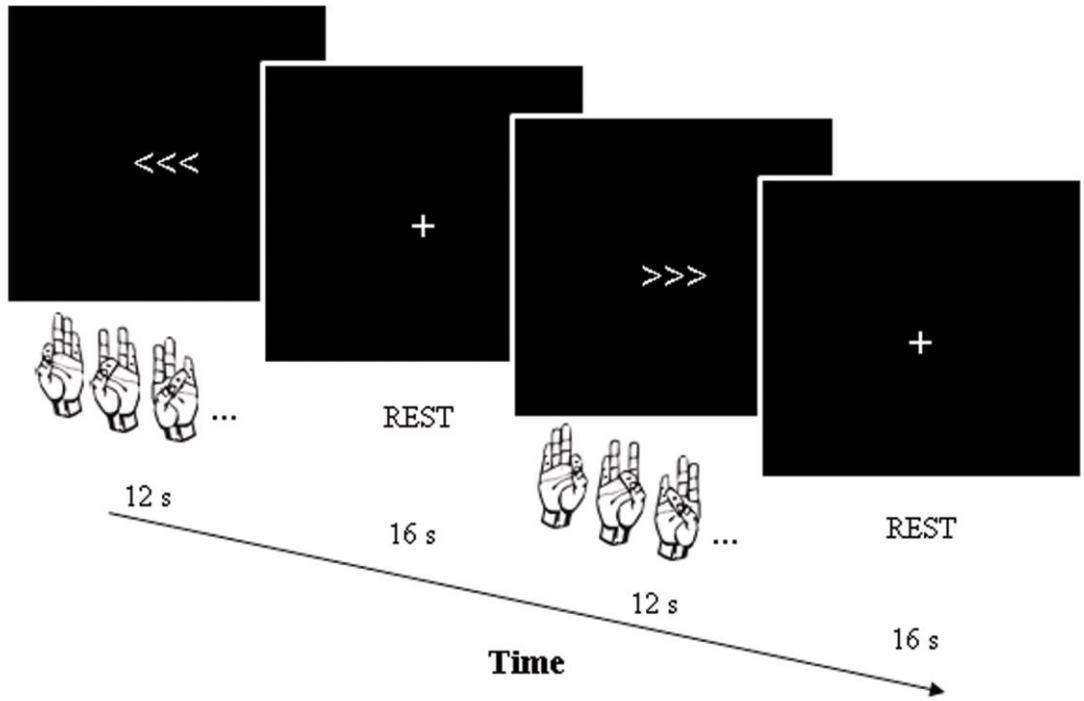

Figure 15. Schematic representation of the sequential finger-tapping task.

2.4. MRI data analysis

SPM8 was used to perform standard preprocessing routines and analysis. We conducted slice timing correction and spatial smoothing as described in Chapter 5, section 5. The threshold for volume correction was 1mm for motion and 1.3% for signal fluctuation. Those participants who required correction of more than 25% of total functional volumes or who presented a drift over 3 mm in any run were removed from the final sample (i.e., two PD-ICD participants). There were no differences in the proportion of corrected volumes per group ($F_{2,51} = 0.34$, $p = 0.72$, $\eta_p^2 = 0.01$). To perform whole-brain contrasts, we used normalized data executing the remaining steps of preprocessing (i.e., registration, normalization, last spatial smoothing, and temporal filtering) as described in Chapter 5, section 5. Nevertheless, our main interest was to analyze ROI and connectivity data on the individual space. For that, we analyzed the data without normalizing it, resampling functional images to 1 mm cubic

voxels, the voxel resolution of the T1-weighted images. Before applying ArtRepair, we performed a spatial smoothing of 2 mm, the only smoothing applied to the data.

Statistical analyses were performed on individual participant's data applying the GLM. The fMRI time series data were modeled by a series of events convolved with a canonical hemodynamic response function. Two fMRI experimental conditions were modelled (i.e., left, right), corresponding to the hand completing the finger-tapping. Each condition was analyzed separately as epochs from the onset of the block. The study followed a 3 (Group: PD-ICD, PD-noICD, HC) by 2 (Conditions: left, right) experimental design. We had a main comparison of interest: *Left* > *Right* which allowed us to observe motor regions associated with one hand versus the other, eliminating additional components such as attentional or proprioceptive components.

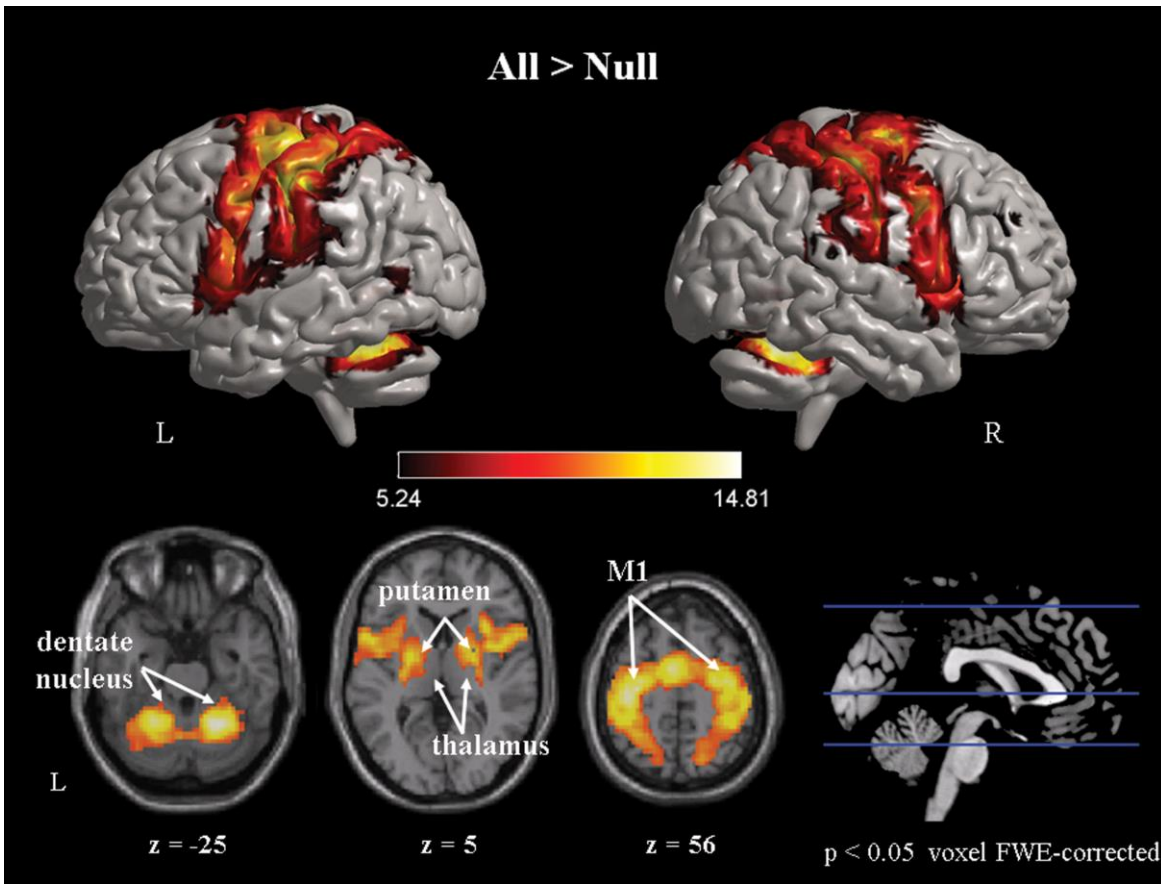

Figure 16. Brain renderings and axial sections showing activations for the whole-brain contrast All > Null for all participants at a statistical threshold of $p < 0.05$ voxel FWE-corrected.

To confirm the expected task activation, we performed whole-brain contrasts in the normalized dataset. We used the least-squares parameter estimates of the height of the best-fitting canonical hemodynamic response function (HRF) for each condition. Contrast images were computed on a participant-by-participant basis. These images were then used for the group analysis where we looked at activations across all subjects as well as separately for the three groups. At the group level, whole-brain contrasts of interest were calculated by performing a one-sample t-test on the images, considering participants as a random effect. The finger-tapping observed in the contrast All > Null revealed the expected activation pattern (see Figure 16).

Specific analyses were carried out in the four relevant motor ROIs: three key regions of the DTCT motor pathway (i.e., M1, DN, and VLp) and in the motor control component of the BG, the putamen. ROIs were obtained from each subject, on native space (see Figure 17 for an example). Due to the extent of the M1 and DN, we used the task as a localizer to pinpoint the local maxima of each subject. fMRI contrasts Left > Null and Right > Null were plotted for each subject to locate the local maximas in the M1 and DN, bilaterally (see Figure 17*A*). Those local maximas were used as center of 3 mm radius ROIs, built for each participant using the MARSBAR toolbox (Brett et al., 2002) for SPM8. Subcortical structures were extracted from atlases: to do so, first the T1-weighted images were analyzed using FreeSurfer 6.0.0. The putamen was extracted from Freesurfer's standard segmentation, while the VLp was extracted from a probabilistic thalamic atlas (Iglesias et al., 2018) included in FreeSurfer (see Figure 17*B*).

All ROIs were extracted bilaterally. We therefore extracted two ROIs for the M1, the DN and the VLp, one corresponding to the left, and another to the right region. We extracted scaled percent signal changes (Mazaika, 2009) for the bilateral M1, DN, VLp and putamen at the individual subject level. Before performing any analyses, we controlled for participants' degree of manual proficiency. This was necessary as the finger-tapping task provided no behavioral measure and each PD patient presented a slightly different motor profile. By controlling for the quality of participants' manual movement, we ensured that the effect of the hemibody more affected in each PD patient and the individual level of manual impairment suffered by PD patients would not confound our results. We operationalized manual proficiency by employing the three items assessing the degree of motor impairment

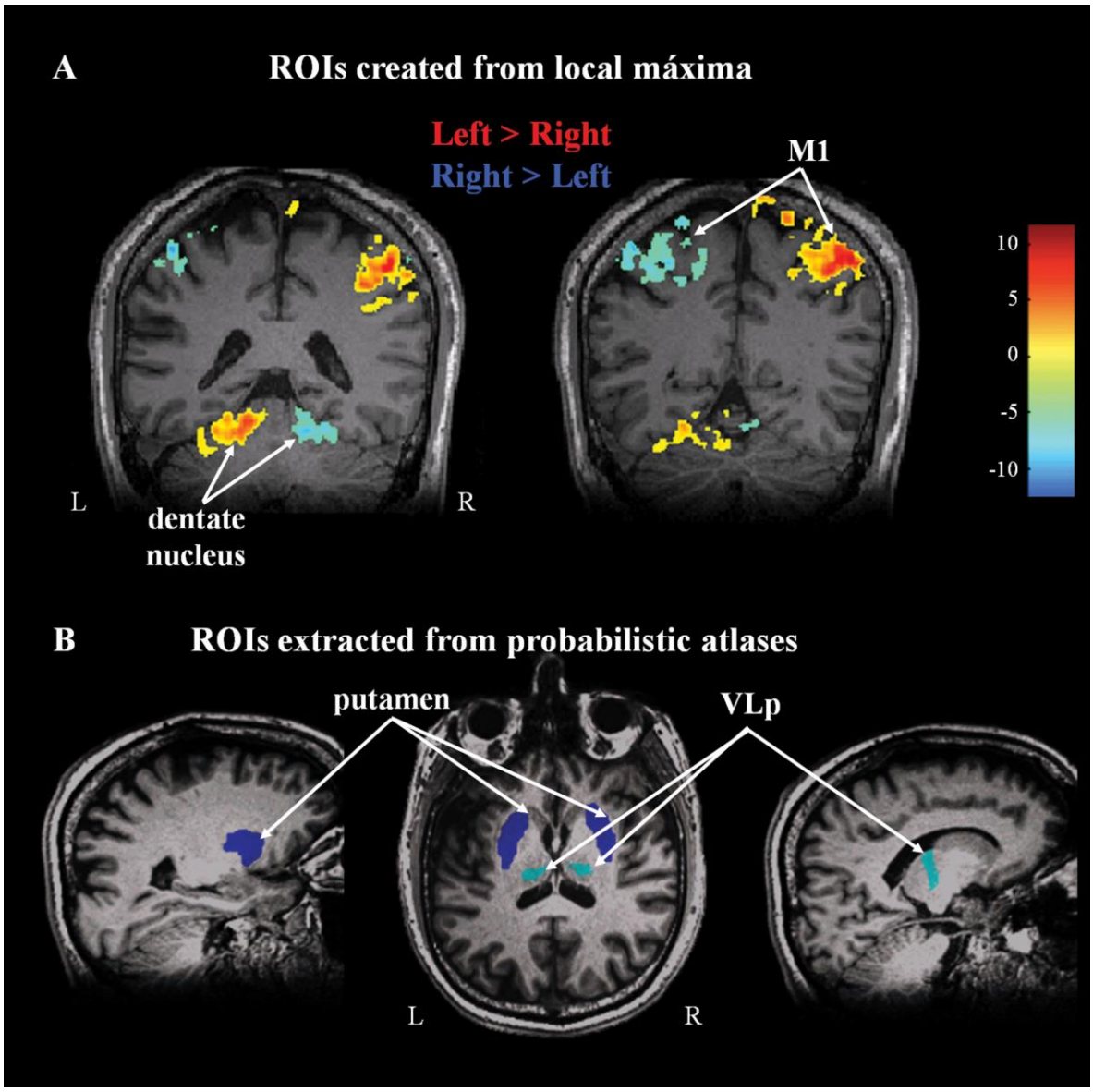

Figure 17. Example of selected ROIs in individual-subject space. (A) ROIs created based on a local maxima were the M1 and the DN. (B) ROIs extracted from atlases: VLp and putamen.

of each hand of UPDRS-III: tapping of index against thumb, opening-closing movements of the whole hand, and finally pronation-supination movements of each hand in a vertical position. The quality of the movement was assessed from 0, no impairment, to 4, almost unable to perform the movement, based on speed and amplitude of the movement. For each participant, we calculated their manual proficiency index by adding the three indices of each hand and subtracting the values of the right hand to those of the left (Left hand - Right hand), to simulate our contrast of interest Left > Right. For each ROI, we generated studentized

residuals to remove the effect of manual proficiency. These values will be our dependent variables in ROI analysis.

We then generated studentized residuals of the scaled percent signal changes of each ROI using the subtracted value mentioned above. We first performed confirmatory 2 (Condition: Left, Right) repeated measures ANOVA on the residualized scaled percent signal change of each ROI. Then, for the contrast Left > Right, we analyzed the residualized scaled percent signal change group differences in each ROI through a 3 (Group: PD-ICD, PD-noICD, HC) ANOVA. In addition, we examined associations between ROI activation parameters for the contrast Left > Right and PD severity-related factors: disease duration, daily levodopa intake ($LEDD_{L\text{-}DOPA}$) and motor state (UPDRS-III). With that aim, we conducted two-tailed Spearman correlation analyses between residualized ROI values and the disease severity-related factors for each PD group, correcting for multiple comparisons ($q < 0.05$, FDR). To further examine the relationship of each regressor (disease duration and $LEDD_{L\text{-}DOPA}$) with the residualized activation of the ROIs for each PD group, we used linear regression. The R package lsmeans:lstrends was used to estimate and compare the slopes of both groups (Lenth, 2016).

To better understand the dynamics of the differential pattern of associations with disease severity-related factors observed in PD-ICD, we conducted mediation analysis between the PD severity-related factors disease duration and $LEDD_{L\text{-}DOPA}$ and activation of the regions significantly associated with them. Following the four steps process described by Baron and Kenny (1986), a significant mediator appears when the relationship between the ROI activation and a PD severity-related factor ceases to be significant after controlling for the mediator.

To examine interactions between motor regions, we investigated FC via the beta-series correlation method (Rissman et al., 2004) implemented in SPM8 with custom Matlab scripts. The canonical HRF in SPM was fit to each occurrence of each condition. The beta values, the resulting parameter estimates, were sorted according to the conditions of interest to create a condition-specific beta series per voxel. Pairwise FC analyses were executed for Left > Null and Right > Null contrasts calculating beta-series correlation values for the co-activation between regions showing a differential association pattern with disease

factors in PD-ICD. Due to the nature of the correlation coefficient, restricted in a range of -1 to +1, and in order to make the underlying distribution approach that of a normal distribution, we applied an arc-hyperbolic tangent transformation to the beta-series correlation (Fisher, 1921). We examined group differences by conducting 3 (Group: PD-ICD, PD-noICD, HC) by 2 (Putamen: Left, Right) mixed model ANCOVA of the FC for the contrasts Left > Null and Right > Null using the right VLp as seed and controlling for manual proficiency of the appropriate hand selected in each contrast. We included the left and right putamen as factor in the ANCOVA to take into account ipsilateral connections and capture the network fully, as we have been doing during ROI analysis. We performed the ANCOVAs for the contrasts Left > Null and Right > Null to consider the relationship between both hands, since previous results suggested the imbalance between non-dominant and dominant hands was relevant. We applied multiple comparisons correction ($q < 0.05$, FDR) to the ANCOVAS and follow-up tests.

3. Results

3.1. Demographic and clinical data

There were no statistically significant differences between groups in age, years of education, and premorbid intelligence measured by the WAIS-III's Vocabulary subtest (see Table 1). PD-noICD and PD-ICD groups did not differ in time since diagnosis, daily dose of dopaminergic medication or motor severity measured by the HY scale and UPDRS-III.

3.2. MRI results

3.2.1. Whole-brain analyses

To show the activation elicited by our finger-tapping task, we employed the normalized dataset to compute whole-brain functional contrasts for Left > Right and Right > Left across participants. We applied a voxel-level correction of $p < 0.05$ FWE to verify the contralateral activation of the motor cortex and subcortical motor structures along with ipsilateral activation of the cerebellum. We confirmed the expected motor activation corresponding to the movement of each hand (see Figure 18). This analysis was just intended to verify the expected activation associated with a finger-tapping task. For specific analyses, we performed ROI analyses in the subjects' individual space.

