UNIVERSITAT DE BARCELONA

Visuospatial and visuoperceptual impairment and its structural correlates as measures of cognitive decline in Parkinson's disease

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Visuospatial and visuoperceptual impairment and its structural correlates as measures of cognitive decline in Parkinson's disease

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Unitat de Psicologia Mèdica · Departament de Medicina

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"It did make the throwaway assumption that the mind was simply the operation of the brain, an idea that struck me with force; it startled my naïve understanding of the world. […] *Literature provided a rich account of human meaning; the brain, then, was the machinery that somehow enabled it. It seemed like magic."*

Paul Kalanithi- *When breath becomes air*

Als meus pares
A la meva germana

Dr. Carme Junqué i Plaja and Dr. Bàrbara Segura i Fàbregas, professors at the Universitat de Barcelona,

CERTIFY that they have guided and supervised the doctoral thesis entitled 'Visuospatial and visuoperceptual impairment and its structural correlates as measures of cognitive decline in Parkinson's disease' presented by Anna Isabel Garcia Diaz. They hereby assert that this thesis fulfills the requirements to present her defense to be granted the title of doctor.

Signatures,

Dr. Carme Junqué i Plaja

Dr. Bàrbara Segura i Fàbregas

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CONTENTS

FOREWORD

The thesis hereby presented to obtain the degree of Doctor by *Universitat de Barcelona* is the result of the work carried out over a four-year period at the *Unitat de Psicologia Mèdica of the Departament de Medicina, Facultat de Medicina i Ciències de la Salut*. Following a format based on published articles, this thesis includes three papers published in peer-reviewed journals as follows:

1. **Garcia-Diaz** AI, Segura B, Baggio HC, Marti MJ, Valldeoriola F, Compta Y, Vendrell P, Bargallo N, Tolosa E, Junque C. Structural MRI correlates of the MMSE and pentagon copying test in Parkinson's disease. *Parkinsonism Relat Disord* 2014; 12:1405-10

2. **Garcia-Diaz** AI, Segura B, Baggio HC, Marti MJ, Valldeoriola F, Compta Y, Bargallo N, Uribe C, Campabadal A, Abos A, Junque C. Structural Brain Correlations of Visuospatial and Visuoperceptual Tests in Parkinson's Disease. *J Int Neuropsychol Soc* 2018; 24:33-44.

3. **Garcia-Diaz** AI, Segura B, Baggio HC, Uribe C, Campabadal A, Abos A, Marti MJ, Valldeoriola F, Compta Y, Bargallo N, Junque C. Cortical thinning correlates of changes in visuospatial and visuoperceptual performance in Parkinson's disease: A 4-year follow-up. *Parkinsonism Relat Disord*, 2018; 46:62-8.

During this period, the candidate has collaborated in additional related academic works, published as follows:

1. Garcia-Diaz AI, Segura B, Baggio HC, Junque C. Visuospatial and visuoperceptual impairment in relation to global atrophy in Parkinson's disease. *UB J Psychol* 2013;2:147-58.

2. Segura B, Baggio HC, Marti MJ, Valldeoriola F, Compta Y, Garcia-Diaz AI, Vendrell P, Bargallo N, Tolosa E, Junque C. Cortical Thinning Associated with Mild Cognitive Impairment in Parkinson's Disease. *Mov Disord* 2014; 29:1495-503.

3. Abós A, Baggio HC, Segura B, Garcia-Diaz AI, Compta Y, Marti MJ, Valldeoriola F, Junque C. Discriminating cognitive status in Parkinson's disease through functional connectomics and machine learning. *Sci Rep* 7:45347.

4. Campabadal A, Uribe C, Segura B, Baggio HC, Abos A, Garcia-Diaz AI, Marti MJ, Valldeoriola F, Compta Y, Bargallo N, Junque C. Brain correlates of progressive olfactory loss in Parkinson's disease. *Parkinsonism Relat Disord* 2017;41:44-50.

5. Campabadal A, Segura B, Baggio HC, Abos A, Uribe C, Garcia-Diaz AI, Marti MJ, Valldeoriola F, Compta Y, Bargallo N, Junque C. The use of the University of Pennsylvania Smell Identification Test in Parkinson's disease- diagnostic accuracy and item analysis in a Spanish population *(submitted)*

GLOSSARY OF ABBREVIATIONS

3MS Modified Mini-Mental State

AD Alzheimer's disease

APOE Apolipoprotein E

BNT Boston Naming Test

BPP Bistable Perceptual Paradigm

CDIC Centre de Diagnòstic per la Imatge Clínic

CDR Clinical Dementia Rating scale

COMT Catechol-O-methyltransferase

CSF Cerebrospinal fluid

DAT Dopamine transporter

DLB Dementia with Lewy bodies

DSM Diagnostic and Stastistical Manual of Mental Disorders

DTI Diffusion tensor imaging

DWI Diffusion weighted imaging

EEG Electroencephalography

FA Fractional anisotropy

FDG-PET Fludeoxyglucose Positron Emission Tomography

FLAIR Fluid-Attenuated Inversion Recovery

fMRI Functional Magnetic Resonance Imaging

FRT Facial Recognition Test

FWE Family wise error

GBA Glucosylceramidase

H&Y Hoehn & Yahr scale

ICV Intracranial volume

JHU John Hopkins University atlas

JLOT Judgment of Line Orientation Test

LGN Lateral geniculate nucleus

MAO Monoamine oxidase

MAPT Microtubule associated protein tau

MCI Mild cognitive impairment

MD Mean diffusivity

MDS Movement Disorders Society

Met Methionine

MMSE Mini-Mental State Examination

MoCA Montreal Cognitive Assessment

MRI Magnetic resonance imaging

PCT Pentagon Copying Test

PD Parkinson's disease

PDD Parkinson's disease dementia

PD-MCI Parkinson's disease mild cognitive impairment

RAVLT Rey Auditory Verbal Learning Test

RD Radial diffusivity

RBD REM-sleep behavior disorder

REM Rapid eye movement

ROFC Rey-Osterrieth Figure Copy

ROI Region of interest

SDMT Symbol Digit Modalities Test

SPECT Single-photon emission computed tomography

TBSS Tract-based Spatial Statistics

TMT Trail Making Test

UPDRS Unified Parkinson's disease Rating Scale

Val Valine

VBM Voxel-based morphometry

VFDT Visual Form Discrimination Test

VVT Vienna Visuo-constructional Test

WAIS Wechsler Adult Intelligence Scale

CHAPTER 1.
GENERAL INTRODUCTION

A GENERAL VIEW OF PARKINSON'S DISEASE

Parkinson's disease (PD) is the most common neurodegenerative disorder after Alzheimer's disease (AD) and its incidence is expected to only rise as worldwide populations age, especially in developing Eastern nations (Dorsey et al., 2007).

The prevalence of PD in industrialized countries is estimated at approximately 1% at 60 years of age or older (Nussbaum & Ellis, 2003), and it is rarely seen before age 50 (de Lau & Breteler, 2006). Median age-standardized annual incidence rates in high income countries is estimated at 14 per 100,000 inhabitants in the total population and 160 per 100,000 aged 65 years or older (Hirtz et al., 2007). Lifetime risk frequency is estimated to be 2% for men and 1.3% for women (Elbaz et al., 2002). Some studies report a significantly higher prevalence in men than in women, and neuroprotective effects of estrogens have been suggested as a possible mediating factor (de Lau & Breteler, 2006). Similarly, differences in prevalence have been described according to ethnicity, namely, 16.6 in Hispanic, 13.6 in non-Hispanic, 11.3 in Asian and 10.2 in black citizens per 100.000 inhabitants (Kalia & Lang, 2015). Although these data were age-adjusted, diversities could be due to differences in response rates, survival and case-ascertainment (de Lau & Breteler, 2006).

The symptomatology initially described, namely, bradykinesia, muscular rigidity, resting tremor and postural and gait impairment, have largely prevailed as some of the most prominent clinical manifestations in PD (Goetz, 2011). Nonetheless, clinical presentation is characterized by a wide heterogeneity. In addition, an important number of nonmotor symptoms have also been described to affect PD patients, such as cognitive impairment, olfactory dysfunction, rapid-eye-movement (REM) sleep behavior disorder (RBD), excessive daytime sleepiness, psychiatric disturbances, autonomic dysfunction, pain and fatigue. These symptoms appear early in the disease course in the majority of PD patients (Khoo et al., 2013) and are associated with a reduced health-related quality of life (Duncan et al., 2014). Furthermore, some of them are reported as prodromal PD manifestations.

RBD is the preclinical syndrome associated with the highest risk for PD. However, patients who manifest RBD are at an equal risk of suffering dementia with Lewy bodies (DLB) (Goldman & Postuma, 2014). Olfactory dysfunction is also considered a common prodromal feature in PD, and patients diagnosed with hyposmia are at higher risk of cognitive decline over time, progression to mild cognitive impairment (MCI) and dementia (PDD) (Postuma & Gagnon, 2010). In addition, mood disorders and constipation have both been shown to nearly double an individual's risk of subsequently developing PD (Noyce et al., 2014). Autonomic and sensory symptoms, aside from constipation, may consist in symptomatic postural hypotension, drooling, urinary urgency and nycturia (Hely et al., 2008; Duncan et al., 2014). Excessive daytime sleepiness is present in about 25% *de novo* PD patients (Duncan et al., 2014) and may result from advanced PD and/or side effects of dopaminergic medication. Similarly, impulse control disorders are present in approximately 14% of PD patients and are strongly associated with dopaminergic therapy (Weintraub et al., 2013).

The first line of PD treatment, such as levodopa, dopamine agonists, monoaminoxidase (MAO) type B inhibitors or amantadine, consists in enhancing dopamine concentrations or stimulating dopamine receptors (Fox et al., 2011). To date, none of these drugs has evidenced neuroprotective effects or disease-modifying effects. Bradykinesia and rigidity respond early to dopaminergic treatment. MAO B inhibitors have a moderate effect. In contrast, levodopa and dopamine agonists provide the greatest symptomatic relief, but because long-term use evidences motor complications, such as dyskinesia and motor fluctuations, other medication is preferable for the treatment of early PD, such as MAO B inhibitors, especially in young patients. These complications exhibit adequate responses to MAO B or catechol-O-methyltransferase (COMT) inhibitors. In addition, dopaminergic therapy can exhibit certain adverse effects, such as daytime sleepiness, edema and nausea, and frequently triggers impulse control disorders, such as pathological gambling, compulsive spending, hypersexuality or binge eating, as well as psychosis (Kalia & Lang, 2015).

COGNITIVE SPECTRUM IN PARKINSON'S DISEASE

Cognitive decline is among the most important non-motor symptoms of PD. PD patients are twice as likely as healthy individuals to develop cognitive impairment (Foltynie et al., 2004; Aarsland et al., 2009), and 3 to 5 times more likely to develop dementia (Hobson & Meara, 2004; de Lau et al., 2005), which is associated with a reduced quality of life (Levy et al., 2002; Hughes et al., 2004). Cognitive deficits typically increase with PD duration, and are the predominant source of disability as the disease progresses (Aarsland et al., 2000; Hely et al., 2008).

Parkinson's disease MCI (PD-MCI) is regarded as a potential prodromal or transitional state before the emergence of overt dementia. Therefore, this concept implies a continuum from normal cognition to dementia in PD. Although there is great disparity between studies, about 20-57% of patients have MCI within the first 3 to 5 years after PD diagnosis (Janvin et al., 2006; Caviness et al., 2007; Williams-Gray et al., 2007). Furthermore, dementia occurs in 15-20% of PD patients after 5 years from diagnosis (Williams-Gray et al. 2009), 46% after 10 years (Williams-Gray et al., 2013) and 80% after 20 years from diagnosis (Hely et al., 2008). The cumulative prevalence is estimated to reach 75-90% (Buter et al., 2008; Hely et al., 2008).

Early studies portrayed PD-MCI neuropsychological deficits in terms of the evidence seen in AD-type MCI, and was defined by the following criteria: (1) a memory complaint, preferably corroborated by an informant; (2) impairment in memory as documented according to appropriate reference values; (3) essentially normal performance in non-memory cognitive domains; (4) generally preserved activities of daily living; and (5) absence of dementia (Petersen et al., 1999). However, given the diverse features that characterize PD-MCI with respect to AD-type MCI, these criteria were later revised and an algorithmic approach was established, by which PD-MCI and its subtypes were defined: (1) presence of a cognitive complaint that is not normal for age and that represents a decline in cognitive function, but does not characterize dementia or impair functional activities; (2) presence or absence of memory impairment; and (3) number of domains impaired, leading to four MCI subtypes (amnestic or non-amnestic, and single or multiple-domain) (Winblad et al., 2004). Beyond these initial efforts, the need for a further unification in the criteria and the tools used to establish the exact impact on neuropsychological function led to the elaboration of specific PD-MCI diagnostic guidelines (Litvan et al., 2012) (see Table 1 and Table 2).

Table 1. Criteria for the diagnosis of PD-MCI (Litvan et al., 2012)

Inclusion criteria Diagnosis of Parkinson's disease as based on the UK PD Brain Bank Criteria (Gibb & Lees, 1988). Gradual decline, in the context of established PD, in cognitive ability reported by either the patient or informant, or observed by the clinician. Cognitive deficits on either formal neuropsychological testing or a scale of global cognitive abilities. Cognitive deficits are not sufficient to interfere significantly with functional independence, although subtle difficulties on complex functional tasks may be present.
Exclusion criteria Diagnosis of PD dementia based on MDS Task Force proposed criteria (Emre et al., 2007). Other primary explanations for cognitive impairment (e.g., delirium, stroke, major depression, metabolic abnormalities, adverse effects of medication, or head trauma). Other PD-associated comorbid conditions (e.g., motor impairment or severe anxiety, depression, excessive daytime sleepiness, or psychosis) that, in the opinion of the clinician, significantly influence cognitive testing.
Specific guidelines for PD-MCI level I and level II categories <u>Level I (abbreviated assessment)</u> Impairment on a scale of global cognitive abilities validated for use in PD or Impairment on at least two tests, when a limited battery of neuropsychological tests is performed (i.e., the battery includes less than two tests within each of the five cognitive domains, or less than five cognitive domains are assessed). <u>Level II (comprehensive assessment)</u> Neuropsychological testing that includes two tests within each of the five cognitive domains (i.e., attention and working memory, executive, language, memory, and visuospatial). Impairment on at least two neuropsychological tests, represented by either two impaired tests in one cognitive domain or one impaired test in two different cognitive domains. Impairment on neuropsychological tests may be demonstrated by: • Performance approximately 1 to 2 SDs below appropriate norms or • Significant decline demonstrated on serial cognitive testing or • Significant decline from estimated premorbid levels.
Subtype classification for PD-MCI (optional, requires two tests for each of the five cognitive domains assessed and is strongly suggested for research purposes) PD-MCI single-domain—abnormalities on two tests within a single cognitive domain (specify the domain), with other domains unimpaired or PD-MCI multiple-domain—abnormalities on at least one test in two or more cognitive domains (specify the domains).

In alphabetical order: MDS: Movement Disorder Society; PD: Parkinson's disease; PD-MCI: Parkinson's disease with Mild Cognitive Impairment; SD: Standard Deviation.

Table 2. Neuropsychological tests recommended by the MDS in the use for PD-MCI diagnosis (Litvan et al., 2012)

Examples of neuropsychological scales for assessing global cognitive abilities and estimating premorbid intelligence Global cognition MoCA PD-CRS SCOPA-COG MDRS Estimated premorbid intelligence NART WTAR
Examples of tests for cognitive domains Attention and working memory WAIS-IV (or earlier version) Letter Number Sequencing WAIS-IV Coding (or earlier version) or other substitution task, written or oral Trail Making Test Digit span backward or digit ordering Stroop color-word test Executive function Wisconsin Card Sorting Test, or modified (Nelson's modification) Tower of London test–Drexel version, or Stockings of Cambridge (CANTAB) Verbal fluency test, such as letter fluency (COWAT or similar tests), category fluency (animals, supermarket, or similar), or alternating fluency tasks (if a well-standardized version is used). Not more than one verbal fluency test abnormality should be used to satisfy the MCI criterion of two abnormal test performances because of the strong relationship among these tests; 10 points Clock Drawing Test Language WAIS-IV (or earlier version) Similarities Confrontation naming task, such as Boston Naming Test (or short-form validated in PD) or Graded Naming Test Memory Word list learning test with delayed recall and recognition conditions, such as Rey's Auditory Verbal Learning Test, California Verbal Learning Test, Hopkins Verbal Learning Test, and Selective Reminding Test Prose recall test with a delayed recall condition, such as Wechsler Memory Scale-IV Logical Memory subtest (or earlier version) or Rivermead Behavioural Memory Test paragraph recall subtest Brief Visuospatial Memory Test–Revised Visuospatial function Benton's Judgment of Line Orientation 5 to 10 Hooper Visual Organization Test 10 Clock copying (e.g., Royall's CLOX)

In alphabetical order: CLOX: Clock test scoring system by Royall et al., 1999; COWAT: Controlled Oral Word Association Test; MDRS: Mattis Dementia Rating Scale; MoCA: Montreal Cognitive Assessment scale; NART: National Adult Reading Test; PD-CRS: Parkinson's disease-Cognitive Rating Scale; SCOPA-COG: Scales for Outcomes of Parinson's disease cognition; WAIS: Wechsler Adult Intelligence Scale; WTAR: Wechsler Test of Adult Reading.

Similarly, the diagnosis of dementia in PD is a complex process, despite its clear differences with respect to AD dementia. Different tests and criteria have been employed to make the diagnosis of PDD. For example, the Mini-mental State Examination (MMSE), a test more suitable for the detection of AD-type cognitive deficits, has been used with the arbitrary cut-off score of < 24 (Folstein et al., 1975). Other ap-

proaches include the Clinical Dementia Rating scale (CDR) (Morris et al., 1993) or the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria. Given the need for a specialized diagnostic criteria system, specific PDD diagnostic guidelines have also been determined (Emre et al., 2007) (see Table 3).

Table 3. Features associated with PDD and criteria for the diagnosis of probable and possible PDD (Litvan et al., 2012)

Core features

A) Diagnosis of Parkinson's disease according to Queen Square Brain Bank criteria.

B) A dementia syndrome with insidious onset and slow progression, developing within the context of established Parkinson's disease and diagnosed by history, clinical, and mental examination, defined as:

- Impairment in more than one cognitive domain
- Representing a decline from premorbid level
- Deficits severe enough to impair daily life (social, occupational, or personal care), independent of the impairment ascribable to motor or autonomic symptoms.