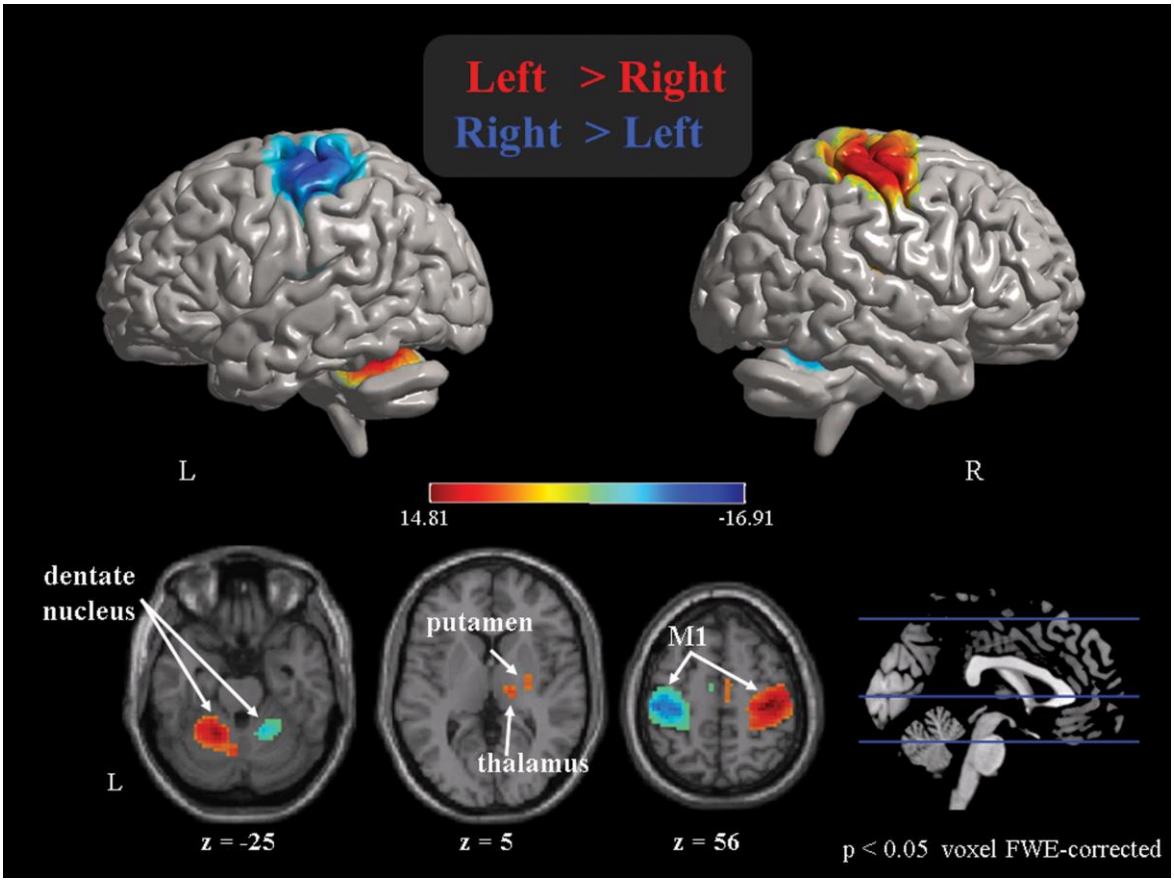

Figure 18. Brain renderings and axial sections showing activations for the whole-brain contrast Left > Right for all participants at a statistical threshold of $p < 0.05$ voxel FWE-corrected.

3.2.2. ROI analyses

To further confirm the expected contralateral and ipsilateral involvement of each ROI, we performed a repeated measures ANOVA per ROI that showed significant contralateral activation of the M1 and right VLp ($Fs > 20.4$, $ps < 0.001$, $\eta_p^2 > 0.28$), significant ipsilateral activation of the DN ($Fs > 10.46$, $ps < 0.002$, $\eta_p^2 > 0.16$), and no significant laterality differences of the putamen and the left VLp ($Fs < 0.11$, $ps > 0.74$, $\eta_p^2 < 0.002$). Due to the bilateral involvement of the putamen, a concept previously reported in the literature (Marchand et al., 2008; Whishaw et al., 1986), following analyses were performed combining left and right putaminal ROIs. To assess differential activation as a function of Group we run a one-way ANOVA per ROI. We found no group differences ($Fs < 1.15$, $ps > 0.3$, $\eta_p^2 < 0.05$).

Posteriorly, within the PD groups we run correlation analysis between the residualized activation of each ROI for the contrast Left > Right and the PD severity-related factors of interest (i.e., disease duration, $LEDD_{L\text{-}DOPA}$, and UPDRS-III score). We analyzed these associations separately for the PD-ICD and PD-noICD groups. Exclusively within the PD-ICD group, we found the activation of the right VLp was positively associated with disease duration ($rs_{16} = .79$, $q = 0.001$) and $LEDD_{L\text{-}DOPA}$ ($rs_{16} = .55$, $q = 0.011$). Similarly, the bilateral putamen correlated positively with disease duration ($rs_{16} = .74$, $q = 0.001$) and $LEDD_{L\text{-}DOPA}$ ($rs_{16} = .51$, $q = 0.04$). These results suggest that increased values in these two PD severity-related factors (i.e., disease duration and $LEDD_{L\text{-}DOPA}$) are associated with greater right VLp and putamen activation. Also for the contrast Left > Right, the left VLp showed a similar pattern with weaker associations that did not survive multiple comparisons correction both for disease duration ($rs_{16} = .51$, $q = 0.06$) and $LEDD_{L\text{-}DOPA}$ ($rs_{16} = .55$, $q = 0.06$). The remaining regions, M1 and DN, did not show these associations ($ps \geq 0.2$). We found no associations between these ROIs and UPDRS-III score ($ps \geq 0.9$). We computed the same analyses on the PD-noICD group and found no associations ($ps \geq 0.4$).

We used linear regression to further compare the different patterns of association between the PD groups (see Figure 19*A*). We found a significant interaction in the relationship of Group to disease duration with the activation of the right VLp for PD-ICD ($B = 0.014$) and PD-noICD ($B = 0.002$); $F_{2,30} = 5.61$, $p = 0.024$, indicating the difference in slopes between the groups. For the relationship of Group to disease duration with the activation of

the bilateral putamen for PD-ICD (*B* = 0.013) and PD-noICD (*B* = 0.002) we found a similar significant interaction as presented above ($F_{2,30}$ = 5.1, *p* = 0.031). We found a marginal interaction for the relationship of Group to $LEDD_{L\text{-}DOPA}$ with the activation of the right VLp for PD-ICD (*B* = 0.0013) and PD-noICD (*B* = 0.00007); $F_{2,30}$ = 3.06, *p* = 0.091; and similarly for the activation of the putamen for PD-ICD (*B* = 0.0014) and PD-noICD (*B* = 0.0001); $F_{1,30}$ = 3.00, *p* = 0.094. Interactions between disease severity-related factors and Group in the linear regression confirm that the slopes derived from the correlation of right VLp and putamen activation with disease duration and $LEDD_{L\text{-}DOPA}$ are different as a function of group (see Figure 19*A*). Notice the slope values do not represent the slope between these disease severity-related factors and the activation, since ROIs' activation represents residualized activation after controlling for manual proficiency, which scales down activation and slope values.

We performed mediational analyses to better understand the dynamics of the association between Left > Right activation in the subcortical motor structures and disease

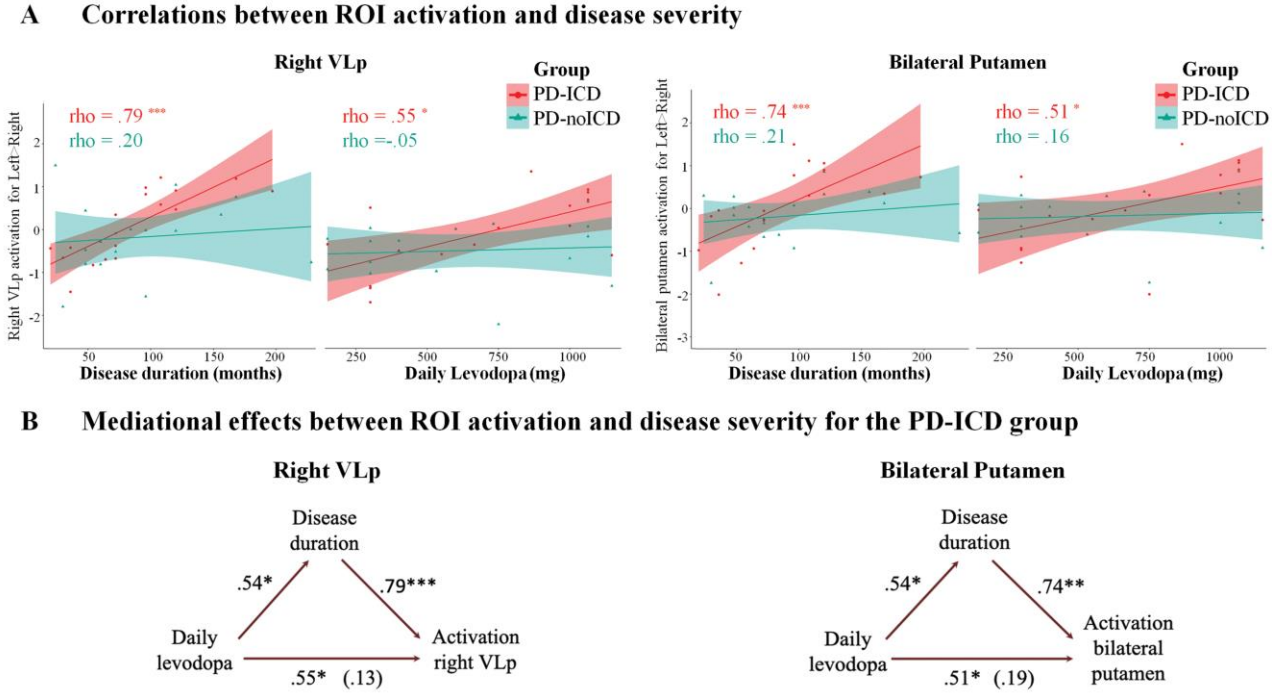

Figure 19. Brain-behavior regression analyses. (A) Correlations between right VLp and bilateral putamen Left > Right ROI activation and disease severity factors for PD-ICD (in red) and PD-noICD (in green) participants. (B) Mediation analyses showing that in PD-ICD patients the factor disease duration mediates associations between daily levodopa consumption and right VLp and bilateral putamen ROI activation.

severity-related factors: disease duration and $LEDD_{L\text{-}DOPA}$. The mediational analysis between the residualized activation of the right VLp and disease severity-related factors revealed that disease duration mediated the association between $LEDD_{L\text{-}DOPA}$ intake and the activation of the right VLp ($F_{2,16} = 15.08$, $p < 0.001$), significantly increasing the explained variance of right VLp activation ($\Delta R^2 = 0.394$). Similarly, the mediational analysis on the residualized activation of the bilateral putamen revealed disease duration mediated the association between $LEDD_{L\text{-}DOPA}$ and putamen activation ($F_{2,16} = 6.85$, $p = 0.008$), significantly increasing the explained variance of putamen activation ($\Delta R^2 = 0.242$) (see Figure 19*B*).

3.2.3. Functional connectivity analyses

We examined the pairwise FC of Left > Null and Right > Null between the bilateral putamen and the right VLp, the regions showing an ICD specific mediation effect with PD severity-related factors. Our aim was to investigate if, despite the lack of activation differences, these ICD-sensitive-regions showed a differential connectivity pattern between groups. For Left > Null, we found a Group effect ($F_{2, 51} = 4.29$, $q = .020$, $\eta_p^2 = .14$), while there was no significant difference for the contrast Right > Null ($F_{2, 51} = 0.11$, $q = 0.471$, $\eta_p^2 = .004$). The group effect in Left > Null increased when controlling for the motor proficiency of the left hand ($F_{2, 50} = 6.11$, $q = 0.004$, $\eta_p^2 = .20$), while controlling for the right hand in Right > Null contrast did not affect the results ($F_{2, 51} = 0.19$, $q = 0.435$, $\eta_p^2 = .007$). To follow up on the Left > Null contrast's main effect, we performed post-hoc t-tests. We observed that the PD-ICD group showed a reduced FC compared to the PD-noICD ($t_{32} = 2.950$, $q = 0.033$, $d = .34$) and to the HC group ($t_{35} = 3.48$, $q = 0.016$, $d = .47$) (see Figure 20).

4. Discussion

In Experiment 1, our objective was to investigate the functioning of the motor network in PD-ICD patients, and two control groups: patients with PD-noICD and HCs. With the use of a sequential finger-tapping task, we examined the activation and FC of main motor nodes

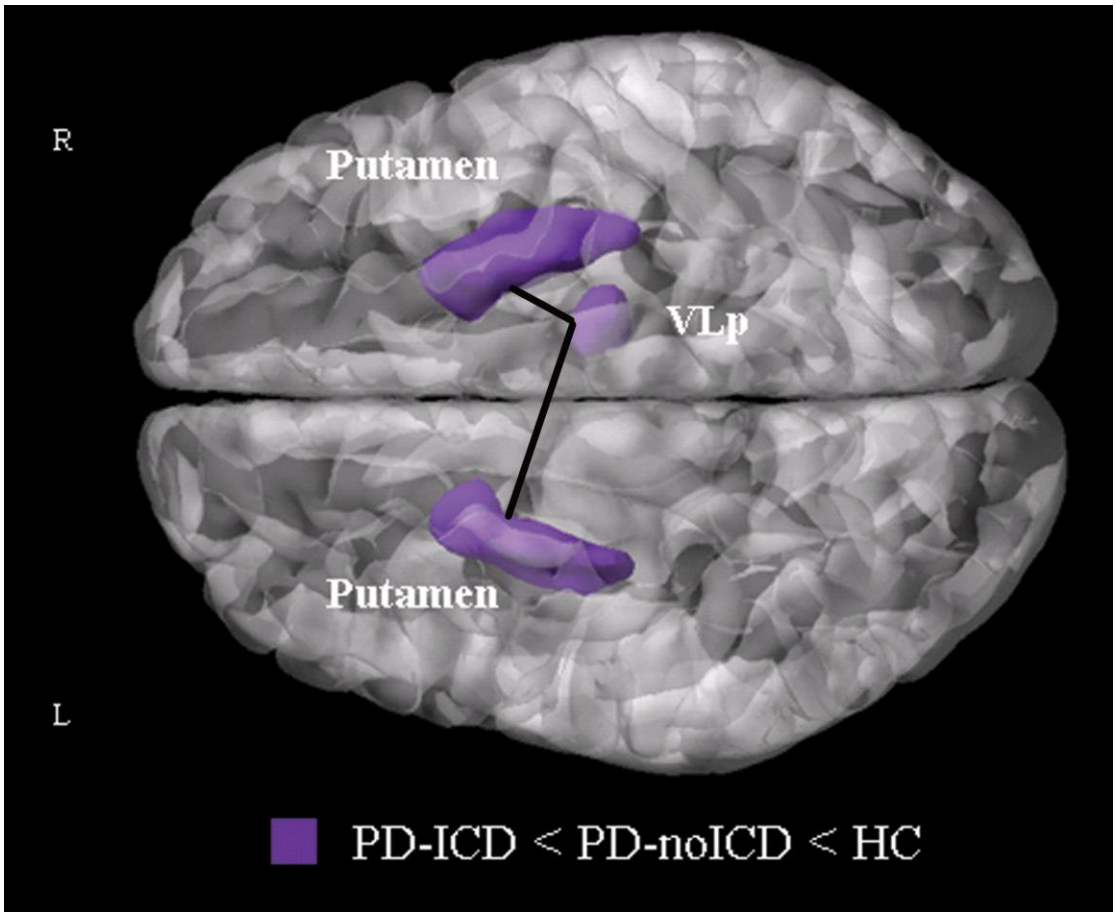

Figure 20. Differential pairwise functional connectivity for left hand activation against null, showing a graded reduction in the functional connectivity strength, with the HC showing the strongest functional connectivity, the PD-ICD group showing the weakest functional connectivity, and the PD-noICD group being intermediate in functional connectivity to the other two groups.

along the DTCT (i.e., the dentate nucleus, the VLp of the Mthal, and the M1 region) as well as the putamen, responsible for motor control, and affected by PD (Playford et al., 1992; Seibyl et al., 1995). The putamen is also specifically altered in PD-ICD, which is reflected in its reduced connectivity with frontal regions (Carriere et al., 2015; Premi et al., 2016). We expected to find a differential recruitment of the motor network for PD-ICD participants, compared to the PD-noICD and HC participants, as a result of the additional changes brought by the ICD.

The sequential finger-tapping task showed the expected activation in all participants, indicating the mainly ipsilateral involvement of the DN, and the contralateral recruitment of the right VLp and M1, with bilateral activation of putamen regardless of the hand used in the

finger-tapping task (i.e., left or right). Despite finding no differences in activation of the examined ROIs as a function of group, we found group differences in the associations between disease severity-related factors (i.e., disease duration and $LEDD_{L\text{-}DOPA}$) and activation of the subcortical motor structures for the contrast Left > Right. These associations were significant exclusively in the PD-ICD group. Positive associations between right VLp and putamen activation with disease duration and $LEDD_{L\text{-}DOPA}$ indicate that, as disease's duration increases and exposure to higher dosage of dopaminergic medication is prolonged in time, these regions would tend towards a hyperactive state. These differential associations suggest that, in PD-ICD patients, the right VLp and bilateral putamen are specifically affected by chronic dopaminergic stimulation during motor execution. In fact, the direction of the associations resembles the modulation levodopa has on the activation of Mthal and putamen in PD-noICD patients, with these regions being the more sensitive to the effect of medication (Kraft et al., 2009).

Both severity-related factors, disease duration and $LEDD_{L\text{-}DOPA}$, are intertwined in the progression of typical PD. As neurodegeneration advances, patients require progressively increased dopaminergic dosage (Carrarini et al., 2019; Nyholm, 2007). The longer a patient has had PD, the more the PD pathology would have affected cortical and subcortical regions and the greater the $LEDD_{L\text{-}DOPA}$ dosage. It is this prolonged exposure to dopaminergic drugs which will trigger ICD in certain patients and change the functioning of the VS, accounting for the pathological behaviors. Therefore, both disease duration and $LEDD_{L\text{-}DOPA}$ have a particular relevance for PD-ICD patients, as they are directly linked to such complication. This is, the degree to which these subcortical structures are affected by PD will have a repercussion on how much impact will additional alterations brought by ICD have on the functioning of these regions. Interestingly, we found no significant associations between the score in the UPDRS-III and any of the activation of the motor regions here examined. It is possible that the differential impact of medication on the right VLp and putamen allows a similar motor performance, therefore masking any associations with UPDRS-III scores. Alternatively, it is possible that the differential pattern of associations is related to the sequential component of the finger-tapping task, an aspect of movement not assessed in the UPDRS-III. We suggest that, in PD-ICD patients, the prolonged exposure to high doses of

dopaminergic medication is not only affecting the VS eliciting the abnormal impulsivity, but also the motor striatum and right VLp.

The VLp of the thalamus is the region that processes input from cerebellum, motor cortex and BG to then relay it back to M1 to initiate movement (Hamani et al., 2006). Given that we are focusing on the activation for Left > Right hand, it is congruent to observe the associations with activation of right VLp, mostly involved in contralateral movements. As presented in the introduction, dopaminergic depletion affects the thalamus (Blesa et al., 2016; Monje et al., 2020; Pifl et al., 2013), altering its shape in PD patients (McKeown et al., 2008). In addition, the VLp is a specifically targeted region in tremor treatment (Gross et al., 2004). Importantly, PD patients included in this study did not suffer from a tremor-dominant PD, since tremor would have interfered with MRI scanning. The positive association of right VLp with indicators of disease severity in PD-ICD patients during finger-tapping indicates that this region is not only relevant for parkinsonian tremor, but also shows functional changes associated to motor performance in PD-ICD. The putamen, key region for motor control (Lehéricy et al., 2006), suffers from dopaminergic degeneration associated to PD pathology (Playford et al., 1992). Importantly, the degree of dopamine depletion in the putamen is related to the severity of bradykinesia and rigidity in PD patients (Seibyl et al., 1995). It is expectable that dopaminergic degeneration related to PD pathology weakens the integrity of the putamen enabling the abnormal connectivity of the putamen with other regions in PD-ICD patients compared to PD-noICD groups (Carriere et al., 2015; Premi et al., 2016). Therefore, the associations between activation of putamen during finger-tapping and the combined effects of PD duration and $LEDD_{L\text{-}DOPA}$ found here would be the effect of chronic dopaminergic stimulation eliciting ICD on an altered motor striatum.

While not observing between-group differences in the activation of right VLp nor putamen, we should note that our PD sample was in the early-mid stages of the disease. As subcortical activation and disease severity-related factors are positively correlated in PD-ICD patients, PD-ICD patients with increased disease duration and $LEDD_{L\text{-}DOPA}$ are likely to show hyperactivation of right VLp and putamen compared to their counterparts. Furthermore, we found a mediational effect of disease duration over the association between $LEDD_{L\text{-}DOPA}$ and the activation of right VLp and bilateral putamen. This mediational effect means that disease duration modulates the effect of medication over the subcortical motor regions examined.

Therefore, higher levels of chronic dopaminergic medication maintained over a long period of time seem to alter the functioning of these regions, similarly to the way in which the VS is affected by chronic dopaminergic exposure in these patients with ICD. Given that medication dosage is influenced by the PD stage of the patient, and the extent of PD duration, among other factors, the direction of the mediational effect is not surprising. We suggest that the associations and mediational effects being restricted to the PD-ICD group is indicative of the effect of prolonged medication intake over the motor network, and therefore not limited to the VS like previously thought.

Lastly, our FC analyses showed PD-ICD patients' reduced co-activation between right VLp and bilateral putamen during Left > Null blocks, in comparison with PD-noICD and HC groups. This reduced FC between motor subcortical regions goes in line with Carriere and colleagues' (2015) finding of a tendency towards reduced co-activation between the posterior putamen and premotor areas, as well as with the proposed theory of putamen as a hub for frontostriatal disconnection observed in PD-ICD patients (Premi et al., 2016). The motor network is able to perform the task with a reduced co-activation of these motor regions, which are affected by PD severity-related factors, and whose increasing malfunction will be more evident as disease progresses. Although we did not find any increased FC between nodes of the motor network for the PD-ICD group, compensating reduced co-activation between right VLp and putamen, it is important to highlight that i) the distinct associative pattern between activation and disease severity-related factors and ii) the reduced co-activation were observed after correcting for manual proficiency. This result indicates that PD-ICD patients operate at a similar level with an altered motor network functioning since the reduced FC that does not affect their motor output.

Activation and FC results should not be understood in isolation but as related indicators of the functioning of the motor network. Interestingly, the tendency towards hyperactivation of right VLp and putamen as disease duration and dopaminergic stimulation increase portrays the opposite activation pattern observed in PD-noICD patients. fMRI studies show that when tested OFF medication, PD-noICD patients show hypoactive putamen and thalamus during movement (Mallol et al., 2007; Spraker et al., 2010; Yu et al., 2007). Taken together with the tendency towards right VLp and putamen hyperactivation as chronic dopaminergic stimulation lengthens over time, the reduced co-activation between

right VLp and putamen suggests an inherent motor facilitation in PD-ICD patients. This is, the differential effect of prolonged exposure to dopaminergic medication in PD-ICD patients could alter the functioning of the motor network, by facilitating movement, and therefore requiring less co-activation at the network level. Therefore, the differential pattern of associations and the observed reduced co-activation suggests an increased dopaminergic stimulation of the right VLp and putamen, akin to an exaggerated effect of medication, this is, an exaggerated ON state in PD-ICD patients. This exaggerated ON state would aggravate as disease progressed and the patients' exposure to increased doses of dopaminergic treatment continued. An exaggerated ON state in PD-ICD patients could be linked to the tendency towards increased motor impulsivity of these patients that we found. Although not significant after multiple corrections, PD-ICD patients showed a tendency towards increased action impulsivity, measured by the Motor subscale of the BIS-11 (see Table 1).

Critically, this study is the first to find differences in motor regions and their FC in PD-ICD patients during a motor task. In addition, identifying right VLp and bilateral putamen, as regions sensitive to maintained dopaminergic stimulation during long periods of time in PD-ICD patients increases the relevance of their reduced co-activation. The specificity of our results to the PD-ICD group suggests that the reduced co-activation between putamen and right VLp is associated with suffering from ICD. Alterations associated with ICD are reflected on the dopaminergic fiber degeneration in striatal and extrastriatal regions (Aracil-Bolaños & Strafella, 2016; J.-Y. Lee et al., 2014), connectivity changes (Carriere et al., 2015; Premi et al., 2016; Verger et al., 2018) and, as shown here, altered the functioning of the motor network. This alteration of regions affected by PD could predispose PD-ICD patients differently to chronic medication intake, creating a susceptibility for hyperactivity in the right VLp and putamen as disease progresses and exposure to dopamine is maintained over prolonged periods of time. We suggest that, on PD-ICD patients, dopaminergic medication could be having a similar effect on the motor striatum and right VLp as it does on the VS, leading to altered functioning of related regions (Navalpotro-Gomez et al., 2019).

Finally, it must be remarked that the positive associations that occurred with activation during the Left > Right contrast in addition to FC changes for Left > Null, indicate that the relationship between disease duration and $LEDD_{L\text{-}DOPA}$ with subcortical activation is related to finger-tapping with the left hand. Due to standard fMRI participation criteria, all

our participants were right-handed. Therefore, the differential association pattern and abnormal FC occur due to a distinct functioning of the non-dominant hand movements. While moving their non-dominant hand, patients with PD-ICD recruited right VLp and bilateral putamen to a degree that was positively associated with disease severity-related factors, which did not happen while they moved their dominant hand. Similarly, the PD-ICD group showed a reduced connectivity between right VLp and putamen during non-dominant hand finger-tapping. Whether this effect is related to an imbalance between the dominant and the non-dominant motor networks needs to be confirmed by including a left-handed group in future studies.

Future studies on PD-ICD patients should consider the impact of ICD on the motor network and try to answer some unresolved questions: Is motor performance affected by the reduced FC between putamen and right VLp in PD-ICD patients? What are the different motor functional correlates between patients with PD-noICD and PD-ICD depending of the stage of PD they are in? Is the effect we observe related to a weaker network for the non-dominant hand or is it related to inherent structural differences between hemispheres?

4.1. Conclusions

This study is the first to show a differential functioning of motor regions in a sample with PD-ICD patients. In the scanner, participants performed a sequential finger-tapping task that relayed the expected ipsilateral and contralateral activation for each ROI (i.e., putamen, VLp, M1 and DN), while showing no between-group differences. However, the PD-ICD group exclusively displayed distinct association patterns between subcortical motor activation and disease severity-related factors. This pattern of associations indicates that the right VLp and the putamen are particularly sensitive to prolonged medication intake in PD-ICD patients. Along with FC results showing a reduced connectivity between the motor subcortical structures examined for this group, this study shows that PD-ICD participants recruit the motor network differentially to the two control groups after controlling for manual proficiency. Therefore, the ICD on PD patients has an additional effect on the motor network

related to elevated levels of dopaminergic stimulation over a long period of time, which results in altered FC of its subcortical components.

Chapter 8: Experiment 2

1. Introduction

In Experiment 2 our objective was to investigate the neural correlates of response inhibition in patients with medication-induced increased impulsivity. Based on previous studies (Claassen et al., 2015; Filip et al., 2018), we expected PD-ICD participants to perform at the same level as the two control groups, and therefore we expected to capture compensatory mechanisms enhancing their performance, via compensation along the stopping network and its interplay with attentional mechanisms. We expected PD-ICD patients to engage in different compensatory mechanisms depending on different inhibitory aspects.

To test response inhibition, we utilized a naturalistic version of the demanding conditional SST (Logan et al., 1984). Compared to other classical response inhibition tasks (e.g., Go/No-Go) the SST paradigm is particularly challenging and differs from other classical response inhibition tasks because it requires participants to stop an action that has already been initiated. This makes the SST particularly demanding for PD-ICD subjects, in contrast to the task used in the only previous fMRI study with PD-ICD patients, in which a non-initiated action had to be inhibited (Filip et al., 2018). fMRI studies using the SST in healthy adults showed activation of right IFG, right STN, and right preSMA (Aron et al., 2007). We

employed a naturalistic version of the SST by ensuring all participants were exposed to the same difficulty levels. We did so to compare the mechanisms different groups deployed to complete the task as well as to assess the possible impairment the PD-ICD group may experience. In order to examine the neural correlates of response inhibition in PD-ICD patients, we focused on two critical aspects of response inhibition – *proactive* and *restrained* inhibition –.

Proactive inhibition refers to the ability to prepare to inhibit (Aron, 2011), which involves recruiting the stopping network before inhibition occurs. It has been proposed as a more valid measure of response inhibition (Aron, 2011; Meyer et al., 2020) than reactive inhibition which does not involve preparation. Because of the taxing nature of our task, we expected PD-ICD patients would show changes in inhibitory regions as they strove to perform correctly. We also expected greater co-activation between the stopping network and the dorsal attention network, responsible for maintaining an alerting state, since PD-ICD patients would need to maintain greater focus to perform successfully.

Restrained inhibition is the ability to disengage from an invalid cue signaling inhibition and perform a motor response despite the incongruence of the cue, this is, to inhibit the impulse to inhibit. Restrained inhibition has not been previously examined in PD-ICD patients. However, this group's increased difficulty regulating behavior suggests restrained inhibition may be particularly affected. We expected PD-ICD patients to show alterations in the stopping network as well as co-activation with areas in the ventral attentional network involved in reorienting attention and disengaging from invalid cues, and regions of the dorsal attentional network that provide optimal focus on a task. The IFG might also be vital for restrained inhibition: right IFG for stopping and reorienting attention to relevant stimuli (Corbetta et al., 2008); left IFG for filtering out irrelevant actions (Chong et al., 2008).

In this experiment, we examined the neural correlates of response inhibition in patients with PD-ICD, and two control groups: PD patients without ICD, or PD-noICD, and HCs. We did so by examining the activation of the stopping network (i.e., right IFG, right STN, and right preSMA) and its left homologues, as well as the FC of these regions with the whole brain during successful proactive and restrained inhibition.

2. Methods

2.1. Participants

The final sample comprised fifty participants: 18 PD-ICD patients (Mean Age = 63.33 years, Mean Disease Duration = 7.13 years, 2 Female), 17 PD-noICD patients (Mean Age = 61.65 years, Mean Disease Duration = 7.5 years, 3 Female), and 15 HC (Mean Age = 61.87 years, 1 Female) matched on age, sex, education, and premorbid intelligence. Out of the initial sample of 59 participants, nine were excluded: three participants (one PD-ICD and two HC) for outlier performance (>2 SDs) on the conditional SST task; three (two PD-ICD and one HC) for excessive head motion during fMRI scanning (see section 2.5 for more details); and three (one PD-noICD and two HC) for problems constructing the functional mask due to motion during structural data acquisition.

2.2. fMRI data acquisition

Functional images were acquired in four functional separate runs using a gradient-echo echo-planar pulse sequence with the following acquisition parameters: TR = 2000 ms, TE = 28 ms, 33 contiguous 3 mm^3 axial slices, 15% inter-slice gap, FA = 90°, FoV = 192 x 192 mm. 172 volumes of interest were collected per run. The first 4 volumes of each run were discarded to allow for T1 equilibration effects. The discriminability of the signal in the fast event-related fMRI design was improved by adding a random period of 1000 to 4000 ms to the inter-stimulus interval. This period was optimized and counterbalanced with the Optseq2 algorithm (http://www.surfer.nmr.mgh.harvard.edu/optseq/) to allow for deconvolution of the fMRI signal time locked to the stimulus presentation (Dale, 1999).

Participants responded to the functional task by button press via a compatible fiber-optic response box. Before performing the in-scanner task, participants completed a practice version of the task outside the MR scanner.

2.3. fMRI paradigm: Conditional Stop-Signal Task

In the scanner, participants completed a conditional variation of the traditional SST (Logan et al., 1984). This conditional SST (see Figure 21*A*) comprised 75% *Go* and 25% *Stop* trials. All trials began with a grey fixation circle. After 500-5000 ms, a green arrow appeared, pointing either left or right. Participants were instructed to press the button corresponding to the direction of the arrow, as quickly as possible. Prior to the scanning, each participant had completed a practice session, learning that one direction (left or right) was *non-critical,* while the other was *critical* (directions counterbalanced across participants). In *Stop* trials, a red arrow appeared 100-250 ms (varying by 50 ms intervals) after – and always in the same direction as – the green arrow. Importantly, on *critical Stop* trials, participants had to inhibit their initiated response as soon as the red arrow appeared, while on *non-critical Stop* trials, they had to ignore the red arrow and respond normally. Trials in which a red arrow did not follow the appearance of the green arrow constituted *Go* trials, which could be *critical Go* or *non-critical Go* trials depending on the direction the arrow was pointing at, even if participants' task remained to press the button. After each trial, a fixation cross appeared on screen for 500 ms. The task design allowed us to measure two aspects of inhibition (see Figure 21*B*): Proactive Inhibition was calculated by subtracting correct non-critical Go trials, which entailed neither preparation to inhibit nor an inhibition, from critical Stop trials, which required both preparation to inhibit and inhibition [critical Stop minus non-critical Go]. Restrained inhibition was measured by subtracting correct non-critical Go trials from correct non-critical Stop trials, in which participants had to ignore an invalid inhibitory stimulus [non-critical Stop minus non-critical Go].

2.4. Behavioral data analyses

Behavioral results were analysed with a 3 (Group: PD-ICD, PD-noICD, HC) by 2 (Direction: critical, non-critical) by 2 (Condition: Go, Stop) mixed-model ANOVA, run on the percent of correct responses on the SST task. Given our specific interest in focusing on proactive and restrained inhibition, we ran separate one-way ANOVAs with the factor Group and the

absolute values of the subtraction between trials for Proactive Inhibition (|critical Stop - non-critical Go|), and Restrained Inhibition (|non-critical Stop - non-critical Go|), with accuracy as the dependent measure.

Participants had to withhold their response in one of the main conditions of interest– critical Stop–, and analyzing RT data without including that key condition either in the whole-experimental design or Proactive/Restrained Inhibition analyses would give us an incomplete, possibly biased, result. Therefore, we focused exclusively on accuracy results. For information on RT see Supplementary Table 2 in Appendix.

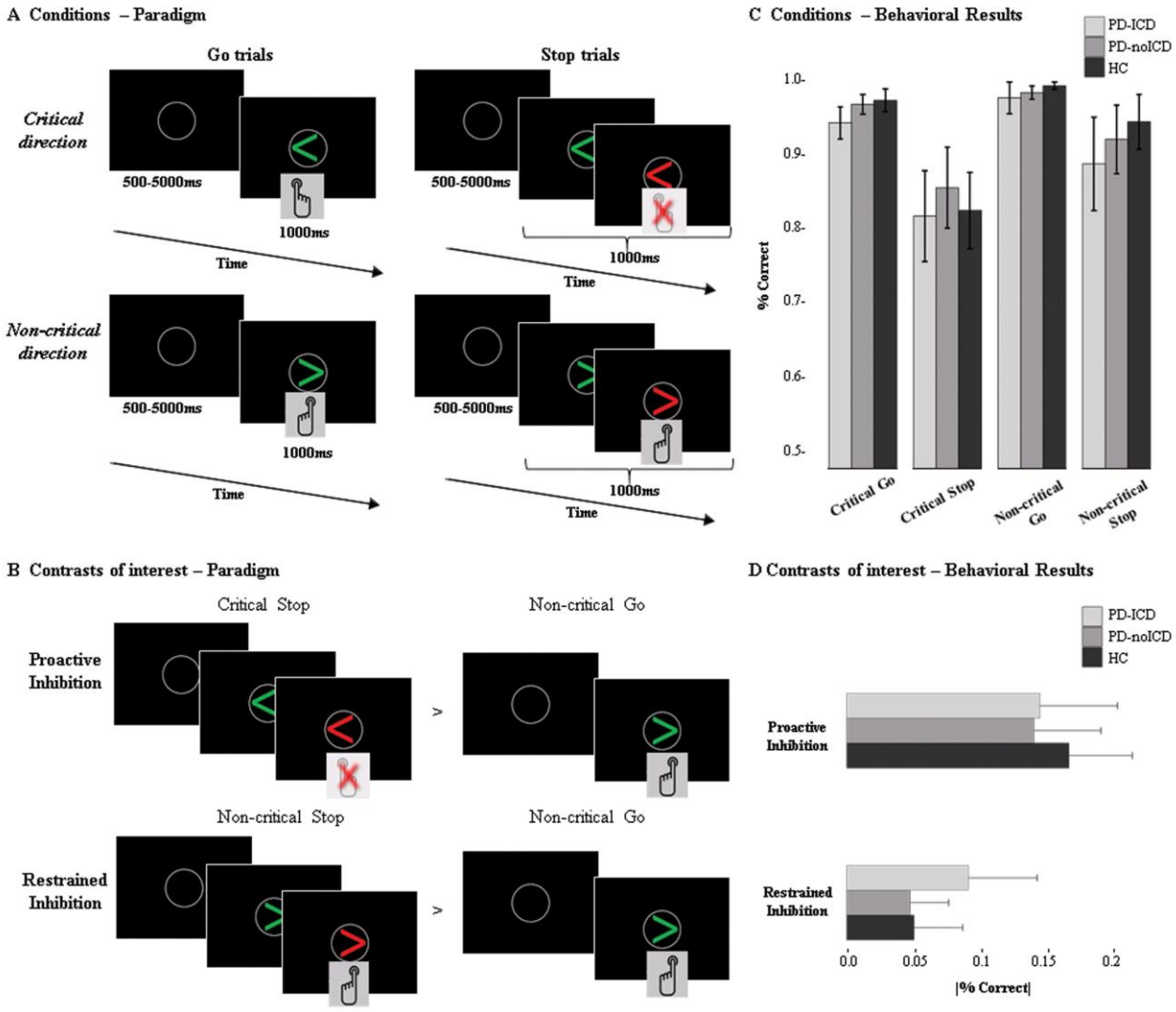

Figure 21. Schematic representation of the conditional SST task by (A) conditions and (B) contrasts of interests; and percentage of correct responses by (C) conditions and (D) contrasts of interests. Error bars represent 95% confidence interval.