Associated clinical features

A) Cognitive features:

- Attention: Impaired. Impairment in spontaneous and focused attention, poor performance in attentional tasks; performance may fluctuate during the day and from day to day.
- Executive functions: Impaired. Impairment in tasks requiring initiation, planning, concept formation, rule finding, set shifting or set maintenance; impaired mental speed (bradyphrenia).
- Visuospatial functions: Impaired. Impairment in tasks requiring visual-spatial orientation, perception, or construction.
- Memory: Impaired. Impairment in free recall of recent events or in tasks requiring learning new material, memory usually improves with cueing, recognition is usually better than free recall.
- Language: Core functions largely preserved. Word finding difficulties and impaired comprehension of complex sentences may be present.

B) Behavioral features:

- Apathy: decreased spontaneity; loss of motivation, interest, and effortful behavior.
- Changes in personality and mood including depressive features and anxiety.
- Hallucinations: mostly visual, usually complex, formed visions of people, animals or objects.
- Delusions: usually paranoid, such as infidelity, or phantom boarder (unwelcome guests living in the home) delusions.
- Excessive daytime sleepiness.

C) Features which do not exclude PDD, but make the diagnosis uncertain:

- Co-existence of any other abnormality which may by itself cause cognitive impairment, but judged not to be the cause of dementia, e.g. presence of relevant vascular disease in imaging.
- Time interval between the development of motor and cognitive symptoms not known.

D) Features suggesting other conditions or diseases as cause of mental impairment, which, when present make it impossible to reliably diagnose PDD:

- Cognitive and behavioral symptoms appearing solely in the context of other conditions such as:
    - Acute confusion due to
        - Systemic diseases or abnormalities
        - Drug intoxication
    - Major Depression according to DSM IV
- Features compatible with 'Probable Vascular dementia' criteria according to NINDS-AIREN (dementia in the context of cerebrovascular disease as indicated by focal signs in neurological exam such as hemiparesis, sensory deficits, and evidence of relevant cerebrovascular disease by brain imaging AND a relationship between the two as indicated by the presence of one or more of the following: onset of dementia within 3 months after a recognized stroke, abrupt deterioration in cognitive functions, and fluctuating, stepwise progression of cognitive deficits).

Probable PDD

A) Core features: both must be present.

B) Associated clinical features:

- Typical profile of cognitive deficits including impairment in at least two of the four core cognitive domains (impaired attention which may fluctuate, impaired executive functions, impairment in visuospatial functions, and impaired free recall memory which usually improves with cueing).
- The presence of at least one behavioral symptom (apathy, depressed or anxious mood, hallucinations, delusions, excessive daytime sleepiness) supports the diagnosis of probable PDD, lack of behavioral symptoms, however does not exclude the diagnosis.

C) None of the group II features present.

D) None of the group IV features present.

Possible PDD

A) Core features: both must be present.

B) Associated clinical features:

- Atypical profile of cognitive impairment in one or more domains, such as prominent or receptive-type (fluent) aphasia, or pure storage-failure type amnesia (memory does not improve with cueing or in recognition tasks) with preserved attention.
- Behavioral symptoms may or may not be present.

OR

C) One or more of the group III features present.

D) None of the group IV features present.

In alphabetical order; DSM: Diagnostic and Statistical Manual of Mental Disorders; NINDS-AIREN: National Institute of Neurological Disorders and Stroke and *Association Internationale pour la Récherche et l'Enseignement en Neurosciences*; PDD: Parkinson's disease dementia.

A number of studies have pointed fronto-executive deficits as the most common in PD-MCI patients (Foltynie et al., 2004; Muslimović et al., 2007). However, among the large number of neuropsychological studies in PD, other cognitive domains have been reported to be more prevalent, albeit less commonly (Aarsland et al., 2010; Galtier et al., 2014).

Interestingly, some frontostriatal-based deficits have been reported to ameliorate after dopaminergic treatment, while others remain unchanged (Hely et al., 2008). For example, deficits in extra-dimensional shifting (*i.e.*, attention shifting between higher-order perceptual dimensions or modalities) remain unchanged after treatment (Cools et al., 2001; Lewis et al., 2005; Slabosz et al., 2006; Kehagia et al., 2009). According to the evidence of dopamine-independent cognitive deficits in PD, a dual model has been proposed, suggesting the existence of two differential, hypothetically independent, but partially overlapping cognitive syndromes of MCI and dementia in PD (Kehagia et al., 2013; Robbins & Cools, 2014).

NEUROBIOLOGICAL BASIS OF COGNITIVE IMPAIRMENT IN PARKINSON'S DISEASE

NEUROPATHOLOGY AND NEUROBIOLOGICAL MECHANISMS

The neuropathological and neurobiological mechanisms that take place in PD are complex and not fully understood. Gradual clinically silent progression, degeneration of nigrostriatal dopaminergic neurons, pathological protein deposition and α-synuclein intraneuronal Lewy inclusions in vulnerable neuron populations are thought to be the most important mechanisms to take place in the development of the disease (Halliday et al., 2014).

NEUROPATHOLOGY

In PD, phosphorylated, ubiquitinated and acetylated insoluble α-synuclein forms accumulate, preceding the formation of inclusions in neuronal bodies (Braak et al., 2003). These changes have been hypothesized to progress following a caudal-to-rostral pattern that starts at the autonomic neurons of the peripheral nervous system, the olfactory bulb at the anterior olfactory nucleus and the dorsal motor nuclei of the vagus and glossopharyngeal nerves. Afterwards, the locus coeruleus, the magnocellular portions of the reticular formation and the posterior raphe nuclei of the pons, as well as the spinal cord gray matter become affected. At this point, the substantia nigra pars compacta, together with the pedunculopontine nucleus, the magnocellular nuclei, including the nucleus basalis of Meynert, and the first structures from the limbic system show signs of degeneration. Degeneration progresses in the limbic system, and the thalamus and the first cortical regions become affected, namely, the entorhinal cortex and certain hippocampal gyrus subfields. Posteriorly, higher-order associative cortices will degenerate, followed by primary associative regions, premotor and, finally, motor areas (del Tredici et al., 2002; Braak et al., 2003).

This model of progression has been validated by studies that evidenced cognitive status correlates with disease stages (Braak et al., 2005). However, findings regarding the specific neuropathological events related to the appearance of cognitive impairment are controversial and need further research. Some studies have found an important relationship between the development of cognitive impairment and Lewy-related pathology. For example, Lewy bodies in cortical regions correlate with the severity of cognitive impairment (Sabbagh et al., 2009), and are found at higher rates in limbic and neocortical regions, especially the temporal lobe in PDD patients (Harding & Halliday, 2001). Furthermore, Lewy-related pathology and AD pathology exhibit an important association in demented PD subjects (Compta et al., 2011). However, the relationship between PD neurodegeneration and other pathological findings is difficult to

assess given the fact that post-mortem studies mostly include elder patients, who commonly exhibit age-related neuropathology (Halliday et al., 2014). Importantly, neuropathological changes appear to have a synergic relationship with age and disease duration, since patients with shorter duration periods preceding death are more likely to have concurrent AD (Halliday et al., 2008).

NEUROBIOLOGICAL MECHANISMS

The ventrolateral dopaminergic neurons of the substantia nigra, which send projections to the putamen and are key to behavioral selection and impulsivity, are the first to degenerate, before Lewy body formation (Milber et al., 2012). Imaging studies evidencing a reduction in cortical dopamine in patients with PDD suggest greater degeneration of certain dopaminergic projections according to cognitive status (Ito et al., 2002). In addition, a marked loss of forebrain Ch4 cholinergic neurons in the nucleus basalis takes place in early PD. A compensatory noradrenergic upregulation in the locus coeruleus is believed to occur in order to make up for the loss of striatal dopamine (Isaias et al., 2011; Pavese et al., 2011).

Serotoninergic projections from the median raphe nucleus towards the cortex and hippocampus have been reported to suffer a certain loss by end-stage PD, especially in the caudate nucleus. Similarly to noradrenaline, there is a correlation between the reduction in striatal dopamine transporter and increased levels of striatal serotonin transporter in early PD, suggesting a potential early compensatory mechanism as well (Kerenyi et al., 2003).

In PD-MCI patients, the functional dysregulation of neurotransmission, particularly dopaminergic frontostriatal pathways, is considered to be the most relevant factor. The progression of these deficits is unclear; however, the neurobiological disruptions seen in PD patients must at least begin to appear in PD subjects with MCI. Loss of dopamine is believed to precede deficits in other neurotransmitter systems, causing the appearance of compensatory mechanisms that further influence cognitive deterioration (Halliday et al., 2014).

GENETIC VARIATIONS AND RISK OF COGNITIVE IMPAIRMENT

In sporadic PD, a growing number of studies have focused on assessing the relationship between common sporadic genetic variations and the risk of cognitive impairment. Even though tau pathology is not a neuropathological hallmark of PD, microtubule-associated protein tau (MAPT) H1 haplotype has been found to hold a higher risk for cognitive impairment in PD (Williams-Gray et al., 2008; Goris et al., 2007). H1/H1 homozygotes exhibit faster decline in cognitive performance.

COMT gene polymorphisms associated with methionine (Met) alleles also exhibit an association with a greater risk for cognitive impairment in patients with PD, specifically in planning functions, compared with valine (Val) gene carriers, either Val/Val homozygotes or Val/Met heterozygotes, presumably because of a more efficient form of COMT that selectively depletes dopamine in the prefrontal cortex due to its dependence for regulation on methylation rather than on re-uptake (Foltynie et al., 2004). However, this pattern of results appears to be reversed after disease progression, showing an inverted U-shaped pattern of regulation (Williams-Gray et al., 2009).