2.5. MRI data analyses

SPM8 was used to perform standard preprocessing routines and analysis. We conducted slice-timing correction and spatial smoothing as described in Chapter 5, section 5. The threshold for volume correction of 0.5 mm for motion and 1.3% for signal fluctuation. Those participants who required correction of more than 15% of total functional volumes or who presented a drift over 3 mm in any run were removed from the final sample (one HC and two PD-ICD). There were no differences in the proportion of corrected volumes per group ($F_{2,53}$=0.04, p=0.96, η_p^2=0.002). The remaining steps of preprocessing (i.e., registration, normalization, last spatial smoothing, and temporal filtering) were executed as described in Chapter 5, section 5.

We performed statistical analysis on individual participant's data applying the GLM. The fMRI time series data were modeled as a series of events convolved with a canonical hemodynamic response function. Five fMRI experimental conditions were modelled (critical Go correct, non-critical Go correct, critical Stop correct, non-critical Stop correct, and critical Stop incorrect), with each trial modeled as an event and time locked to the presentation of each stimulus. The study followed a 3 (Group: PD-ICD, PD-noICD, HC) by 5 (Conditions: critical Go, non-critical Go, critical Stop, non-critical stop, Critical stop incorrect) experimental design. We had two main comparisons of interest comprising correct responses: *Proactive Inhibition* (i.e., critical Stop – non-critical Go), and *Restrained Inhibition* (i.e., non-critical Stop – non-critical Go). These contrasts were examined by means of whole-brain contrasts, region-of-interest (ROI) analyses, and FC analyses.

Whole-brain contrasts were computed using the least-squares parameter estimates of the height of the best-fitting canonical HRF for each condition. Contrast images were first computed on a participant-by-participant basis. These images were then used for the group analysis where we looked at activations across all subjects as well as separately for the three groups. At the group level, whole-brain contrasts of interest were calculated by performing a one-sample t-test on the images, considering participants as a random effect.

ROI analyses were computed with the MARSBAR toolbox for SPM8 (Brett et al., 2002). To ensure that voxels included in the ROIs were relevant to the inhibitory processes

of healthy subjects as well as PD patients with and without ICD, functional ROIs were identified by means of a general whole-brain contrast across all subjects including all the main conditions of our fMRI experimental design: All Conditions > Null. Therefore, ROIs consisted of significantly active voxels identified from whole-brain contrast All Conditions > Null ($p < 0.05$ familywise error rate (FWE) voxel level-corrected) (see Figure 22) across all participants within specific MARSBAR anatomical ROIs. In addition, the ROI of the STN was created anatomically based on the STN ROI previously used in response inhibition literature (Aron & Poldrack, 2006). The following ROIs (the center of mass and the volume in cubic mm are indicated in parentheses) were created: left IFG (-45.9, 21.6, 14.7; 22520 mm^3), right IFG (48.8, 21.6, 16.1; 24544 mm^3), left preSMA (-5.31, 11.1, 55.1; 7752 mm^3), right preSMA (8.38, 11.1, 57; 7080 mm^3), left STN (-11.4, -14.4, -5.59; 968 mm^3), and right STN (12.7, -13.9, -4.58; 496 mm^3). Therefore, we conducted ROI analyses to examine Group effects on key right-lateralized nodes of the stopping network and left-lateralized homologues. We extracted

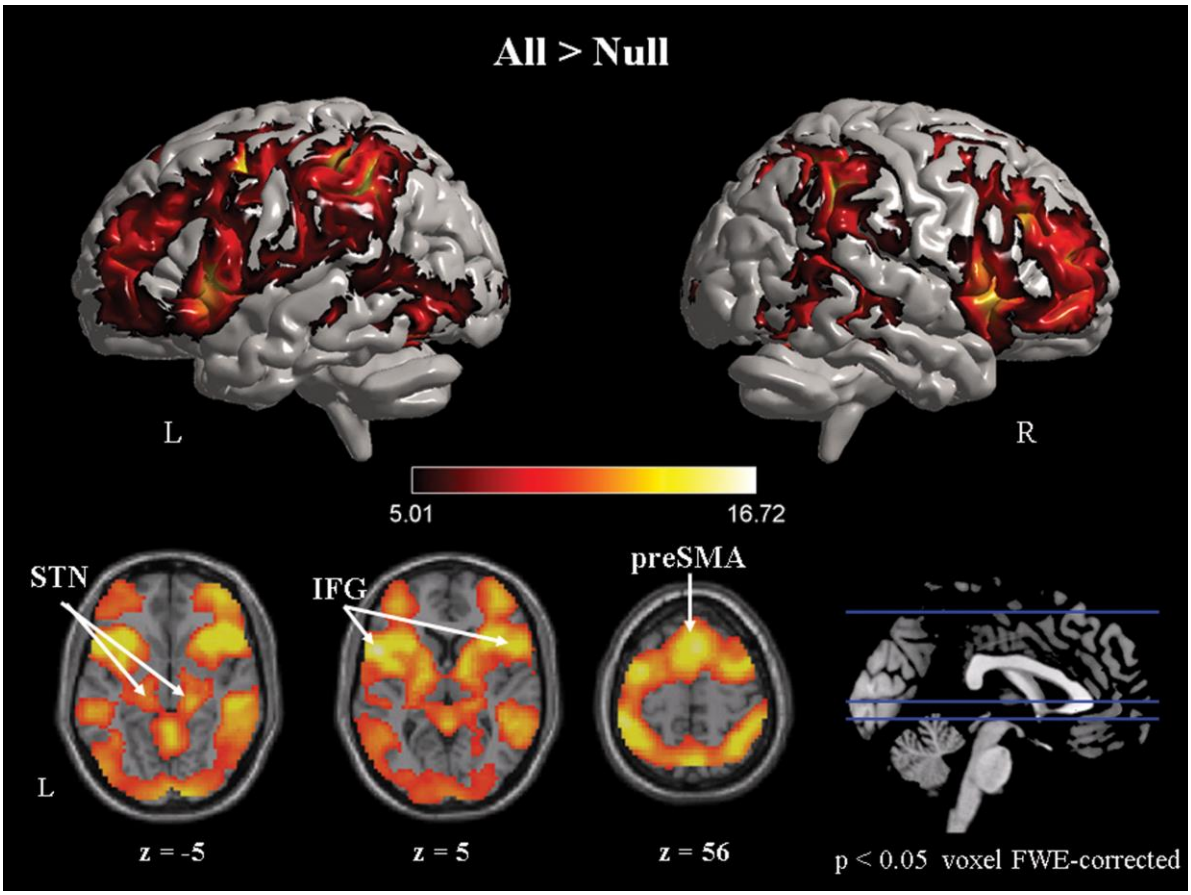

Figure 22. Brain renderings and axial sections showing activations for the whole-brain contrast All > Null for all participants at a statistical threshold of $p < 0.05$ voxel FWE-corrected.

fMRI parameter estimates from the IFG, preSMA, and STN for the contrasts Proactive Inhibition and Restrained Inhibition. For each contrast, we analyzed percent signal change differences each ROI through a 3 (Group: PD-ICD, PD-noICD, HC) by 2 (Hemisphere: Left, Right) mixed-model ANOVA.

Finally, we examined FC via the beta-series correlation method (Rissman et al., 2004) implemented in SPM8 with custom Matlab scripts. The canonical HRF in SPM was fit to each occurrence of each condition. The resulting parameter estimates, the beta values, were sorted according to the conditions of interest to produce a condition-specific beta series per voxel. The beta series associated with the six seeds of interest were correlated with voxels across the entire brain to produce beta-correlation images for each subject for the contrasts Critical stop > Null and Non-critical stop > Null contrasts, associated with proactive and restrained inhibition, respectively. These contrasts were subjected to an arc-hyperbolic tangent transform (Fisher, 1921) to allow for statistical inference based on the correlation magnitudes. To determine differential coupling strength between groups, these whole-brain functional connectivity maps were submitted to two-sample t-tests between the PD-ICD and the PD-noICD groups as well as between the PD-ICD and the HC groups, using a $q < 0.05$ FDR correction at the cluster level (with a voxel-level extent threshold of $p < 0.001$). Depiction of FC analyses was done with BrainNet Viewer (Xia et al., 2013).

3. Results

3.1. Demographic and clinical results

There were no differences between groups in demographic data (see Table 1). PD-noICD and PD-ICD groups did not differ in disease duration, dopaminergic medication, motor severity and cognitive outcomes (see Table 2).

3.2. Behavioral results

The 3 (Group) by 2 (Direction) by 2 (Condition) mixed-model ANOVA revealed main effects of Direction, ($F_{1,43}$=37.36, p < 0.001, η_p^2 = 0.46) and Condition, ($F_{1,43}$ = 117.79, p < 0.001, η_p^2 = 0.73), subsumed by a statistically significant Direction by Condition interaction, ($F_{1,43}$ = 11.42, p = 0.002, η_p^2 = 0.21). There were no main or interactive effects of Group (Fs < 1.1, ps > 0.1, η_p^2 ≤ 0.05). Simple-effect post-hoc analyses examining the Direction by Condition interaction showed trial differences associated with task difficulty (non-critical Go = critical Go > non-critical Stop > critical Stop, ps < 0.02) (see Figure 21*C*). Separate one-way ANOVAs for the contrasts Proactive and Restrained inhibition did not reveal Group effects (Fs < 2, ps > 0.1, η_p^2 < 0.1) (see Figure 21*D*).

3.3. MRI results

3.3.1. Whole-brain analyses

We computed a whole-brain functional contrast for all the task conditions versus the baseline condition (All Conditions > Null) to identify regions activated during the task across all participants (see Figure 22). We observed the recruitment of the right-lateralized nodes of the stopping network (IFG, preSMA, STN) as well as their contralateral homologues for all participants. We computed the same contrast separately for each group and observed that the two PD groups tended to show left-lateralized extended activation (see Figure 23). The bilateral recruitment during inhibitory control in PD patients resembles a previous claim (Mirabella et al., 2017) and highlights the importance of examining not only the right-lateralized nodes from the classical inhibitory control network, but also its left-lateralized homologues.

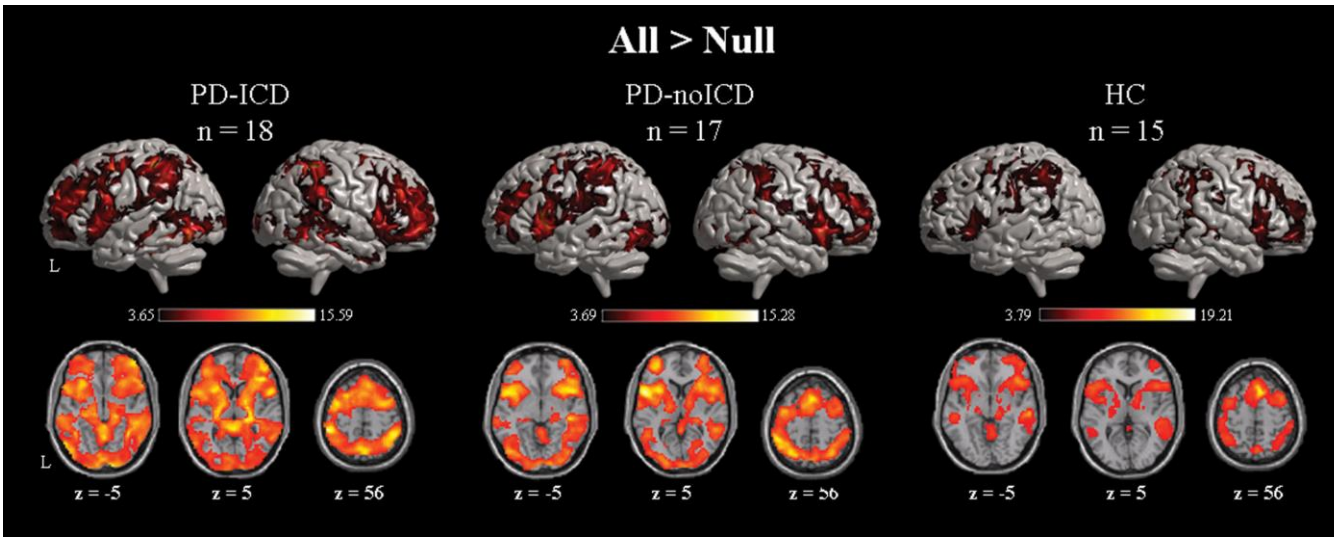

Figure 23. Brain renderings and axial sections showing activations for the whole-brain contrast All > Null for each study group, p < 0.001 voxel-level extent threshold, p < 0.05 cluster-level FWE corrected.

3.3.2. ROI analyses

3.3.2.1. Proactive inhibition

The 3 (Group) by 2 (Hemisphere) mixed-model ANOVA showed a main effect of Group for the percent signal change of the bilateral preSMA ($F_{2,46}$ = 6.74, q = 0.009, η_p^2 = 0.23) and bilateral IFG ($F_{2,46}$ = 3.85, q = 0.043, η_p^2 = 0.14). Post-hoc tests revealed hyperactivation of the preSMA for the PD-ICD group in comparison with both the PD-noICD (t_{33} = 3.29, q = 0.007, d = 0.47) and the HC (t_{31} = 3.01, q = 0.008, d = 0.43) groups, as well as hyperactivation of the IFG for the PD-ICD group compared to the PD-noICD group (t_{33} = 2.59, q = 0.043, d = 0.37). No group differences were observed for the STN (see Figure 24*A*).

This analysis also showed a main effect of Hemisphere for the percent signal change of the preSMA ($F_{2,46}$ = 21.65, q < 0.001, η_p^2 = 0.32), the IFG ($F_{2,46}$ = 62.98, q < 0.001, η_p^2 = 0.58), and the STN ($F_{2,46}$ = 4.51, q = 0.039, η_p^2 = 0.09), with right hemisphere ROIs showing greater activation than their left homologues.

3.3.2.2. Restrained inhibition

The analysis revealed a statistically significant Group by Hemisphere interaction for the percent signal change of the IFG ($F_{2,46}$ = 7.92, q < 0.001, η_p^2 = 0.26). To follow-up on this interaction we performed between-group ANOVAs separately for the left and right IFG. We found an effect only for the left IFG ($F_{2,46}$ = 5.87, q = 0.01, η_p^2 = 0.2), with post-hoc tests revealing hyperactivation of the left IFG in the PD-ICD group compared to the PD-noICD (t_{32} = 2.78, q = 0.013, d = 0.95) and HC groups (t_{30} = 3.13, q = 0.013, d = 1.02) (see Figure 24*B*).

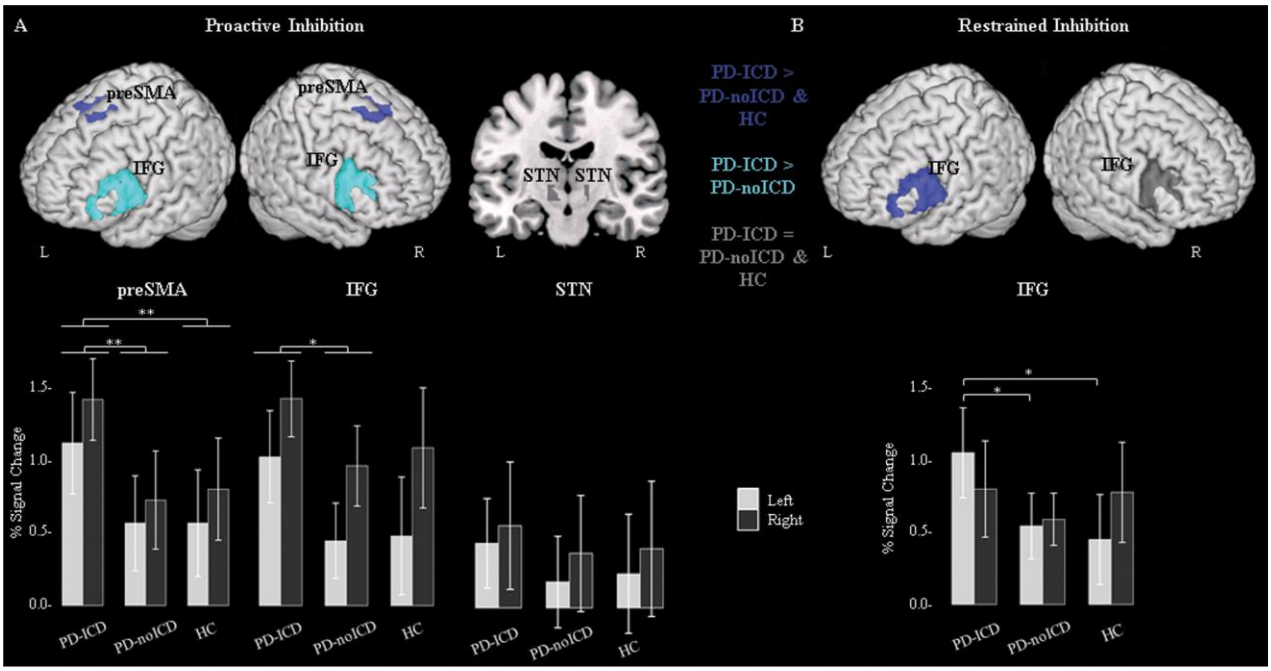

Figure 24. ROI analyses for Proactive and Restrained Inhibition. (A) Proactive inhibition showed a group effect for preSMA and IFG. (B) Restrained inhibition showed a group by hemisphere interaction. Significance of group effects shown in graphs. Error bars represent 95% confidence interval.

3.3.3. Functional connectivity analyses

A previous study suggested that activation changes during inhibition are present beyond the stopping network in PD-ICD patients (Filip et al., 2018). To examine the FC of inhibitory regions and their homologues with other brain areas, we conducted whole-brain functional connectivity analyses seeding the nodes of the traditional stopping network and their left counterparts for the contrasts of interest: Critical Stop vs Null and Non-critical Stop vs Null.

3.3.3.1. Proactive inhibition

No between-group differences in FC emerged using the IFG, preSMA, and STN left and right seeds.

3.3.3.2. Restrained inhibition

Stronger left IFG-IPC/supramarginal (SMG) FC (maxima at MNI coordinates -33, -52, 43, t = 5.99) was observed for the PD-ICD compared to the PD-noICD group (see Figure 25*A*). The left IPC and SMG are areas associated with the dorsal attention network. Also, tighter right IFG-postcentral/SMG FC (maxima at 51, -10, 28, t = 6.17) was found for the PD-ICD compared to the PD-noICD group (see Figure 25*B*). The right SMG has been linked to the ventral attention network.

We also found reduced right preSMA-putamen/insula (maxima at 33, -13, 1, t = 5.06) (see Figure 25*C*) and right STN-precuneus (maxima at 9, -49, 37, t = 4.49) FC for the PD-ICD compared to the PD-noICD group (see Figure 25*D*).

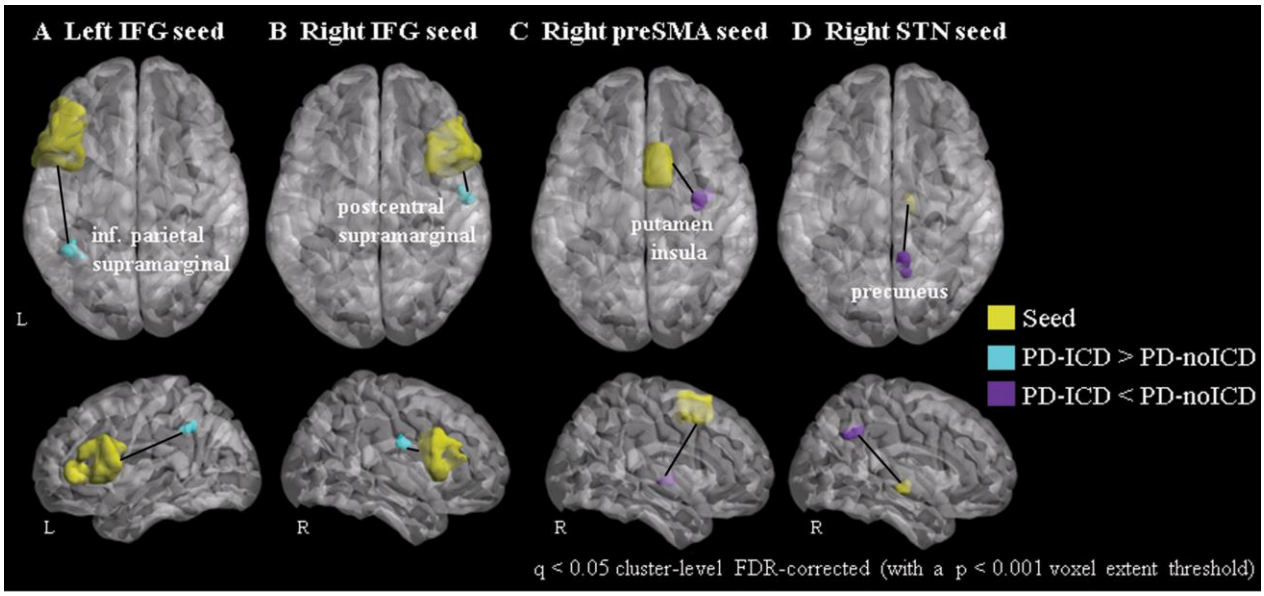

Figure 25. Whole-brain functional connectivity during Restrained Inhibition. Compared to PD-noICD participants, PD-ICD patients showed increased functional coupling of the left IFG (A) and right IFG (B) with parietal regions, plus decreased functional co-activation of the right preSMA (C) with putamen/insula and right STN (D) with precuneus.

4. Discussion

In Experiment 2 we aimed to investigate the neural correlates of response inhibition in patients with medication-induced increased impulsivity through a demanding task with sustained natural difficulty levels. Previous evidence with PD-ICD patients (Claassen et al., 2015; Filip et al., 2018) suggested the presence of a compensatory mechanisms enhancing their performance. By assessing two aspects of response inhibition (i.e., proactive and restrained inhibition) we were able to observe that PD-ICD patients presented no behavioral impairments relative to their PD-noICD and HC counterparts, as expected from previous evidence (Claassen et al., 2015; Filip et al., 2018). However, the underlying functional correlates linked to proactive and restrained inhibition, suggest that PD-ICD patients may be resolving these inhibitory demands differently than PD-noICD and HC participants. Our results suggest that the normal performance in PD-ICD patients is achieved via different compensatory mechanisms involving the stopping network and its interplay with attentional regions. These compensatory mechanisms in PD-ICD patients depended on the demands posed by these two different inhibitory aspects.

While performing *proactive inhibition*, regions of the right-lateralized stopping network showed the highest activation across all groups. However, the PD-ICD group showed strong right-lateralized hyperactivation as well as additional hyperactivation of its left-lateralized homologues. Together with the lack of behavioral impairment and the absence of differences in functional connectivity, the hyperactivation of regions of the stopping network suggests that PD-ICD participants engage in proactive inhibition by strongly activating the stopping network bilaterally and that this form of inhibition is resolved at the regional level without an increase in the recruitment of attentional regions. This suggests that PD-ICD subjects would be exerting a greater effort during proactive inhibition than the other groups. This greater effort cannot be resolved only by means of hyperactivating the stopping network but also requires recruiting the stopping network bilaterally. One of the regions hyperactivated bilaterally in PD-ICD patients during proactive inhibition is the IFG. The right IFG forms part of both the stopping network (Aron et al., 2007) and the ventral attention network (Corbetta et al., 2008), while the left IFG evaluates and

selects appropriate actions (Pobric & Hamilton, 2006; Swick et al., 2008). Therefore, although the hyperactivation is congruent with increased recruitment of the stopping network, attention and response inhibition may be confounded in the IFG, as attentional resources are also needed to perform the task (Criaud & Boulinguez, 2013). Its attentional function could be recruited when inhibition has to be prepared in a critical trial, and needs to be applied if a stop signal appears. The role of the left IFG in response inhibition is under debate, with some authors acknowledging its relevance (Swick et al., 2008) while others do not (Aron et al., 2014). The other hyperactive region, the preSMA, is involved in action selection (Mueller et al., 2007; Tanji, 1994), which is important when deciding whether a motor action should be halted or not. The role of IFG and preSMA in implementing inhibition was previously underscored by a transcranial magnetic stimulation study (Obeso et al., 2013). Furthermore, evidence for compensatory engagement by the left IFG and left preSMA – but not the STN – has been reported when a region of the stopping network is disrupted during proactive inhibition (Obeso et al., 2013). Similarly, we did not observe differential activation of the STN in the PD-ICD group. While these patients exhibit evidence for increased demand in regions responsible for detecting the need to inhibit (i.e., preSMA, IFG) (Aron, 2011), they are still able to execute motor inhibition correctly, showing normal demand in the region that executes the order (i.e., STN). Taken together with evidence that PD-ICD patients can stop faster than controls (Claassen et al., 2015) and that contralateral regions are recruited as in the case of stopping network malfunction (Obeso et al., 2013), this suggests that preparation to inhibit is a relevant challenge for PD-ICD patients.

As opposed to proactive inhibition, *restrained inhibition* did not differentially activate any of the classical components of the right-lateralized stopping network as a function of group. Nonetheless, in PD-ICD patients, relative to PD-noICD and HCs, restrained inhibition was associated with hyperactivation of the left IFG, linked to monitoring relevant and irrelevant actions (Milham et al., 2001; Swick et al., 2008). When presented with invalid stop cues and having to decide whether to respond or instead withhold movement, patients with ICD might be particularly challenged. Their greater need to supervise the action of responding or withholding could explain the hyperactivation of the left IFG.

We found that FC changes were only associated with restrained inhibition. Compared to the PD-noICD group, PD-ICD patients showed greater co-activation between the IFG and

areas related to: alerting (left IPC and SMG) (Cabeza et al., 2008); reorienting attention (right SMG) (Chica et al., 2013; Corbetta et al., 2008) and motor sensation (postcentral gyrus). Moreover, it has been suggested that dorsal and ventral attentional network components interact with each other, that this interaction is led by frontal areas such as the IFG, with both networks being required to shift attention (Vossel et al., 2014). In contrast with PD-noICD patients, increased FC in PD-ICD patients between the IFG and components of dorsal and ventral networks suggests that PD-ICD patients may need to employ additional attentional resources to perform restrained inhibition. Unlike during proactive inhibition, the greater task demands would be reflected in increased attentional demands when asked to make a motor decision while also coping with a contradictory irrelevant stimulus. Therefore, during restrained inhibition, PD-ICD patients would experience a heightened need to maintain attention, shift focus when disengaging from the invalid stop stimulus to return to the button-press task, and receive feedback on that motor response.

However, also while performing restrained inhibition, PD-ICD patients showed weaker functional co-activation between the right preSMA, involved in motor planning, and both the right posterior insula and putamen – tightly connected areas (Chikama et al., 1997), associated with somatosensory awareness (Chang et al., 2013) and sensorimotor abilities, respectively, relative to PD-noICD patients. This reduced functional co-activation for PD-ICD relative to PD-noICD patients could reflect PD-noICD patients' well-established difficulty in initiating movement (Dietz et al., 1990), known to alter preSMA's activity even at an early stage of PD disease manifestation (Eckert et al., 2006). During restrained inhibition, PD-ICD patients' impulsivity might alleviate movement initiation difficulties, eliminating the need for strong co-activation of areas involved in planning a movement and sensorimotor areas. Finally, PD-ICD patients showed weaker co-activation than PD-noICD subjects between right STN and right precuneus. A previous study suggested increased co-activation between those regions –right STN and right precuneus– for PD-noICD compared to HC during resting state (Fernández-Seara et al., 2015). We found, however, this abnormal connectivity was reduced in PD-ICD patients during restrained inhibition. This discrepancy might be due to the increased impulsivity of PD-ICD patients and the fact that the BOLD signal was not obtained at rest but during the inhibition of an inhibitory signal, facilitating the action. Such facilitation is associated with reduced FC between the STN and the precuneus, which is responsible for

integration of perceptual information (Cavanna & Trimble, 2006) and cue reactivity (Starcke et al., 2018). This finding is in keeping with the observation that STN stimulation, which reduces STN activity and therefore its FC, speeds up patients' decisions under conflict conditions (Ballanger et al., 2009; Frank et al., 2007) such as restrained inhibition. In fact, although not significant, in our experiment, PD-ICD patients showed higher accuracy for restrained inhibition, probably due to a facilitation for inhibiting the stop signal, whereas the three groups behaved similarly during proactive inhibition (see Figure 18*D*). This finding could indicate that, for PD patients with abnormal impulsivity, it is easier to ignore inhibition signals than to obey them, an effect linked to the STN.

To our knowledge, no previous study has examined the functional correlates of different aspects of response inhibition in PD-ICD, and leaves open questions for future studies, such as: Which aspects of inhibition impose higher demands on PD-ICD than PD patients? Do these demands force PD-ICD patients to recruit additional attentional resources during response inhibition? What influence do alerting and orienting mechanisms exert on PD-ICD patients' ability to inhibit a response? And, does task difficulty play a role in the performance of PD-ICD patients?

4.1. Conclusions

This study is the first to address functional alterations of the stopping and attentional network in PD-ICD patients by examining different aspects of response inhibition. Subjects performed a taxing response inhibition task, in which participants were required to stop an ongoing action or instead to finalize a movement. Although performing normally, the mechanisms by which the PD-ICD group executed the task differed from both control groups for both aspects of inhibition. For proactive inhibition, PD-ICD patients hyperactivated the network more bilaterally than their control counterparts. For restrained inhibition, PD-ICD patients activated the left IFG to a greater extent and recruited additional attentional resources, while also showing reduced co-activation between the right STN and precuneus. Therefore, the aspects of inhibition assessed here posed specific challenges for the PD-ICD

group, reflected in differences in the functional correlates of inhibition exhibited by PD-ICD patients.

Chapter 9: Experiment 3

1. Introduction

In Experiment 3 we aimed to investigate the neural correlates of semantic processing in patients with medication-induced increased impulsivity. We were particularly interested in observing how the ICD dimension would interfere with semantic processing. As presented in the introduction, there is ample evidence of language and memory being among the cognitive domains affected in PD. Semantic processing involves both linguistic and memory systems. Semantic deficits in PD patients have previously been linked to the deterioration of the cortico-striato-cortical system along with difficulties inhibiting semantic and phonological competitors (Angwin et al., 2006; Copland, 2003; L. L. Murray, 2008), with dopamine optimizing semantic processing in PD (Angwin et al., 2006). Interestingly, PD-ICD patients show reduced cortico-striatal connectivity functionally and structurally (Carriere et al., 2015; Premi et al., 2016; Verger et al., 2018). Yet, to our knowledge there are no studies assessing semantic processing in PD-ICD patients. We would expect PD-ICD patients to present greater difficulties, reflected by differential neural correlates, either in the form of deficit or compensation, than their ICD free counterparts, especially if they are presented with stimuli that they may find challenging to disengage from.

To help fill the gap in the literature, we decided to design a comprehension task to avoid motor confounding factors associated with production in PD (Illes et al., 1988; L. L. Murray & Lenz, 2001). To examine the effect ICD may have on semantic processing, we tested semantic processing auditorily with a focus on the processing of words associated with ICD, this is, ICD-laden words, in contrast with laden-free words. We expected PD-ICD patients to experience more difficulties processing ICD-laden words as a consequence of the incremental deterioration in their cortico-striato-cortical system, due to the additional impact of the ICD on these regions (Aracil-Bolaños & Strafella, 2016; Carriere et al., 2015). We also expected that, while listening to each word, PD-ICD patients would experience additional difficulties inhibiting the representations of semantic or phonological competitors to a greater level than PD-noICD patients. However, given the lack of previous studies, we decided to perform an exploratory whole-brain analysis, and examine the FC of the regions highlighted by the whole-brain analysis.

Therefore, in this experiment, we measured the differential neural correlates of semantic processing of ICD-laden and laden-free words for patients with PD-ICD, and two control groups: patients with PD-noICD and HCs. We did so in a 3 (Group) by 2 (Condition: ICD-laden words, control words) design examining whole-brain activation as well as the FC between the regions sensitive to ICD-laden words.

2. Methods

2.1. Participants

Fifty-two participants constituted the final sample: 18 PD patients with ICD (PD-ICD), 15 PD patients without ICD (PD-noICD), and 19 healthy controls (HC). Out of the initial sample of 59 participants, three participants did not complete current the task (two PD-ICD and one PD-noICD). Additionally, two participants (one PD-ICD and one PD-noICD) were excluded for excessive head motion during fMRI scanning (see section 2.4 for more information), and

another two (one PD-noICD and one HC) for problems with the functional mask due to motion during structural data acquisition.

2.2. fMRI data acquisition

Functional images were acquired in two separate functional runs using a gradient-echo echo-planar pulse sequence with the following acquisition parameters: TR = 2500 ms, TE = 28 ms, 41 contiguous 3 mm^3 axial slices, 10% inter-slice gap, FA = 90ª, FoV = 192 x 192 mm. 221 volumes of interest were collected per run. The initial 4 volumes of each run being discarded to allow for T1 equilibration effects. In order to improve the event related design by obtaining a correct estimation of participant's BOLD responses for each trial type, we used the Optseq2 algorithm (http://www.surfer.nmr.mgh.harvard.edu/optseq/) to counterbalance stimulus presentation and distribute an additional period to the inter stimulus intervals. Optseq2 allowed for the fMRI signal deconvolution time locked to the stimulus presentation (Dale, 1999). With Optseq2, eleven pseudo-randomized lists of stimuli were prepared, with lists being randomly assigned to participants. Participants responded to the task via button-press in a 4-button optical response pad (Current Designs) that recorded their answers.

Before performing the task inside the scanner, participants got familiarized with a practice version outside the scanner. Once in the scanner, before starting the functional sequence, participants heard and repeated a practice word list to ensure the volume was correct for each participant.

2.3. fMRI paradigm

The task participants completed in the scanner was an auditory semantic decision task. During scanning, participants heard different words and their task was to press a button when the word they were hearing was a brand. Brand words were selected for representing well-known companies and products, which was ensured by asking twenty different healthy participants to identify the brand names. This group correctly recognize brands 88.75% of

the time (SD = 8.67). In total there were three types of words: brands (e.g., Ferrari), laden-free or control words (e.g., lizard, daisy), and words associated with an ICD dimension, which we will refer to as ICD-laden words (see Figure 26). Words were matched by log-frequency, word duration, and number of syllables (see Supplementary Table 3, Supplementary Table 4, and Supplementary Table 5 in the Appendix for the full list of stimuli). ICD-laden words were related to the four most common behavioral addictions experienced by ICD patients. ICD-laden words could be of a sexual nature (e.g., strip-tease), related to gambling (e.g., bet), referring to food (e.g., cake) or to shopping (e.g., sales). All words were recorded by a Spanish female speaker with a local accent. The task followed a fast event-related design. During the task, participants were exposed to a word trial lasting 2500 ms, followed by a jittered inter-stimulus interval of 2500 to 12500 ms, another word trial and so on for 16 minutes, with conditions being pseudo-randomized using Opseq2 (Dale, 1999). During this time, participants underwent 60 brand trials, 80 control trials and 160 ICD-laden trials, 40 related to each type of ICD. Participants heard each word once during the experiment.