In addition, carriers of the glucocerebrosidase gene mutation (GBA) have also been commonly reported to stand at a higher risk of developing PD dementia (Brockmann et al., 2011; Alcalay et al., 2012; Chahine et al., 2013), and exhibit significant differences in neuropsychological measures with respect to non-carriers (Alcalay et al., 2012). On the other hand, Apolipoprotein E (APOE) ε4 genotype carriers have a moderate risk of developing cognitive impairment (Williams-Gray et al., 2009; Morley et al., 2012). Similarly, other studies have found that APOE ε4 allele is an independent predictor of PDD (Irwin et al., 2012).

STRUCTURAL NEUROIMAGING IN PARKINSON'S DISEASE

With the advances in computational sciences, in recent years, a rapidly growing field of research has pursued a neuroimaging-based approach to study neurodegenerative changes in PD. This approach is of special interest in the study of cognitive changes in PD, since it can shed light on the relationship between neurodegeneration and cognitive decline, and contribute to answer the questions of whether these changes follow different patterns in PD, as well as the existence of prognostic parameters that can eventually determine cognitive outcome.

GRAY MATTER DEGENERATION

The early studies that assessed the integrity of gray matter and its changes used a voxel-based morphometry (VBM) approach. VBM is a volume or density-based technique that estimates the amount of gray matter in a voxel through its signal intensity.

However, among other limiting factors, VBM is affected by ambiguities in discerning between actual gray matter atrophy and changes in folding or gyrification as well as variability in specific individual anatomical patterns that may result in misregistration and cause falsely positive results, even after statistical correction by multiple comparisons (Bookstein, 2001).

To surpass the approach of a parallel-oriented topography to the highly folded cortical mantle, surface-based cortical thickness measures assess the distance between the white matter and gray matter surfaces measured at each vertex of the mantle (Fischl et al., 1999). The most commonly used software to address this parameter is FreeSurfer (http://surfer.nmr.harvard.edu). FreeSurfer allows the identification of variations in gray matter with submillimeter accuracy, implying the ability to distinguish focal atrophy in small patient populations. In addition, given its high within-subject test-retest reliability, it is also able to detect subtle localized cortical thinning over time (Fischl & Dale, 2000), making it possible to address changes after disease progression. However, the precision of the thickness measurements is constrained by the contrast-to-noise ratio and fidelity of the underlying Magnetic Resonance Imaging (MRI) data, as well as its intrinsic automaticity, which can lead in a few occasions to preprocessing errors.

FreeSurfer uses methods of construction and transformation models of the human cerebral cortex and the pattern of cortical folding derived from these to drive high resolution intersubject alignment (Fischl & Dale, 2000). In preprocessing steps, motion correction and removal of non-brain tissue are applied before automated Talairach transformation (Sled et al., 1998). In addition, subcortical segmentation of white matter and deep gray matter volumetric structure is addressed (Fischl et al., 2002).

Intensity normalization (Sled et al., 1998), tessellation of the gray/white matter boundary, automated topology correction (Ségonne et al., 2007) and surface deformation by intensity gradients are applied to ensure that the surfaces are optimally located at the greatest shift in intensity with respect to the boundaries (Fischl & Dale, 2000). Surface inflation, registration to a spherical atlas (Desikan et al., 2006), parcellation of the cerebral cortex and maps of curvature and sulcal depth are created (see Figure 1). Processing of data must be statistically corrected by multiple comparisons to avoid type I errors (Fischl et al., 1999; Fischl & Dale, 2000).

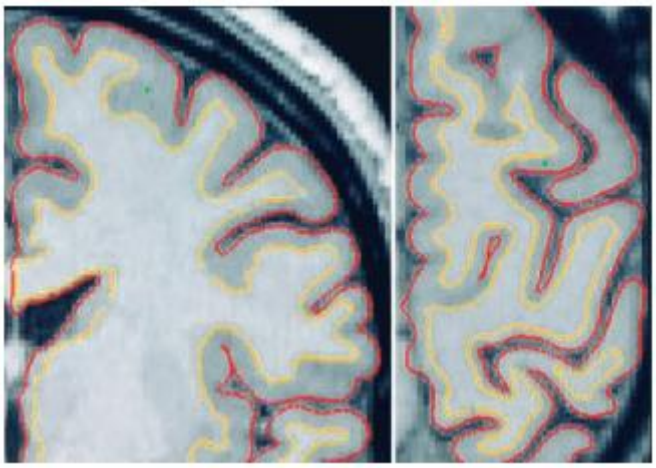

Figure 1. Reproduced from Fischl & Dale (2000). Coronal (left) and horizontal (right) slices of the left hemisphere with gray/white (yellow) and pial (red) surfaces overlaid.

A number of neuroimaging studies have addressed the gray matter changes that take place in PD. Although findings are far from establishing a conclusive pattern, a linear progression of atrophy across cognitive stages seems to take place in PD, which affects predominantly fronto-temporo-parietal regions (Burton et al., 2004; Beyer et al., 2007; Weintraub et al., 2011; Melzer et al., 2012; Zarei et al., 2013; Hanganu et al., 2014; Mak et al., 2014; Mak et al., 2015).

In PD patients without evidence of cognitive impairment, the majority of studies report an absence of gray matter degeneration, using cortical thickness (Hanganu et al., 2013; Mak et al., 2014; Pereira et al., 2014), as well as VBM measures (Melzer et al., 2012).

In PD-MCI patients, studies using VBM have reported atrophy in temporal, parietal and frontal areas (Song et al., 2011; Melzer et al., 2012). Cortical thickness analyses have found a predominant pattern of degeneration in temporal and parietal regions (Pagonabarraga et al., 2013; Pereira et al., 2014; Segura et al., 2014). Changes in specific hippocampal gyrus subfields CA2-3 and CA4-dentate (Pereira et al., 2013) have also been described. In contrast, PDD patients exhibit a widespread pattern of cortical degeneration (Nagano-Saito et al., 2005; Compta et al., 2013; Hwang et al., 2013; Zarei et al., 2013), as well as an important involvement of subcortical structures, such as the caudate (Burton et al., 2004; Apostolova et al., 2010), putamen (Burton et al., 2004), amygdala (Junque et al., 2005; Zarei et al., 2013), thalamus and hippocampus (Burton et al., 2004).

An approach especially useful in providing information about the relationship between cognitive deterioration and neurodegeneration are longitudinal surface-based cortical thinning analyses. However, there is currently only a limited number of studies providing such data. PD patients exhibit a more pronounced rate of cortical thinning than healthy subjects in bilateral fronto-temporal regions (Ibarretxe-Bilbao et al., 2012; Compta et al., 2013). Moreover, large cohort studies have shown that PD-MCI patients exhibit greater cortical degeneration in temporo-parietal posterior cortices (Hanganu et al., 2014; Mak et al., 2015), as well as volumetric changes in subcortical structures, such as the caudate and hippocampus (Mak et al., 2015; Foo et al., 2016). Longitudinal volumetric studies have also suggested a higher rate of global atrophy in PDD patients (Burton et al., 2005).

WHITE MATTER INTEGRITY

Integrity of the white matter has been widely addressed using Diffusion Weighted MRI (DWI). Through mathematical models such as diffusion-tensor imaging (DTI), DWI allows for the indirect *in vivo* assessment of microdiffusion of water molecules in a tissue, providing information about its microstructure. The diffusion tensor model represents the diffusion as an ellipsoid with three orthogonal axes (eigenvectors), each with a corresponding eigenvalue, which represents the magnitude of water diffusion along that axis.

The existence of a preferential direction of water diffusion is known as anisotropic diffusion. In the white matter, anisotropy is the result of coherent fiber organization. Fractional anisotropy (FA) is a scalar parameter computed through the diffusion tensor model by which the degree of diffusion anisotropy can be obtained, ranging from 0 – isotropic – where diffusion occurs equally in all directions, to 1 – anisotropic – where diffusion is restricted to a single direction. Other parameters also commonly reported are mean diffusivity and radial diffusivity. Mean diffusivity (MD) is obtained as a mean of the three eigenvalues, and relates to the mean diffusion in a voxel, related to the size of the ellipsoid and the overall presence of obstacles in diffusion. The average diffusivity in the two minor axes results in radial diffusivity (RD), providing information regarding the perpendicular diffusion. Although FA is related to myelin integrity (Le Bihan, 2003), the etiology of variations in these parameters cannot be inferred, since changes can also be due to differences in axon diameter and axon packing or increased membrane permeability (Jones et al., 2013).

One of the most commonly used imaging techniques to assess white matter integrity is called Tract Based Spatial Statistics (TBSS). In this method, FA images are created by fitting a tensor model to the averaged motion corrected diffusion data and then brain-extracted (Smith, 2002). Mean FA images are created and thinned to obtain mean FA skeletons, which represent the centers of all tracts common to the group of subjects. Aligned FA data are projected onto this skeleton and resulting data fed into voxelwise cross-subject statistics. Statistical analyses must also be corrected for multiple comparisons (Smith et al., 2006) (see Figure 2).