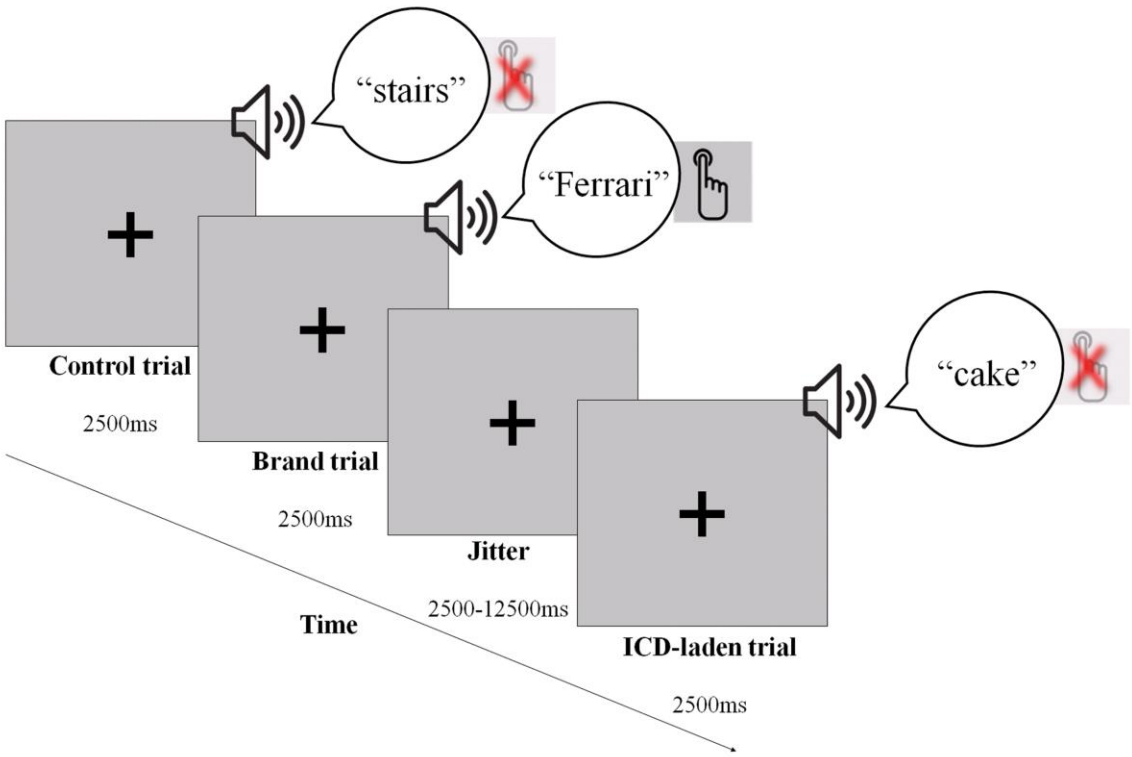

Figure 26. Schematic representation of the auditory semantic processing task.

2.4. MRI data analysis

SPM8 was used to perform standard preprocessing routines and analysis. We conducted slice timing correction and spatial smoothing as described in Chapter 5, section 5. The threshold for volume correction of 1 mm for motion and 1.3% for signal fluctuation. Those participants who required correction of more than 15% of total functional volumes or who presented a drift over 3 mm in any run were not included in the final sample (one PD-ICD and one PD-noICD). There were no statistically significant differences in the proportion of corrected volumes in each group ($F_{2,53}$ = 0.77, p = 0.469, η_p^2 = 0.028). The remaining steps of preprocessing (i.e., registration, normalization, last spatial smoothing, and temporal filtering) were executed as described in Chapter 5, section 5.

For the statistical analyses on the imaging data, the GLM was then applied on individual participant's data. The fMRI time series data were modeled by a series of events convolved with a canonical haemodynamic response function. We modelled three experimental conditions: brand words, control words, and ICD-laden words), with each trial modeled as an event and time locked to the presentation of each stimulus.

Whole-brain contrast analysis was performed with the least-squares parameter estimates of the height of the best-fitting canonical HRF for each condition. Contrast images were computed on a participant-by-participant basis and posteriorly used for the group analysis where activations across all subjects as well as for each of the three groups were checked. At the group level, we calculated whole-brain contrasts of interest by performing a one-sample t-test, with participants entered in the analysis as a random effect. Our condition of interest was ICD-laden words, whereas the laden-free words acted as our control condition. Brand words were inserted in the experiment to ensure and check participants' attention, and, more importantly, force participants to access the semantic representation of every word. Hence, we were not interested in analysing brand words, a condition which unlike ICD-laden and control words required a button press and therefore included confounding motor activation. We calculated an All > Null contrast including ICD-laden and control trials, but excluding brand trials (see Figure 27, Table 3 for details). In consequence, we performed a whole-brain 3 (Group: PD-ICD, PD-noICD, HC) by 2 (Word: ICD-laden,

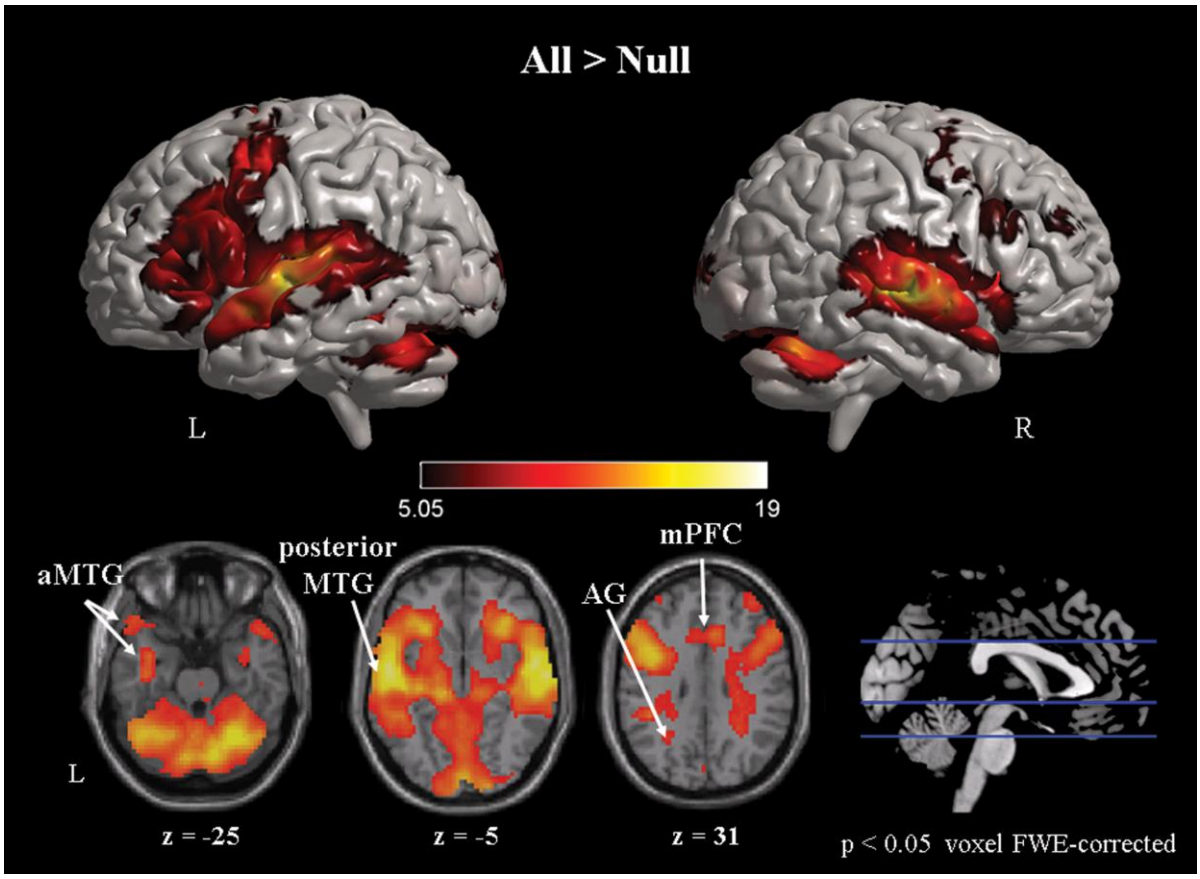

Figure 27. Brain renderings and axial sections showing activations for the whole-brain contrast All (excluding brand word trials) > Null for all participants at a statistical threshold of $p < 0.05$ voxel FWE-corrected.

control) ANOVA, which we corrected applying FWE cluster level correction $q < 0.05$, with a $p < 0.001$ voxel extent threshold.

To further explore the previous ANOVA results, we focused on the clusters with significant activation for ICD-laden > Control words. Those clusters were extracted and computed with the SPM8 MARSBAR toolbox (Brett et al., 2002), becoming our ROIs. Therefore, the ROIs consisted of significantly active clusters activating to a greater extent for the condition ICD-laden words in comparison with the condition control words across all subjects, as shown by the whole-brain ANOVA. The following ROIs (the center of mass and the volume in cubic mm are indicated in parentheses) were created: bilateral medial prefrontal cortex (mPFC) (-5, 51, 28; 13041 mm^3), left anterior middle temporal gyrus (aMTG) (-55, 0, -27; 4779 mm^3), left AG (-46, -62, 33; 5265 mm^3), and used in the FC analysis.

Table 3. Whole-brain main activation peaks for All > Null contrast.

Brain regions	Voxels	*t* -value	Coordinates		
			x	y	z
L Middle/Superior Temporal Gyrus	1822	19.00	-54	-13	1
R Superior Temporal Gyrus	1161	17.47	60	-7	1
Supplementary Motor Area	884	14.74	-3	11	55
R Posterior Lobe of the Cerebellum	467	14.60	27	-61	-23
L Postcentral gyrus	562	13.20	-48	-4	52
L Posterior Lobe of the Cerebellum	1206	12.74	15	-76	-29
L IFG Opercularis	314	12.49	-39	8	28
L IFG Triangularis	733	12.39	-45	23	25
L Insula	434	12.32	-27	23	-2
L Precentral	728	12.29	-42	2	58
R Insula	384	12.12	33	23	-2
R Inferior Temporal gyrus	134	11.68	-54	-55	-17
L Calcarine sulcus	488	11.25	3	-91	-2

Note: Statistical threshold of $p < 0.05$ voxel FWE-corrected.

We examined FC via the beta-series correlation method (Rissman et al., 2004) implemented in SPM8 with custom Matlab scripts to examine the associations between the three previously described ROIs. We fit the canonical HRF to each occurrence of each of our conditions of interest: ICD-laden words and control words. We sorted the resulting parameter estimates, the beta values, to our conditions of interest to create a condition-specific beta series per voxel. We performed pairwise FC analyses for ICD-laden words > Null and Control words > Null by calculating the beta-series correlation values for each pair of ROIs. We applied an arc-hyperbolic tangent transformation to the beta-series correlation values (Fisher, 1921) to make the distribution of the values approach that of a normal distribution, since the original correlation values are restricted to the range -1 to +1. We examined group differences in the FC of each pair of ROIs by conducting a 3 (Group: PD-ICD, PD-noICD, HC) by 2 (Condition: ICD-laden word, control word) mixed model ANOVA per pair. Our interest was on Group by Condition interaction effects and not in main effects, since the selected ROIs were selected for showing a Condition effect on their activation.

3. Results

3.1. Demographic and clinical data

We found no between-group statistically significant differences for age, years of schooling, and premorbid intelligence, as measured by the Vocabulary subtest of the WAIS-III (see Table 2). Further, PD-ICD and PD-noICD groups did not differ in disease duration, amount of dopaminergic medication, or motor severity.

Within the PD-ICD group, eight presented combined ICDs, nine presented a single ICD. The main ICD was binge eating, with eight patients suffering from it either as primary or as secondary ICD, while seven patients suffered from pathological hypersexuality, five from compulsive shopping, and one from pathological gambling (see Supplementary Table 1 in for more details).

3.2. MRI results

3.2.1. Whole-brain analysis

We computed a whole-brain 3 (Group: PD-ICD, PD-noICD, HC) by 2 (Condition: ICD-laden word, control word) ANOVA to explore between group differential recruitment of linguistic nodes depending on the word condition. However, applying a $p < 0.05$ cluster-level FWE correction (with a $p < 0.001$ voxel extent threshold), we found no group effect nor an interaction. Nonetheless, we found a Condition main effect in three regions that showed more positive activation for ICD-laden words in comparison with control words (see Figure 28*A*). These regions were the left aMTG (-57, 2, -29) the mPFC (-6, 53, 28), and the left AG (-48, -64, 31).

Two of the regions, the left aMTG and mPFC, presented a similar pattern with increased activation for ICD-laden words, and reduced activation for control words. The left AG, on the other hand, presented reduced activation for control words, and a smaller reduction for ICD-laden words (see Figure 28*B*). This is, during the auditory exposure to ICD-

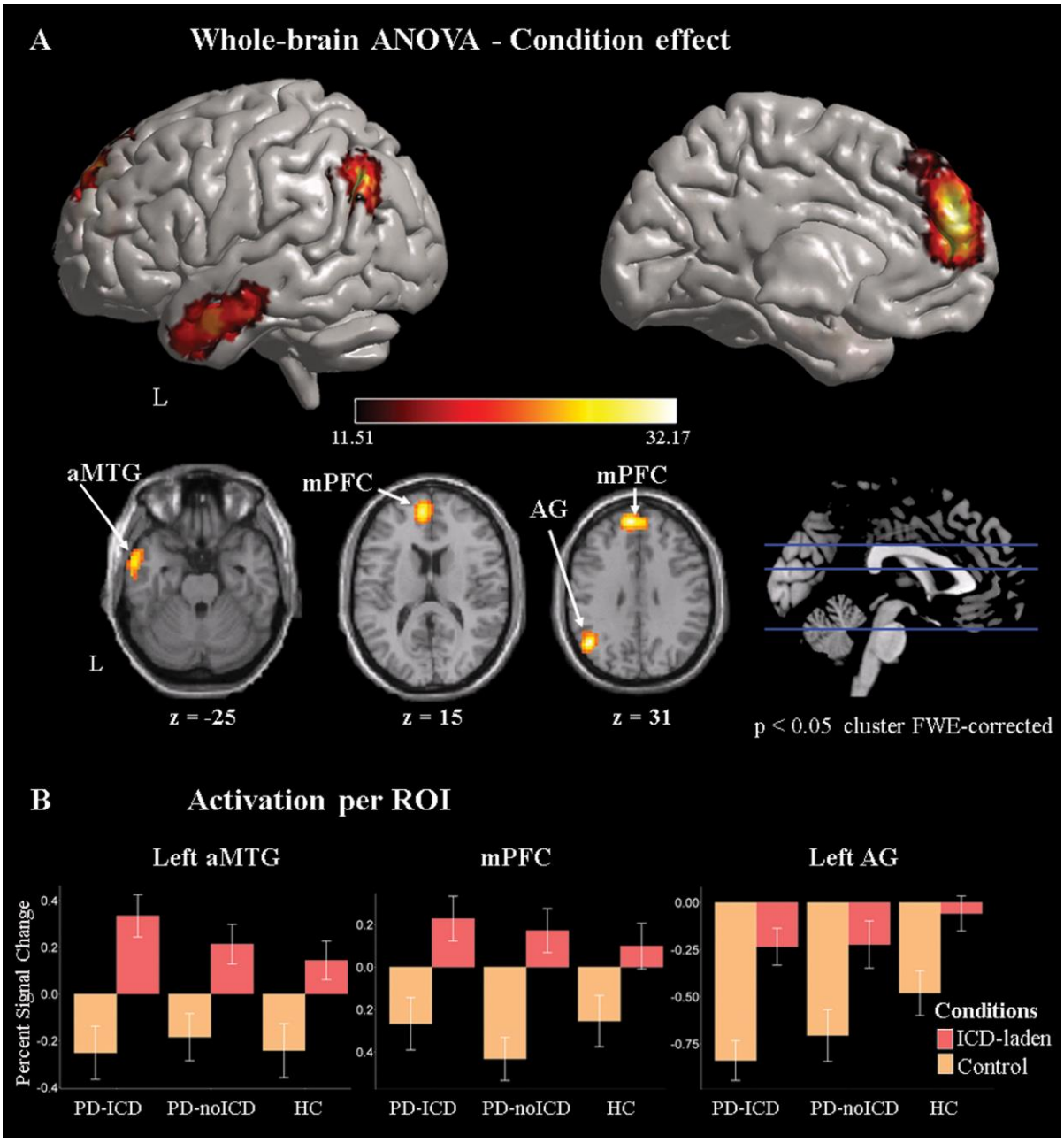

Figure 28. Whole-brain ANOVA. (A) Brain renderings and axial sections showing the Condition (ICD-laden words, control words) main effect, $p < 0.001$ voxel-level extent threshold, $p < 0.05$ cluster-level FWE corrected. (B) Plot of the ROI activation for each significant cluster observed in the Condition main effect. Error bars represent the standard error.

laden words compared to control words, all participants showed increased activation in the left aMTG and mPFC, and less deactivation in the left AG.

3.2.2. Functional connectivity analysis

We examined pairwise FC between the three regions who showed increased activation for ICD-laden words, to investigate if groups differed in the way these regions interacted during processing of ICD-laden or control words. Considering that these regions were obtained from the Condition effect of the whole-brain ANOVA, we will exclusively focus on Group by Condition interactions.

For the FC between the left aMTG and left AG, we found a Group by Condition interaction ($F_{2, 47} = 3.44$, $p = 0.040$, $\eta_p^2 = 0.13$). To follow up on the interaction, we performed one-way ANOVAs for ICD-laden and control words. We found a marginal effect for the ICD-laden condition ($F_{2, 47} = 3.17$, $p = 0.051$, $\eta_p^2 = 0.12$) but no effect for control words ($F_{2, 47} = 1.49$, $p = 0.235$, $\eta_p^2 = 0.06$). To further explore the interaction, we decided to analyze the difference in connectivity between ICD-laden and control words in each group performing three paired sample T-tests between conditions. For the PD-ICD group, we found a significant difference in the connectivity for ICD-laden and control words ($t_{16} = 2.97$, $q = 0.027$, $d = 0.72$) whereas no

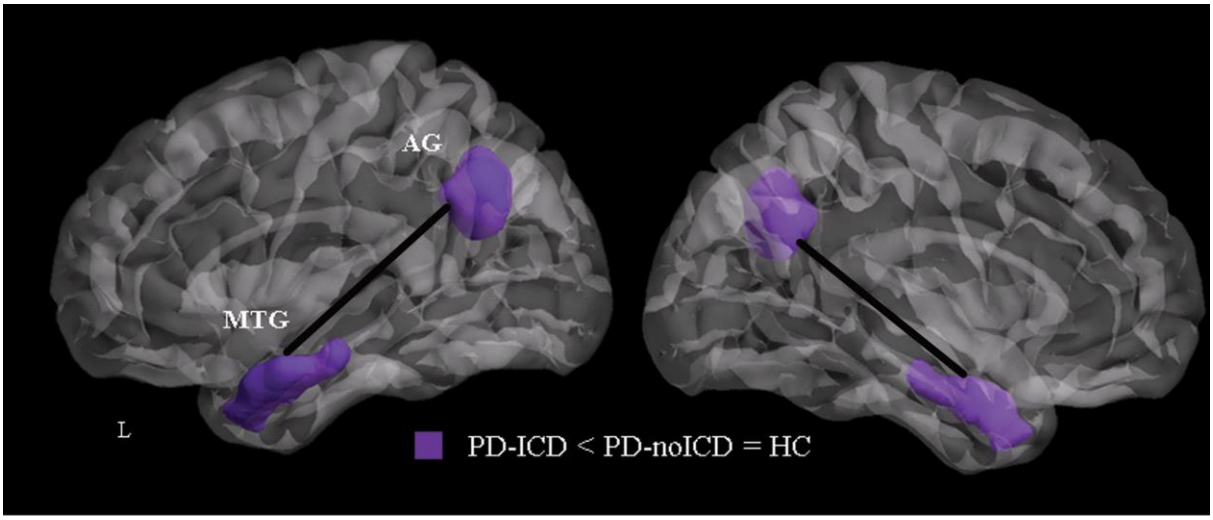

Figure 29. Functional pairwise connectivity results. Compared to PD-noICD and HC participants, PD-ICD subjects show reduced co-activation between left MTG and left AG for processing ICD-laden words > Null. MTG = middle temporal gyrus; AG = angular gyrus.

significant difference was found for the PD-noICD (t_{14} = 0.34, q = 0.740, d = 0.09), nor the HC group (t_{17} = 1.26, q = 0.339, d = 0.3) (see Figure 29). These results indicate that whereas for PD-noICD and HC participants the FC between left aMTG and left AG was similar for ICD-laden and control words, PD-ICD participants showed a reduced connectivity for ICD-laden words as compared to control words.

There was no interaction for the FC between the left aMTG and the mPFC ($F_{2, 43}$ = 1.75, p = 0.185, η_p^2 = 0.07) as well as between the left AG and the mPFC ($F_{2, 43}$ = 0.8, p = 0.457, η_p^2 = 0.04).

4. Discussion

In Experiment 3 we aimed to investigate the neural correlates of semantic processing in patients with PD-ICD through an auditory comprehension task. Semantic deficits associated with PD pathology are linked to impaired cortico-striato-cortical system. Taking into account additional striatal damage and consequential frontostriatal disconnection (Aracil-Bolaños & Strafella, 2016; Carriere et al., 2015; Premi et al., 2016) suffered by patients with PD-ICD, in comparison with PD-noICD patients, we expected semantic processing to be more severely altered in the sample with medication-induced impulsivity. By including a condition composed of ICD-laden words in addition to a control condition, we were able to observe which regions of the brain responded more strongly to ICD-laden words for all participants. Furthermore, PD-ICD patients' showed reduced co-activation between left aMTG and left AG, regions sensitive to ICD-laden words relative to their PD-noICD and HC counterparts, which suggests that PD-ICD patients process ICD-laden words differently.

Initially, the exploratory whole-brain analysis did not show the main effect of Group or the Group by Condition interactive effect. In contrast, the main effect of Condition revealed three regions showing stronger activation during ICD-laden versus control words. These three regions (i.e., the mPFC, the left aMTG, and the left AG) play a role in semantic

processing (Binder et al., 2009; Xu et al., 2016), although each region is associated with specific processing aspects that are discussed next.

While the left aMTG and AG are considered "core" nodes within the semantic network (Fedorenko et al., 2011), the mPFC is considered to play a critical role in self-related cognitive control and outcome monitoring (W. H. Alexander & Brown, 2010, 2011; Gazit et al., 2020). In addition, the mPFC has also been specifically associated with implicit emotional processing (Phan et al., 2002) and the modulation of attentional resources to those emotional stimuli (Bermpohl et al., 2006). Although the ICD-laden words are slightly different to the other emotional stimuli used in previous studies, they do refer to self-related cravings and wishes. In the current task, participants were focused on processing every word to detect brand words, the target they were instructed to respond to. When hearing ICD-laden words, participants implicitly processed the ICD nature of the words while possibly dedicating more attentional resources to these words than to control words. These functions would be met by the mPFC equally in all participants.

The left aMTG is another region with increased activation for ICD-laden words in comparison with control words. The anterior temporal pole (ATP), an area encompassing the aMTG region observed in our whole-brain analysis, has been considered as an important semantic hub, responsible for accessing the selected features and binding them together (Ralph et al., 2010; Patterson et al., 2007; Zhao et al., 2017). Rooted on the evidence from patients with semantic dementia, these studies consider the ATP as an amodal hub where features with different qualities, such as shape or action, are combined and processed together. Research evidence from studies using emotionally-laden materials indicates that the left MTG as a whole is a relevant region, showing increased activation for emotional concrete words compared to emotional abstract words (Pauligk et al., 2019), as well as for positive compared to negative emotional words (Kuchinke et al., 2005). Given previous evidence, it is not surprising that left aMTG shows higher activation for ICD-laden words, which are salient and engaging words. At the level of activation, we found no group differences suggesting that left aMTG is equally recruited for all participants in the processing of ICD-laden materials.

The left AG also showed increased recruitment for ICD-laden *versus* control words. While left aMTG and mPFC showed an increased activation for ICD-laden words in contrast with control words, left AG showed a general deactivation for all participants. However, left AG showed reduced deactivation during ICD-laden trials in contrast with control trials. This pattern of reduced deactivation during semantic processing is typical of the AG due to its involvement in the Default Mode Network (DMN) (Seghier et al., 2010). The AG, together with ATP, is involved in amodal binding and integration (Binder & Desai, 2011; Bonner et al., 2013; Lau et al., 2008). The supramodal processing executed by these regions is supported by the recruitment of, first ATP, followed by AG, during auditory and visual tasks indistinctively (Bemis & Pylkkänen, 2013). However, these semantic hubs may be establishing different relationships, both necessary for semantic processing. Davis and Yee (2019) have recently suggested the connectivity between AG and hippocampus would support thematic processing in AG, while ATP would be involved in taxonomic processing due to its connectivity with the perirhinal cortex. In other words, AG would bind representations that share a common theme, and ATP would bind representations that share multiple features. When participants heard an ICD-laden word (e.g., *hamburger*) they would automatically make associations with concepts sharing a common theme (e.g., their favorite restaurant, the counter where they order, or fries) and belonging to the same taxonomy (e.g., a sandwich, minced meat). Possibly due to the more appealing nature of ICD-laden words, they would convey a more complex semantic map than for control words, explaining the increased activation in left AG for ICD-laden words relative to control words.

Although the activation pattern of mPFC, left MTG and left AG suggest a similar semantic processing for all participants, pairwise FC results suggest otherwise. We found that, for ICD-laden words, the PD-ICD group showed reduced left aMTG-AG co-activation compared to PD-noICD and HC participants. These regions have been previously shown to co-activate strongly during resting-state, connecting anterolateral ATP with the DMN (Pascual et al., 2015) as well as during semantic processing of conflicting elements (e.g., dry rain) requiring additional semantic integration efforts (Molinaro et al., 2015). The increased co-activation between the two semantic hubs, as in the Molinaro and colleagues (2015) study, suggests a deeper or more elaborated semantic processing. Yet, we found no increases in the strength of the FC for ICD-laden compared to control words for any group,

suggesting it is not the apparent salience of ICD-laden words that require increased processing. On the contrary, we find an interactive effect of Group by Condition. Therefore, while whole-brain analysis showed increased recruitment of left aMTG and left AG for ICD-laden words for all groups, FC analysis showed reduced left aMTG-AG coupling in PD-ICD patients, that could affect the processing of the ICD-laden words. If this was the case, the processing of a word (e.g., *hamburger*), would evoke a less integrated semantic map, reducing the semantic representations of concepts they could find distracting or triggering, and shielding patients from the impact of ICD-laden words. This would indicate that PD-ICD patients process ICD-laden words to a lesser degree than PD-noICD and HC participants. It is possible the reduced co-activation observed in PD-ICD patients is related to distinct functioning of the semantic network, directly affecting two semantic hubs, or that altered DMN co-activation in PD-ICD patients (Tessitore et al., 2017) is influencing FC differentially in these patients by disengaging AG involvement in semantic processing.

The current study is the first to examine semantic processing in PD-ICD patients. Despite the novelty of the present study, semantic impairments in PD patients (Angwin et al., 2006; Copland, 2003), their difficulty inhibiting semantic and phonetic competitors (Castner et al., 2007; L. L. Murray, 2008), and the additional cortico-striatal changes encountered by PD-ICD patients (Carriere et al., 2015; Premi et al., 2016) led us to hypothesize an aggravated semantic processing difficulty in these patients. We expected the structural and functional differences in the cortico-striato-cortical network observed in PD-ICD patients (Carriere et al., 2015; Premi et al., 2016) to difficult semantic processing. Yet, our results indicate a differential semantic processing of ICD-laden words in patients with impulsivity due to an impaired FC between semantic hubs. Furthermore, the differential FC observed could be interpreted as a compensatory mechanism protecting PD-ICD patients from triggers. Yet, further research is necessary to clarify unresolved questions: Are the semantic maps evoked by ICD-laden words poorer than in PD-ICD as compared to PD-noICD patients? Is the observed effect a general effect of ICD or would patients with different ICDs be affected in different ways? And finally, does the reduced FC between aMTG and AG benefit PD-ICD patients?

4.1. Conclusions

This study is the first to indicate functional alterations in PD-ICD patients during semantic processing. Participants completed an auditory semantic task in which they were required to detect brand words to ensure the processing of all trials. By including ICD-laden and control words, we were able to detect three regions that responded differentially to ICD-laden words for all participants: mPFC, left aMTG, and left AG. However, compared to their counterparts, PD-ICD patients showed a reduced co-activation between the two semantic hubs, left aMTG and left AG, for ICD-laden words compared to control words. While most studies assessing the effect of PD-ICD on patients focus on very restricted cognitive functions such as inhibition and reward, this study indicates altered semantic processing, a very distinct function.

Discussion

Chapter 10: General discussion

In the current doctoral dissertation, I investigated the scope of ICD on PD patients in functions either not assessed before in this population, or where the previous behavioral evidence is contradictory. fMRI was employed to investigate the functional correlates of three different domains (i.e., sequential movement, motor inhibition and semantic processing) in patients with PD-ICD, and two control groups composed of PD-noICD and HC participants. The relevance of employing fMRI was to assess the functional neural changes and functioning of the motor, stopping, and semantic networks in the same sample of PD-ICD patients.

Most of the previous work from the cognitive neuroscience discipline has focused on reward-related tasks that tap directly into the pathological behaviors that patients with PD-ICD engage in, and into the related dopaminergic hyperstimulation of the VS that associates the altered functioning of the VS with the pathological behaviors that PD-ICD patients exhibit. Yet, research evidence from molecular and functional imaging studies indicates that differences between PD-ICD and PD-noICD patients are not limited to the VS, which is considered the hub of the reward system. In fact, as it has been presented in Chapter 2, section 1.2, abnormalities associated with PD-ICD are also observed in the motor striatum (Premi et al., 2016), and frontal regions (Joutsa et al., 2012; J.-Y. Lee et al., 2014). Furthermore, these abnormalities seem to involve several neurotransmitter systems such as the dopaminergic, serotoninergic and noradrenalinergic systems (Vriend, 2018). A resting

state FC study also indicates that the hyperdopaminergic state of PD-ICD patients is reflected in reduced cortico-striatal co-activation (Carriere et al., 2015). The extent of the alterations in this population suggests a broader implication on functions beyond reward, including movement and the two cognitive functions investigated here, response inhibition and semantic processing, therefore highlighting the need of the current work.

Thus, with this doctoral dissertation I aim to extend the previous research done on ICD in PD beyond the reward system and cognitive impulsivity, by examining the functional correlates of the three domains described in Chapter 7, Chapter 8, and Chapter 9. Thus, the main goal of the present work is to investigate whether the effects of the functional and structural cortico-striatal alterations found in PD-ICD patients (Carriere et al., 2015; Premi et al., 2016; Verger et al., 2018) impact the motor, stopping, and semantic networks. Specifically, we are interested in how the functions examined here are rearranged based on the neural changes associated with ICD in PD. As such, this is the first work to investigate the functional correlates of multiple domains, different from cognitive impulsivity, in a sample of PD-ICD, PD-noICD and HC participants. Below, I will elaborate on how these experiments contribute to increase our knowledge about ICD in PD.

1. ICD beyond reward

The first hypothesis of the current doctoral dissertation (see Chapter 4 section 1) was that PD-ICD patients would present differential neural correlates while performing the tasks here included (i.e., finger tapping, response inhibition, and semantic processing tasks), indicating that the effect of ICD in PD patients is present beyond reward-related mechanisms. Despite the varied nature of the three experiments performed with the present sample, the domains examined here were thought to be sensitive to the neural changes experienced by PD-ICD patients. In line with widespread molecular imaging and resting state functional imaging abnormalities (Carriere et al., 2015; Joutsa et al., 2012; Premi et al., 2016; Verger et al., 2018), this work indicates that the functional effect of ICD on these patients is more widespread

than previously thought, and it can have an overarching impact on patients' daily functioning and quality of life.

Experiment 1 investigated the motor network via a sequential finger tapping task. The putamen, responsible for motor control, is depleted of dopamine since the early stages of PD (Aracil-Bolaños & Strafella, 2016; Playford et al., 1992; Seibyl et al., 1995), and PD-ICD patients show greater reduction of DAT availability (Premi et al., 2016). In addition, indications of disconnection between putamen and premotor and associative cortices in PD-ICD patients (Carriere et al., 2015; Premi et al., 2016) led us to consider that putamen malfunction could affect the functioning of the motor network. Our results confirmed that, only in PD-ICD patients, two regions sensitive to high doses of dopaminergic medication over a long time (i.e, right VLp and putamen) showed altered FC. Specifically, compared to both control groups, PD-ICD patients showed reduced co-activation between right VLp and bilateral putamen, while performing the sequential finger tapping task with their non-dominant hand. Importantly, these analyses were controlled for manual proficiency as measured in the UPDRS-III.

Experiment 2 assessed the functioning of two aspects of response inhibition. Although most research in impulsivity on PD-ICD patients has focused on cognitive inhibition, the increased impulsivity and failure to disengage from pathological behaviors PD-ICD patients experience suggests response inhibition difficulties. Yet, behavioral results on response inhibition on patients with PD-ICD, although mixed, indicated performance could be unimpaired (Claassen et al., 2015; Filip et al., 2018; Meyer et al., 2020). Therefore, PD-ICD patients could be employing compensatory mechanisms to preserve adequate behavior. As expected, our results showed no behavioral differences between groups. However, PD-ICD patients recruited a hyperactive and bilateral stopping network while participants performed the more demanding form of inhibition, proactive inhibition. When participants performed restrained inhibition, withholding the impulse to inhibit, PD-ICD patients showed increased co-activation of the IFG with attentional regions. Thus, the challenges that each aspect of inhibition created for PD-ICD patients were addressed with compensatory activations and co-activations that could account for their unimpaired performance.

Finally, Experiment 3 dealt with semantic processing, a cognitive function not previously examined in PD-ICD patients, much less in a neuroimaging study. However, impaired semantic processing has been linked to depleted dopaminergic cortico-striato-cortical system observed in PD patients (Angwin et al., 2006). Therefore, it was relevant to examine semantic processing in PD patients with additional cortico-striatal alterations linked to dopaminergic intake (Carriere et al., 2015; Premi et al., 2016; Verger et al., 2018). By focusing on the processing of ICD-laden stimuli, we observed a reduced co-activation between two semantic hubs (i.e., left aMTG and left AG) in PD-ICD patients compared to their control counterparts, which can be interpreted as a reduced semantic processing of ICD-laden words.

Hence, as hypothesized, our results suggest PD-ICD patients experience functional alterations of the motor, stopping, and semantic networks. The differences observed in these three studies, none of which revolved around cognitive impulsivity, indicate that the impact of ICD on PD patients is not restricted to the impulse to engage in pathological behaviors and to a faulty reward system. The functional extent of the alterations in PD-ICD patients is in line with previous findings suggesting that PD-ICD is not only associated with aberrant VS functioning (e.g., Callesen et al., 2013; Gatto & Aldinio, 2019; Santangelo et al., 2019). While examining the functioning of domains believed to be spared in PD-ICD patients, this work showed differential functioning in PD-ICD patients unrelated to motor or cognitive impairment. Our results highlight the importance of examining the functional correlates of PD-ICD as a means to better understanding this complication.