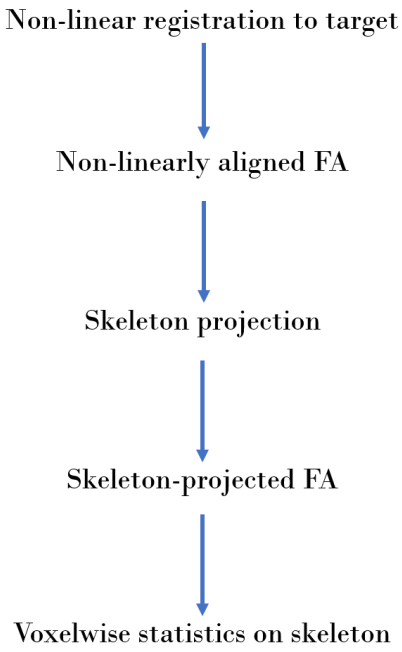

Figure 2. Tract Based Spatial Statistics workflow representation. FA: Fractional anisotropy images

TBSS projects the data onto an alignment-invariant tract representation, and is more restrictive than whole brain voxel-wise group comparisons, improving sensitivity, objectivity and interpretability of multi-subject diffusion analysis. However, some authors have pointed it may be less sensitive to detect voxels further from tract centers (Zalesky, 2011), and that FA-reducing abnormalities could be a confounding factor (Jones & Cercignani, 2010).

Although a growing field, studies assessing white matter parameters in PD are still relatively scarce. However, a general pattern of degeneration can be inferred, by which microstructural white matter changes can be found in several brain regions (Hattori et al., 2012; Melzer et al., 2013; Theilmann et al., 2013; Koshimori et al., 2014; Duncan et al., 2016), with frontal and temporal lobes being the most involved (Karagulle et al., 2008; Gattellaro et al., 2009; Zhang et al., 2011; Agosta et al., 2014; Koshimori et al., 2014).

Interestingly, certain studies have reported impairment of white matter microstructure in absence of gray matter degeneration (Hattori et al., 2012; Agosta et al., 2014; Duncan et al., 2016). These studies have proposed that white matter abnormalities occur prior to gray matter involvement, and suggested the possibility that it acts as a sensitive precedent for neuronal loss in associated gray matter regions. However, this comparability may be hindered by the techniques used and the different properties of the methodological approaches.

VISUAL COGNITION IN PARKINSON'S DISEASE

A FOREWORD ON THE HEALTHY VISUAL SYSTEM PATHWAYS

Vision processing starts in the retina, where photoreceptors hyperpolarize by light exposure. Such hyperpolarization produces a series of neuronal responses that use dopamine as a neurotransmitter. Their signal is transmitted through the optic nerve, which transfers information from visual fields to the contralateral lateral geniculate nucleus (LGN). Visual inputs are processed by primary visual areas, which are divided in functionally specialized pathways to process complex visuospatial and visuoperceptual information.

FROM THE RETINA TO THE CORTEX

The fovea is a small anatomical structure in the retina that contains the highest number of photoreceptors, providing high visual acuity; in addition, it holds the highest contrast sensitivity, the ability by which individuals are able to discern between different levels of luminance in a static image. In spite of its limited size, a large number of cortical neurons per unit of visual field are devoted to foveal input.

Foveal contrast sensitivity contributes to the detection and discrimination of visual stimuli and is thus an important structure in low-level visual processing of object recognition. Retinal output from the fovea is further augmented by the computational properties of the visual cortex subserving object recognition (Bodis-Wollner, 2013). In addition, behavioral as well as functional evidence suggests that high-level visual object representations are at least somewhat position-dependent, arising from retinotopic position (Kravitz et al., 2008).

This function is further supported by the multilayer architecture that organizes the neural elements in the retina and the complex cellular-diversified pathways that forward achromatic and chromatic vision to the LGN (Bodis-Wollner, 2013). At this stage, higher-order thalamic nuclei will transfer modulated visual information to primary cortical areas. Other visual pathways project towards the superior colliculus, which may also reach the cortex through takeover in the lateral posterior-pulvinar complex of the thalamus (Kolb & Whishaw, 2006). The existence of this pathway precludes a complete loss of the visual experience after damage of the geniculostriate pathway (Tamietto et al., 2010).

Visual information in the cortex will be combined with precise saccade information conveyed by corollary discharge (Wurtz et al., 2011). In addition, efferent and afferent connections from the basal ganglia towards parietal and temporal lobules support the notion of a subcortical involvement in visual processing (Rektorova et al., 2014).

VISION PATHWAYS. THE CASE FOR FUNCTIONALLY SPECIALIZED VISUAL PROJECTIONS

Classically, higher-order visual processing was conceived as the subdivision of visual information into two anatomically and functionally distinct pathways that originate in the striate cortex. Evidence from animal models as well as lesional studies pointed to the existence of a 'ventral' stream – from the occipitotemporal cortex to the anterior temporal and ventrolateral prefrontal cortex – that encompassed visuoperceptual abilities, such as perception and recognition of shape, orientation, size, objects, faces and text; and the existence of a 'dorsal' stream – from the occipitoparietal and dorsolateral prefrontal cortices to the posterior half of the inferior parietal lobule – subserving visuospatial functions, *i.e.*, the spatial layout features of the outside world, such as location, distance, relative position, position in egocentric space and motion (Ungerleider & Mishkin, 1982). Because of their distinct functional implications, these projections were also referred to as the 'what' and 'where' vision pathways.

However, later revisions bearing the structural and functional connections that these areas hold have pointed to the inaccuracy of a hierarchical and lineal fractionation of the architecture of visual processing, and should be conceived as a more complex network with several interconnections between the classical streams initially described (de Haan & Cowey, 2011).

In fact, whereas the 'what' characterization of the ventral stream has remained widely unchallenged, the general functional terminology of the dorsal stream as 'where' projections has been largely debated (Kravitz et al., 2011; Kravitz et al., 2013). Milner & Goodale (2008) proposed that these pathways could be better regarded in terms of the output systems that the two streams mediate. Namely, the 'ventral' stream transforms visual inputs into perceptual representations that embody the enduring characteristics of objects and their spatial relations, whereas the 'dorsal' stream mediates the visual control of skilled actions, such as reaching and grasping, by registering visual information about the goal object on a moment-to-moment basis. Consequently, 'dorsal' projections may be better considered as a 'where/how' output of the visual system.

Recent research has also pointed out to a more specific subdivision of highly specified and interconnected cortical and subcortical projections arising from these areas (see Table 4). According to this notion, the parietal component of the original dorsal stream serves as a neural nexus of visuospatial function, giving rise to a set of processing pathways that mediate both spatial perception and visually guided action across multiple cortical areas within the frontal, temporal and limbic lobes. This set of connections enables the coordination of spatial working memory and navigation based on long-term memory, as well as associative retrieval of the contents of one form of memory by the other (Kravitz et al., 2011) (see Figure 3).

In the ventral projections, visual information from the occipitotemporal network contributes to the function of the target structures. Cortico-subcortical output pathways are critical to forming associations between visual stimuli and non-visual information, whereas cortico-cortical output pathways are bidirectional and appear as critical in long- and short-term visual memory. In this network, connectivity enables distinct areas to perform specialized processing of distinct aspects of stimuli, which are eventually synthesized into unified representations within neural populations (Kravitz et al., 2013).

Computations along the two pathways proceed independently and in parallel, reintegrating within shared target brain regions. Processing along the separate pathways is modulated by the existence of recurrent feedback loops, and information is transferred directly between the two pathways at multiple stages and locations along their trajectories (Cloutman, 2013; Kravitz et al., 2013). The redundancy of these connections likely contributes to the recuperation of this network after its damage, although not of its outputs (Kravitz et al., 2013) (see Figure 3).

Table 4. Summary of the specialized projections of the visual system revised by Kravitz et al. (2011; 2013).

Domain	Pathway	Regions	Functions
Visuospatial (Kravitz et al., 2011)	Parieto-prefrontal	Areas LIP, VIP, MT and MST target towards the occipi-to-parietal circuit	Spatial working memory. Top-down control of eye movements
	Parieto-premotor	Projects from area V6A and MIP, towards dorsal premo-tor cortex. VIP targets the ventral premotor cortex	Spatial navigation. Visually guided action
	Parieto-medial temporal (two sets of projec-tions)	Runs from cIPL directly to a zone between the CA1 and subculum, to the pre- and parasubicular subdivisions of the hippocampal formation, and to the posterior para-hippocampal areas TF and TH Projects medially to the posterior cingulate cortex and retrosplenial cortex	Spatial navigation. Com-plex spatial processing.
Visuoperceptual (Kravitz et al., 2013)	Occipitotempora-neostriatal	From every subregion of the occipitotemporal network except V1 and projects to the striatum	Supports formation of links between stimuli and responses
	Occipitotempora-ventral striatum	Arises from AIT and projects to the ventral striatum	Association with and processing of stimulus balance
	Occipitotempora-amygdaloid	Projections from the occipitotemporal network towards the amygdala	Affective processing of stimuli
	Occipitotempora-medial temporal	Arises from every region in AIT and TEPV and targets the medial temporal lobe	Mnemonic functions. Long-term cognitive visu-al memories
	Occipitotempora-orbitofrontal	Arises from the STSv/f, TEAV and area TGV granular (Dissociation between lateral OFC -stimulus-reward associations- and medial OFC -fine-grained comparisons between reward values)	Supports the association of visual stimuli with reward. Object reversal learning
	Occipitotempora-ventrolateral prefrontal	Arises from the STSv/f area with only a minor projection from the TEAD	Object-based working memory. Maintenance and manipulation, switching task of task relevant in-formation

In alphabetical order; AIT: anterior inferior temporal cortex, cIPL: caudal and rostral portions of the inferior parie-tal lobule, LIP: lateral intraparietal area, MST: medial superior temporal area, MIP: medial intraparietal area, TEAV: ventral subregion of anterior rostral inferior temporal cortex, OFC: orbitofrontal cortex, STSv/f: fundus of the superior temporal sulcus, TEAD: dorsal subregion of anterior rostral inferior temporal cortex, TEPV: ventral subregion of posterior rostral inferior temporal cortex, TGV: ventral temporal pole, VIP: ventral intraparietal area; V1: primary visual cortex.