Importantly, the current work has focused on examining neural changes, rather than behavioral ones. Yet, Experiment 2, where behavior was measured, showed no impaired response inhibition in PD-ICD patients compared to their control counterparts. Experiment 1 and 3 did not measure behavior of target trials. Still, functional results of Experiment 1 were controlled for the degree of manual impairment associated to PD, suggesting that behavior was not driving the abnormal FC observed in PD-ICD patients. Similarly, Experiment 3 was centered around the passive listening and processing of ICD-laden and control words. Consequently, there was no performance measure of ICD-laden or control trials. However, all participants underwent a thorough neuropsychological battery, and PD-ICD patients showed no differential results in semantic fluency, naming, or memory tests, suggesting that

the semantic processing of the three groups was similar (see Table 2). Therefore, while performing the tasks differentially, our results suggest an absence of behavioral impairment. Yet, PD-ICD participants recruited for this doctoral thesis are in the initial stages of the disease, with a Hoehn and Yahr score between 1.5 and 3 (see Table 1). PD-ICD patients with greater disease severity should present greater damage related to the PD pathology, which could make them more sensitive to the additional changes associated with the ICD and difficult compensatory mechanisms.

Research examining the impact of ICD severity in PD-ICD patients as well as the progression of ICD on PD patients from before it is developed until it stops being a clinical concern is needed. Understanding how severity and progression of ICD in PD relates to neural correlates across a broad spectrum of domains can shed light into the full impact of the complication in patients' daily living. A thorough examination of additional cognitive functions that could be further affected (e.g., attention, stimuli- and task-switching, and memory) and their association with neuroimage measures would extend our knowledge of the impact of ICD on PD patients. Future work should also attempt to replicate these findings and to associate behavioral markers with the functional changes of the motor, stopping, and semantic network. Yet, this work attempts to frame PD-ICD as a disorder with far-reaching implications, that cannot be reduced to the combination of PD pathology and a faulty reward system. Thus, PD-ICD patients will face functional alterations distinct to their PD-noICD counterparts that need to be understood and considered in their treatment.

2. Altered functional connectivity across tasks: compensation or deterioration?

The second hypothesis of the current work proposed two major mechanisms that could account for PD-ICD patients' differential functional correlates: PD-ICD patients could either display compensatory mechanisms to preserve optimal functioning as intact as possible or they could display aberrant functional activation and co-activation reflecting the damage

associated with ICD in PD, preventing correct functioning and performance. On this regard, Experiment 1, 2, and 3 have highlighted the importance of FC, with PD-ICD patients showing altered co-activation between task-relevant regions, compared to their PD-noICD and HC counterparts. We found reduced co-activation for PD-ICD participants in Experiment 1 and 3, and increased co-activation between regions of the stopping network and attentional regions for PD-ICD participants in Experiment 2. Typically, increased co-activation is interpreted as compensation, in the sense in which a more extended network is required to perform the same task. Reduced co-activation, on the other hand, has been interpreted by previous studies as a functional reflection of the anatomical damage or dysfunction associated with ICD in PD (Carriere et al., 2015; Filip et al., 2018). Yet, interpreting reduced co-activation in Experiments 1 and 3 as an effect of the structural degeneration or malfunction may not be accurate.

As discussed in Experiment 1, the reduced co-activation between motor regions right VLp and bilateral putamen must be analyzed considering these regions' association with $LEDD_{L\text{-}DOPA}$ dosage and disease duration in PD-ICD participants. Our results suggest that prolonged exposure to dopaminergic stimulation in PD-ICD patients have an effect on the activation of right VLp and putamen. Specifically, these regions would become hyperactive in PD-ICD patients with longer PD duration, and continued exposure to higher doses of levodopa. Interestingly, the opposite tendency, hypoactivation of thalamus and putamen, is seen in PD patients OFF medication (Jahanshahi et al., 1995; Spraker et al., 2010; Yu et al., 2007). Given that all PD patients underwent MRI scanning ON medication, the tendency towards hyperactivation of the right VLp and putamen as disease progresses can be interpreted as an exaggerated effect of levodopa in these regions for PD-ICD participants, boosting the dopaminergic effect of medication. This is, PD-ICD patients could be showing an exaggerated ON state. After controlling for manual proficiency, PD-ICD patients showed reduced co-activation between right VLp and bilateral putamen, indicating a bypass of the expected putamen-VLp connection present in the healthy motor network. We suggest that the tendency towards hyperactivation, associated with increased chronic dopaminergic stimulation, together with the reduced FC of these regions indicate motor facilitation, probably due to a differential effect of chronic dopaminergic stimulation in the right VLp and putamen. Therefore, PD-ICD patients would require less integration of the motor network to

perform non-dominant manual movements, although it remains possible that PD-ICD patients' movement had a different quality associated with the results we found. As we did not measure in-scanner movement, we cannot ensure the quality of the movement performed during scanning was similar across groups. Yet, we controlled for manual proficiency as measured by the UPDRS-III, which should be similar to the proficiency displayed in the scanner, suggesting in-scanner movement is not confounding our results. However, due to its relevance, future studies should study the relationship between online behavior and fMRI data. These results suggest that the presence of ICD on PD patients establishes a unique association with disease duration and dopaminergic dosage. If chronic medication stimulation had an exaggerated effect on Mthal and putamen in PD-ICD patients, similar to its effect in the VS, it could alter the FC of the motor network. As a result, PD-ICD patients could experience a compensation of the hypoactivation induced by PD, and need less co-activation between these regions to perform non-dominant movements. Therefore, the exaggerated effect of dopaminergic medication on PD-ICD patients could alleviate to a greater extent motor difficulties associated with PD, than in PD-no ICD patients. Future studies assessing movement initiation difficulties and bradykinesia in PD-ICD and PD-noICD patients are needed to assess the quality of in-scanner movement and ensure similar speed and amplitude between groups, as well as to confirm the link between the observed results in Experiment 1 and motor facilitation, possibly alleviating some motor symptoms of PD in PD-ICD patients.

Similarly, Experiment 3 showed that, compared to both control groups, PD-ICD patients co-activated two semantic hubs (i.e., left aMTG and left AG) to a lesser extent when presented with ICD-laden words. Although further studies are needed, our results suggest that the reduced co-activation that we observed in PD-ICD patients could hinder the deep semantic processing of ICD-laden words, possibly activating a poorer semantic map. A reduced semantic processing of ICD-laden words, could, accordingly, protect them from triggering stimuli and thoughts, reducing their engagement with pathological behaviors. Thus, the reduced co-activation presented by PD-ICD participants could be interpreted as a compensatory mechanism to reduce pathological effects, this is, the urge towards pathological behaviors in ICD.

Experiment 2, on the other hand, highlighted the increased co-activation between the IFG and attentional regions during restrained inhibition, probably reflecting an additional engagement of attentional mechanisms to deal with the contradictory signal and shift attention to task execution. Thus, in response to increased impulsivity, PD-ICD patients engaged additional attentional areas maintaining unimpaired performance. As such, the increased involvement of attentional mechanisms can be interpreted as another compensatory mechanism put in place to compensate for increased impulsivity.

The study of co-activation between regions highlights the importance of the brain's integrated functioning. Interestingly, most functional changes reported in this doctoral dissertation occurred at the level of FC. Thus, this work suggests that FC alterations are a determinant factor in the pathophysiology of PD-ICD, and opens the door to further in-depth-study of task FC to better understand ICD in PD. Here, we suggest that compensation through altered FC results in the lack of observed cognitive and motor impairment in PD-ICD patients, compared to their PD-noICD and HC counterparts. However, if this is the case, it is likely that in extremely severe cases of ICD, compensatory mechanisms may not suffice to balance performance, and ICD in PD could result in unique behavioral impairments.

3. Conclusions

In the present doctoral dissertation, we examined ICD in PD patients from a cognitive neuroscience approach. Specifically, we assessed the functional correlates of the motor, stopping, and semantic network in an attempt to observe the extent of PD-ICD-related alterations on domains unrelated to cognitive impulsivity and reward. Our results indicate that PD-ICD patients present functional alterations, mostly on the form of abnormal FC, that could be interpreted as compensatory mechanisms to maintain adequate motor and inhibitory control, and to control the impact of potential triggers. Yet, more studies are needed to replicate these findings and to examine the link between behavior and neural correlates in these patients, which could provide further support for neural changes being compensatory.

This work is insufficient to propose new models and to determine if changes associated with PD-ICD capture predisposing alterations leading to the development of ICD on PD patients on dopaminergic medication, if they capture the consequence of developing ICD, or if they represent an adaptation to ICD. Yet, the functional alterations presented in this work could be interpreted as compensatory mechanisms easing the effects of impulsivity and motor impairment and extend beyond cognitive impulsivity and the dopaminergic system.

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Appendix

1. Participants

Below we detail the ICD characteristics of PD-ICD participants, along with information about their inclusion in the three experiments that comprise this doctoral dissertation. Primary ICDs represent their highest scoring pathological behavior according to the QUIP-RS. Other ICDs include the remaining pathological behaviors scoring above the optimal cut-off point described by Weintraub and colleagues (2012).

Supplementary Table 1. ICD characteristics of PD-ICD participants.

SUBJECTS	Sex (M/F)	Age (years)	Primary ICD	Other ICDs	Included in Experiment 1	Included in Experiment 2	Included in Experiment 3
PD-ICD 1	M	56	PH	-	○	○	●
PD-ICD 2	F	69	BE	-	○	●	○
PD-ICD 3	M	64	HB	-	●	●	●
PD-ICD 4	M	64	PH	-	●	●	●
PD-ICD 5	M	59	HB	-	●	●	●
PD-ICD 6	F	64	CS	HB	●	●	●
PD-ICD 7	F	53	CS	-	●	○	○
PD-ICD 8	M	60	CS	HB	●	●	●
PD-ICD 9	M	61	CS	PN	●	●	●
PD-ICD 10	M	48	PH	-	●	●	●
PD-ICD 11	M	77	HB	BE, PN, PH	○	●	●
PD-ICD 12	M	68	PH	-	●	●	●
PD-ICD 13	M	57	PG	BE	●	●	●
PD-ICD 14	M	44	HB	BE	●	●	●
PD-ICD 15	M	61	BE	-	●	●	●
PD-ICD 16	M	58	BE	-	●	○	●
PD-ICD 17	M	71	PH	CS, BE	●	●	●
PD-ICD 18	M	75	PH	-	○	●	○
PD-ICD 19	M	68	CS, HB	PH	●	●	●
PD-ICD 20	M	65	PH, BE	-	●	●	●
PD-ICD 21	M	65	BE	HB	●	●	●

Abbreviations: PH = pathological hypersexuality; BE = binge eating; HB = hobbysm; CS = compulsive shopping; PN = punding; PG = pathological gambling

2. Behavioral results

Below we include further behavioral measures for the SST task described in Chapter 8. It presents mean RTs and SDs of the main conditions of interest per group.

Supplementary Table 2. Response times of the conditional SST task.

Condition	PD-ICD n = 18	PD-noICD n = 17	HC n = 15
Critical Go			
RT (ms)	622 (77.61)	624 (57.55)	581 (52.83)
Critical Stop			
RT incorrect responses (ms)	552 (110.95)	541 (104.87)	507 (77.82)
Non-critical Go			
RT (ms)	570 (85.14)	559 (54.42)	510 (38.66)
Non-critical Stop			
RT (ms)	619(118.81)	631 (78.71)	578 (65.42)

Note : *Values expressed in Mean (SD). Response times (RTs) refer only*

3. Stimuli

Beneath, we display all the words presented to participants in the semantic processing task described in Chapter 9. To improve readability, words are displayed in three separate tables. Supplementary Table 3 presents ICD-laden words classified into the predominant pathological behaviors they associate with: pathological gambling, compulsive shopping, pathological hypersexuality, and binge-eating. Supplementary Table 4 displays control words, and Supplementary Table 5 brand words. For ICD-laden and control words we include an approximate English translation, while for brand words we include the product they associate with.

Supplementary Table 3. ICD-laden words presented in Experiment 3.

ICD-laden words							
Pathological gambling		**Compulsive shopping**		**Pathological hypersexuality**		**Binge-eating**	
Spanish	English	Spanish	English	Spanish	English	Spanish	English
apostador	gambler	accesorios	accessories	anal	anal	bizcocho	cake
apuesta	bet	barato	cheap	beso	kiss	bollería	pastry
baraja	deck of cards	bisutería	jewelry	bikini	bikini	bollo	bun
bingo	bingo	boutique	boutique	bragas	panties	bombón	chocolate
bonoloto	a form of lottery	capricho	whim	camisón	nightgown	calamares	squid
bote	saved winning	centro comercial	Mall	caricia	caress	caramelo	candy
casino	casino	chollo	bargain	chocho	cunt	chocolatina	candy bar
concurso	contest	colonia	perfume	coño	cunt	chorizo	chorizo
crédito	credit	compra	purchase	cubana	cuban	chuleta	chop
crupier	croupier	comprador	buyer	cuello	neck	churro	fritter
cupón	coupon	conjunto	set	cuerpazo	body	confitería	confectionery
cuponazo	a form of lottery	cosméticos	cosmetics	cuerpo	Body	crepe	crepe
dinero	money	descuento	discount	culo	ass	croissant	croissant
El Gordo	a form of lottery	escaparate	showcase	desnudo	nude	croqueta	croquette
escalera de color	color ladder	estrenar	wear for the first time	erección	erection	donuts	donuts
euromillón	a form of lottery	ganga	bargain	escote	neckline	dulces	candy
ficha	token	grandes almacenes	department store	fantasía	fantasy	galleta	biscuit
fortuna	fortune	guardaropa	wardrobe	lencería	lingerie	hamburguesa	burger
ganancias	profits	joyas	jewels	ligue	flirt	helado	ice cream
juego	game	joyería	jewelry	magreo	magreo	jamón	cured meat
jugador	player	lujo	luxury	mamada	blow job	mazapán	marzipan
lotería	lottery	maquillaje	make-up	masturbación	masturbation	merienda	afternoon snack
millonario	millionaire	marca	brand	minifalda	mini skirt	mermelada	marmalade
moneda	currency	moda	fashion	ninfómana	nymphomaniac	paella	paella
naipe	card	obsequio	gift	orgía	orgy	panceta	bacon
partida	game	oferta	discount	pechugona	busty	panchineta	a sweet dessert
poker	poker	ostentación	ostentation	pelotas	balls	pastas	pastry
premio	prize	outlet	outlet	pezón	nipple	pastel	cake
primitiva	a form of lottery	precio	price	polla	cock	pastelería	cake shop
puja	bid	rebaja	sales	pornografía	pornography	pintxo	pintxo
quiniela	football pools	reloj	clock	prostituta	prostitute	polvorón	christmas sweet
quinigol	a form of lottery	ropa	clothing	puta	bitch	postre	dessert
rico	rich	ropero	wardrobe	puticlub	whorehouse	roscón	christmas sweet
rifa	raffle	subasta	auction	semen	semen	rosquilla	donut
ruleta	roulette	supermercado	supermarket	sexo	sex	salchichón	cured meat
salón de juegos	playroom	tele-tienda	home shopping network	sostén	bra	tarta	pie
sorteo	lottery	tienda	store	striptease	striptease	torrija	typical dessert
timba	a form of lottery	venta	sale	sujetador	bra	tortilla	Spanish tortilla
tómbola	a form of lottery	zapatería	shoe shop	tanga	thong	trufa	truffle
tragaperras	slot machine	zapatos	shoes	tetas	tits	turrón	nougat

Supplementary Table 4. Control words presented in Experiment 3.

Control words			
Spanish	English	Spanish *(continued)*	English *(continued)*
acordeón	accordion	hormiga	ant
aguila	eagle	lagarto	lizard
alicates	pliers	lápiz	pencil
ancla	anchor	lechuga	lettuce
antena	antenna	león	lion
araña	spider	libro	book
arbol	tree	maíz	corn
arbusto	bush	maletín	briefcase
auriculares	headphones	manzana	apple
avión	plane	margarita	daisy
bisturí	scalpel	mechero	lighter
bolígrafo	pen	melón	melon
bomba	bomb	molino	windmill
buzón	mailbox	monóculo	monocle
cacahuete	peanut	montaña	mountain
cachorro	puppy	motor	engine
cactus	cactus	narciso	daffodil
cajero	cashier	navaja	razor
cámara	camera	paloma	dove
canario	canary	pañuelo	handkerchief
candelabro	chandelier	paracaídas	parachute
cebolla	onion	peine	hair comb
champiñón	mushroom	pepinillo	pickle
cinturón	belt	plátano	banana
cobaya	guinea pig	portatil	laptop
cremallera	zipper	puerta	door
cuchara	spoon	rábano	radish
cuchillo	knife	rana	frog
cuervo	raven	ratón	mouse
escaleras	stairs	satélite	satelite
escoba	broom	saxofón	saxophone
espárragos	asparagus	semáforo	traffic light
espátula	spatula	taza	bowl
estufa	stove	teléfono	phone
furgoneta	van	televisión	TV
ganso	goose	trofeo	trophy
gatito	kitten	trombón	trombone
hamster	hamster	tuba	tuba
helicóptero	helicopter	valla	fence
hierba	herb	violín	fiddle

Supplementary Table 5. Brand words presented in Experiment 3.

Brand words			
Name	Product	Spanish *(continued)*	English *(continued)*
Alcampo	supermarket	Mcdonalds	restaurant
Amazon	computing	Mercadona	supermarket
Bershka	clothes	Mercedes	cars
Bimbo	food	Microsoft	computing
BMW	cars	Mitsubishi	cars
Cartier	clothes	Movistar	phone
Colacao	food	NASA	space
Colgate	cosmetics	Nestle	food
Correos	mail	Neutrogena	cosmetics
Disney	media	Nokia	technology
Dominos	food	Panasonic	technology
Duracell	batteries	Porsche	cars
Endesa	energy	Prada	clothes
Eroski	supermarket	Pringles	food
Fagor	supermarket	Renault	cars
Fanta	food	Renfe	transport
Ferrari	cars	Repsol	fuel
Ford	cars	Ryanair	transport
Gillette	cosmetics	Samsung	technology
Heineken	food	Sanex	cosmetics
Honda	technology	Seat	cars
Iberdrola	energy	Sony	technology
Iberia	transport	Starbucks	restaurant
Ikea	furniture	Tampax	cosmetics
Kas	food	Telefonica	phone
Kelloggs	food	Toyota	technology
Kleenex	cosmetics	Visa	bank
Lays	food	Vodaphone	phone
Levis	clothes	Yamaha	technology
Lufthansa	transport	Zara	clothes