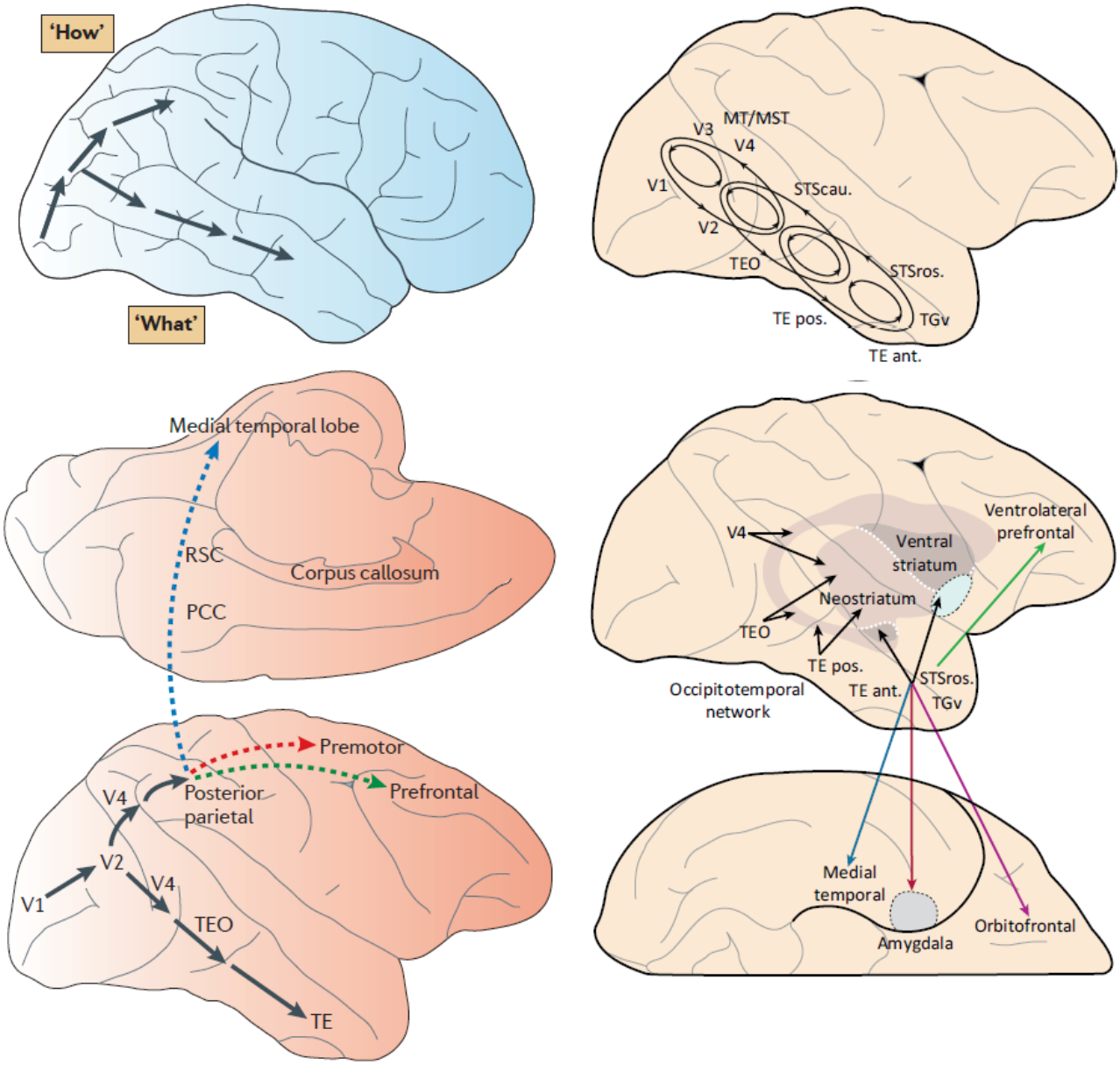

Figure 3. Modified from Kravitz et al. (2011; 2013). New neural frameworks for visuospatial and visuoperceptual processing. **Left)** At least three distinct pathways emanate from the posterior parietal cortex to mediate visuospatial processing: the parieto-prefrontal (green), the parieto-premotor (red) and the parieto-medial temporal (blue). **Right)** The occipitotemporo-neostriatal pathway that devotes visuoperceptual processing originates from every region in the network and supports visually dependent habit formation and skill learning. The six projections that emerge are the neostriatum (black), ventral striatum (black), amygdaloid (red), medial temporal (blue), orbitofrontal (purple) and ventrolateral prefrontal (green). MT: medial temporal area; MST: medial superior temporal area; PCC: posterior cingulate cortex; RSC: retrosplenial cortex; STScau: caudal superior temporal sulcus; STSros: rostral superior temporal sulcus; TE: rostral inferior temporal cortex; TEO: posterior inferior temporal cortex; TGV: ventral temporal pole.

FACE RECOGNITION

Face perception is perhaps the most developed visual perceptual skill in humans and plays a critical role in social interactions (Haxby et al., 2002). A complex distributed neural system lying in multiple regions in the extrastriate visual cortex supports this function. Two main systems have been proposed for the visual analysis of faces: a core system for the visual analysis of faces and an extended system for further processing of the meaning of face information (Haxby et al. 2000) (see Figure 4). A ventral stream mediates structure and surface properties of a face in the posterior face-selective areas and matches these representations with stored representations of familiar faces in the anterior temporal face-selective area. The dorsal stream plays a role in ongoing social interactions, which require the extraction of constantly changing information from moving faces (Duchaine & Yovel, 2015).

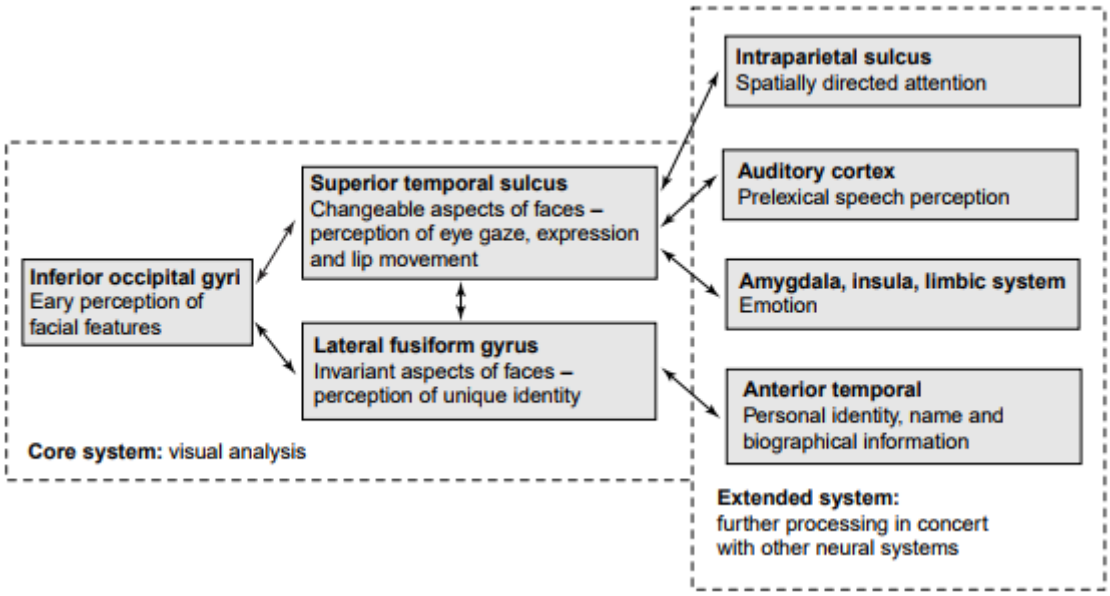

Figure 4. Reproduced from Haxby et al. (2000). The face perception model is divided into a core system, consisting of three regions of occipitotemporal visual extrastriate cortex, and an extended system, consisting of regions that are also parts of neural systems for other cognitive functions. Changeable and invariant aspects of the visual facial configuration have distinct representations in the core system. Interactions between these representations in the core system and regions in the extended system mediate processing of the spatial focus of another's attention, speech-related mouth movements, facial expression and identity.

VISUOCONSTRUCTIVE FUNCTIONS

There is no uniform definition of visuoconstructive function and many different terminologies have been used. One of the first terms used was 'constructional praxis', which included two classes of activities: free drawing or copying of a drawing template and building or assembling. These activities require visual and tactile abilities, which include attention, spatial integration, and motor response integration (Lezak et al., 2012). Simple and complex graphomotor tasks have been found to be localized in different brain regions.

Neuroanatomical disposition of visuoconstructive function extends well beyond spatial abilities in the brain. Whereas free drawing and draw-to-command may rely more in frontostriatal circuitry, model copying may rely on posterior cortical regions as well. Areas subserving motor planning and control processes interact with visuospatial-devoted regions and hold multidirectional functional relationships (Trojano et al., 2009).

OCULAR AND VISUAL DYSFUNCTION IN PARKINSON'S DISEASE

A variety of ocular and primary vision deficits have been reported in PD patients, such as visual field defects, visual acuity, contrast sensitivity, color vision and oculomotor disturbances. In addition, findings have highlighted significant dysfunctions of the retina (Archibald et al., 2009; Bodis-Wollner, 2009). Understanding the basic visual deficits is important to contextualize and interpret impairment in visuospatial, visuoperceptual and visuconstructive functions.

VISUAL FIELDS AND GLAUCOMATOUS DISTURBANCES

Information from visual fields is processed at multiple levels from the retina to higher cortical regions. In PD, irrelevant objects located in the periphery have a greater impact in the main task than in healthy subjects (Davidsdottir et al., 2005). Similarly, PD patients show a greater difficulty in discriminating details and a weaker perception of the stimuli in peripheral fields (Sampaio et al., 2011).

Visual field defects can also be seen as a result from glaucomatous lesions. However, epidemiologic data on the association between glaucoma and PD are scarce, and there is poor evidence regarding the consistency of these deficits (Ture et al., 2007). Studies have reported a higher prevalence of glaucoma in PD patients than in individuals without PD (Bayer et al., 2002). The majority of cases in PD concern primary open-angle glaucoma, with a lower intraocular pressure than other subjects with glaucoma, but higher than in the normal population (Bayer et al., 2002; Nowacka et al., 2014).

Apart from glaucoma, patients with PD are at risk for visual field defects and retinal nerve fiber layer thinning not caused by glaucoma (Tsironi et al., 2012; Yu et al., 2014). The underlying pathology of these deficits is still unclear, and different possible mechanisms have been suggested. Retinal degeneration due to progressive dopamine depletion and α-synuclein mediated axonal degeneration could intervene in the genesis of these findings (Nucci et al., 2015).

Visual field defects have also been seen as a resulting consequence of posterior pallidotomy, appearing as deficits such as quadrantanopsias and scotomas, together with disturbed ocular fixation and apraxia of eyelid opening (Ekker et al., 2017).

VISUAL ACUITY

Visual acuity is the ability to perceive the details of a stimulus and is determined by ophthalmic factors, including retinal deficits, rather than cortical disease. There is little evidence about changes in visual acuity in PD. Studies have shown that it is not seen in early-stage untreated patients (Biousse et al., 2004), and it has been described to act as a risk factor for the development of chronic hallucinations in PD (Matsui et al., 2006). Visual acuity deficits are not corrected by medication. PD patients often complain of poor vision, possibly resulting, together with other factors, from impaired visual acuity, with low-contrast acuity being especially affected (Armstrong, 2011).

CONTRAST SENSITIVITY

Contrast sensitivity is the ability to discriminate an object from its background, and can be affected by lesions in the eye, thalamus and cortical regions. Loss of contrast sensitivity can occur across a range of spatial frequencies, predominantly high and intermediate (Armstrong, 2015), and in both foveal (central) and peripheral locations (Silva et al., 2005). Abnormal contrast sensitivity could be related to dopamine dysfunction in the retina, but the specificity of the orientation deficits suggests a cortical involvement (Weil et al., 2016). Unlike visual acuity, contrast sensitivity is partly reversible with levodopa; however, it eventually deteriorates with disease progression (Diederich et al., 2002). Apomorphine significantly improves non-color spatial contrast sensitivity at all frequencies (Buttner et al. 2000).

COLOR VISION

Color vision is processed by photoreceptor cones in the retina and at higher levels from primary to extrastriate visual cortices. Some studies have shown that color discrimination may be an early sign of dopamine dysfunction in PD (Piro et al., 2014) and a disease-specific feature (Castelo-Branco et al., 2004; Silva et al., 2005; Piro et al., 2014). Color discrimination is altered even at early stages of the disease in untreated PD patients and progresses with the disease in both treated and untreated patients (Diederich et al., 2002). Color vision dysfunction correlates with motor speed, axial motor symptoms and their severity, and disease duration (Armstrong, 2011). The most affected color axis in PD is still unclear; however,

when assessed with tests that are less susceptible to confounds, the protan and deutan (red-green) axes seem particularly affected. Vision may be blurred using colored stimuli with reduced perception of monochromatic contours, especially for dark green, light blue and dark red stimuli (Weil et al., 2016).

Deficiency of retinal dopamine is thought to result in impaired processing of visual stimuli, leading to decreased contrast sensitivity and color discrimination (Ekker et al., 2017). In addition, visual evoked potentials in response to colored stimuli, especially for those using blue-yellow horizontal gratings, show decreased amplitude and increased latency (Sartucci & Porciatti, 2006), and delays in different visual processing system have also been reported, pointing a relationship with other neurotransmitters, such as the cholinergic system (Armstrong, 2015). Neuroimaging of gray and white matter correlational studies have demonstrated a relationship between right posterior brain regions and poor color vision in cognitively impaired PD patients (Bertrand et al., 2012). Given these findings, it is likely that color vision dysfunction arises from a multifactorial etiology.

PUPIL REACTIVITY

Disturbances in pupil reactivity have also been reported in PD. After light adaptation, patients exhibit significantly larger pupil diameters with unequal pupil sizes. Similarly, longer light reflex latencies and constriction times, together with reduced contraction amplitudes have also been reported (Biousse et al., 2004). In addition, anticholinergic drugs have a significant mydriatic effect, and photophobia and decreased accommodation can also occur (Armstrong, 2008). These findings may be relative to an autonomic imbalance in PD involving the parasympathetic system, and are of high relevance because it is an early manifestation of PD (Postuma et al., 2013).

SACCADES, OCULOMOTOR DISTURBANCES AND CONVERGENCE

Saccadic and smooth pursuit eye movements are well established deficits reported in about 75% of PD patients. Electrooculography responses are often normal in PD patients when the eyes are in the primary position or when resting, however, reaction times and the maximum saccadic velocity of horizontal gaze are slower (Armstrong, 2008). Latency and velocity are preserved, but amplitude is reduced, producing hypometric saccadic movements (Kimmig et al., 2002; MacAskill et al., 2002), which have also been referred to as ‘under reaching of task’, suggesting a dysfunction of the striatocollicular inhibitory pathway produced by dopamine deficiency in the basal ganglia (Armstrong, 2015). Interestingly, saccades to a remembered target are particularly impaired and show a multistep pattern thought to arise from deficits in oculomotor pathways in the brainstem, cerebellum, basal ganglia and frontal lobes (Weil et al., 2016). A change in externally cued saccades to self-paced saccades produces an increase in the amplitude of sac-

cadic eye movements in healthy subjects, but this effect is more pronounced in PD patients (Winograd-Gurvich et al., 2006). In addition, smooth pursuit movements may also be interrupted by small additional saccades. These smooth pursuit movements could appear affected in the prodromal phase and are under dopaminergic control (Bares et al., 2003). On the other hand, abnormal optokinetic nystagmus, poor convergence, resulting in diplopia, and restricted gaze are also impaired in PD (Hanuska et al., 2015). Jerkiness, cogwheeling and limitation of eye movement, especially in the vertical axis (up-gaze limitation), are characteristic of the abnormal eye movements present in PD. However, pronounced oculomotor abnormalities are more indicative of atypical parkinsonism syndromes (Bak et al., 2006).

Convergence insufficiency can result from exophoria (Lepore, 2006) and produce double vision on reading (Almer et al., 2012; Nowacka et al., 2014), blurred near vision and binocular diplopia (Lepore, 2006). Convergence insufficiency is relatively prevalent in PD (Ekker et al., 2017) and the incidence of diplopia increases as the disease progresses (Archibald et al., 2011). Diplopia is more common in patients with pre-existent ocular misalignment and with daytime somnolence (Archibald et al., 2011), and may improve with dopaminergic therapy when it is resulting from convergence insufficiency (Almer et al., 2012). Similarly, in patients with visual hallucinations, selective diplopia, a phenomenon by which only focused objects in the visual field appear duplicated, might improve when treating hallucinations, and has also been associated with dementia (Sauerbier & Ray Chaudhuri, 2013). The pathophysiology underlying these deficits is not clear, and some studies suggest that it is related to dopamine deficiency in the basal ganglia, whether other research points at an extranigral etiology (Ekker et al., 2017).

BLINKING AND BLINK REFLEX

PD patients have difficulties opening the eyelids after voluntary closure, a phenomenon referred as to 'apraxia of eyelid opening' (Lamberti et al., 2002). PD patients exhibit a reduced frequency of blinking, which can lead to a staring appearance (Biousse et al., 2004). Reduced blink rate can cause an abnormal tear film, dry eye and reduced vision. However, some studies have pointed that eye blink rate does not appear to be significantly different in PD, and thus may not be a good indicator of bradykinesia (Chen et al., 2003). Blink duration and excitability appear to be increased in PD and may reflect loss of dopamine neurons (Armstrong, 2008).

Blink reflex is a reflex response elicited by a light tap on the glabella above the bridge of the nose. Healthy subjects habituate to successive tapping and the response diminishes (Peshori et al., 2001). In PD patients, the blink reflex may not disappear, and this reaction may be present in a high proportion of patients. Habituation may improve after treatment with levodopa or amantadine (Armstrong, 2008), suggesting a dopaminergic and frontal involvement in its pathophysiology.

RETINAL INVOLVEMENT

Pathological studies have revealed an important implication of the retina in PD. The inner retinal layer is thinner in PD patients and cell loss is more prominent in the peripheral segments (Hajee et al., 2009).

Autopsy studies in PD patients show a decreased retinal dopamine concentration. Dopaminergic depletion in the retina may result in attenuated electroretinogram responses to peak stimuli (Bodis-Wollner, 2003). In fact, retinal electric activity is decreased under different light conditions and improves with levodopa. Dopamine has also been related with retinal processing, since D2 receptors are necessary for spatial-temporal tuning of pattern vision (Bodis-Wollner, 2013).

In addition, misfolded α-synuclein (Bodis-Wollner et al., 2014) and phosphorylated α-synuclein (Beach et al., 2014) have been found in the inner retinal layer, providing important evidence of PD pathology in structures of the first steps of visual perception (Weil et al., 2016).

VISUOSPATIAL, VISUOPERCEPTUAL AND VISUOCONSTRUCTIVE IMPAIRMENT IN PARKINSON'S DISEASE

The first evidence that PD courses with symptoms of a certain impairment in visual cognition processes came from patients and family members who observed difficulties determining the appropriate maneuvers to reach spatial goals (Hovestadt et al., 1987; Raskin et al., 1990). For instance, PD patients may have difficulty moving about within and outside the home imitating movements, and judging personal orientation of body parts; freeze when required to go through a doorway if a change in spatial position or direction is required (Raskin et al., 1990), and lose orientation in previously known locations when changes in usual settings appear (Hovestadt et al., 1987). Specifically, rather than navigation difficulties, PD patients exhibit significant deficits in both personal and extrapersonal spatial orientation (Raskin et al., 1990).

Davidsdottir et al. (2005) reported that the most common symptoms related to visual and visuospatial dysfunctions are double vision, difficulty estimating spatial relations, hallucinations, freezing in narrow spaces and bumping into doorways. PD patients also manifest difficulties detecting unnoticed peripheral objects, a phenomenon known as 'blind to blindsight' (Diederich et al. 2002), which is otherwise a usual property of the healthy vision pathways. Moreover, PD patients misjudge the adequacy of their impaired copy drawings (Davidsdottir et al., 2005; Friedman, 2017), and are manifestly concerned about their micrographia (Friedman, 2017).

GENERAL ASPECTS

Impairment in visual cognition has been commonly reported in PD patients since early studies that assessed all neuropsychological cognitive domains. However, there is a wide disparity of results regarding frequency, characteristics, relationship with other disease variables and cognitive dysfunctions and implications of visual cognition deficits (see **Table 5**).

Prevalence of visuospatial impairment in PD, using different neuropsychological tests, cognitive diagnosis criteria, sample characteristics and cognitive domains assessed, can range from 2.2% to the most common subtype of MCI (Galtier et al., 2014; Stefanova et al., 2015; Lawrence et al., 2016). Nonetheless, the majority of studies agree in that, albeit usual, visual cognition is not the most commonly affected domain (Green et al., 2002; Muslimović et al., 2005; Aarsland et al., 2010; Kudlicka et al., 2011; Kalbe et al., 2016; Lawrence et al., 2016).

At the same time, the majority of these studies also report a significant decline in visuospatial, visuoperceptual and visuoconstructive functions over the years (Muslimović et al., 2009; Broeders et al., 2013; Santangelo et al., 2015; Johnson et al., 2016; Caspell-Garcia et al., 2017) and may have prognostic value for cognitive decline and evolution to dementia (Williams-Gray et al., 2007; Williams-Gray et al., 2009; Williams-Gray et al., 2013; Kaul & Elble, 2014; Johnson et al., 2016).

A particularly debated subject of visual cognition processes is their dependence on frontal-executive functioning. Some authors argue that disorders reported in visuospatial, visuoperceptual and visuoconstructive functions in PD result more from a decrease in central processing resources than from a specific alteration of visuospatial function (Dubois & Pillon, 1997). However, whereas a certain degree of visual cognition impairment could be related to low level perceptual deficits and compromised executive functions (Waterfall & Crowe, 1995), it has also been demonstrated that visuospatial deficits exist beyond executive dysfunction (Cronin-Golomb & Braun, 1997; Crucian et al., 2000; Kemps et al. 2005; Leek et al., 2014). Furthermore, these cognitive domains can suggest differential evolution in the progression of cognitive decline (Kehagia et al., 2013).

From the current findings, we can conclude that there are few available data on specific visuospatial and visuoperceptual impairment in PD (Ekker et al., 2017), and this may explain the lack of meta-analyses on this topic. In addition to the few published studies, the disparity in results may be due to heterogeneity of study settings, simplification of a multidimensional cognitive domain and lack of control of variables that can influence cognition in PD, such as medication, mood disorders and variations in progression (Lazaruk, 1994).

Table 5. Visuospatial, visuoperceptual and visuoconstructive impairment reported in studies assessing all cognitive domains

Authors (year)	Design	Sample	Cognitive diagnosis criteria	Cognitive domains assessed (as described in study)	Test	Findings regarding visual cognition processes
Green et al. (2002)	Cross-sectional	61 non-demented PD subjects	Screened for dementia with the DRS and excluded of the study	General intellectual function, memory, executive function, visuospatial ability and language	JLOT	Patients are more likely to show clinically significant impairment on neuropsychological measures sensitive to changes in dorsolateral prefrontal regions related to basal ganglia-thalamocortical circuits
Verbaan et al. (2007)	Cross-sectional	400 PD patients 150 healthy subjects	Cognitive burden was reported with lower scores on cognitive tests used	Global cognition, memory, attention, executive and visuospatial domains	Mental reconstruction of figures from SCOPA-COG	Visuospatial abilities significantly differed between healthy subjects and PD patients ($p<0.01$), but the largest differences were seen in executive functions and memory
Williams-Gray et al. (2007)*	Longitudinal (3-year follow-up)	122 PD patients (109 non-demented, 13 PDD)	Presence of dementia was assessed with MMSE <24 cut-off	General cognitive functioning, language, memory, executive functions and visuoconstructive skills	PCT	PCT score evidenced a significant rate (change in score/year) of decline over follow-up ($p=0.03$)
Aarsland et al. (2009)	Cross-sectional	196 non-demented, drug naïve PD patients 201 healthy subjects	MCI and PDD were assessed using MDS criteria (Litvan et al., 2012; Emre et al. 2007 respectively)	Memory, attention and executive functions and memory	VOSP cube and silhouettes subtests	Differences between healthy subjects and PD patients were significant for both subtests
Muslimović et al. (2009)+	Longitudinal (3-year follow-up)	89 newly-diagnosed PD patients 52 established PD	Excluded global cognitive deterioration with MMSE <24 cut-off	Psychomotor speed, attention, language, memory, executive functions, and visuospatial and visuoconstuctive skills	JLOT Clock drawing VRGIT	Baseline vs. follow-up score JLOT: $p<0.001$ Clock drawing: $p<0.001$ VRGIT: $p=0.248$
Williams-Gray et al. (2009)*	Longitudinal (5-year follow-up)	122 PD patients (88 non-demented PD, 21 PDD, 13 unknown)	Presence of dementia was assessed with MMSE <24 cut-off	General cognitive functioning, language, memory, executive functions and visuoconstructive skills	PCT	PCT score evidenced a significant rate (change in score/year) of decline over follow-up ($p=0.003$)
Aarsland et al. (2010)	Mutli-center pooled analysis	1346 were included from different PD cohorts	Diversified; depending on the study	Executive functions, memory, language and visuospatial skills	JLOT VOSP cube and silhouettes subtests Clock copy ROFC	After memory domain, visuospatial was the most commonly impaired function in MCI patients

Arnaldi et al. (2012)	Longitudinal (4-year follow-up)	25 drug naïve PD patients	CDR scale	Attention and executive functions, language, memory and visuospatial and visuoconstructive abilities	Figure copy Block design	Visuospatial functions exhibited a decline (p=0.003), and were predicted by disease severity.
Yu et al. (2012)	Cross-sectional	94 PD patients 84 healthy subjects	MCI was diagnosed using MDS criteria (Litvan et al., 2012) Diagnosis of dementia was based on DSM-IV	Executive functions, memory, psychomotor speed, attention, and visuoconstructive and language functions	Block design PCT	Significant differences were found between healthy subjects, cognitively normal PD patients and PD patients with MCI in visuoconstructive abilities ($p<0.0001$) with a moderate-to-high effect size ($d>0.50$)
Broeders et al. (2013)+	Longitudinal (5-year follow-up)	59 PD patients 40 healthy subjects	Patients were diagnosed with PDD according to MDS criteria (Dubois et al., 2007; Emre et al., 2007)	Psychomotor speed, attention, language, memory, executive functions, and visuospatial and visuoconstructive skills	JLOT Clock drawing VRGIT	All measures of visuospatial and visuoperceptual skills evidenced a group and group by time significant effect ($p<0.001$)
Williams-Gray et al. (2013)*	Longitudinal (10-year follow-up)	49 incident PD patients	Presence of dementia was assessed with MMSE <24 cut-off	General cognitive functioning, language, memory, executive functions and visuoconstructive skills	PCT	PCT was a predictor of dementia (HR=2.55; p=0.001).
Galtier et al. (2014)	Cross-sectional	43 non-demented PD patients 20 healthy subjects	PD patients with dementia (Emre et al., 2007) were excluded MCI was also assessed with MDS criteria (Litvan et al., 2012)	Visuospatial, visuoperceptual and visuoconstructive skills, executive functions and memory (verbal learning, delayed memory and visuospatial learning)	JLOT FRT block design VOSP cube subtests	Patients exhibited visuoperceptual (p=0.001), visuospatial (p=0.007) and visuoconstructive functions (p=0.017), visual span ($p<0.05$) and visuospatial learning (p=0.016)
Yarnall et al. (2014)	Cross-sectional	Data of clinical assessment: 219 PD patients (75 cognitively normal)	MCI was diagnosed using MDS criteria (Litvan et al., 2012)	Attention, memory, executive function, visuoconstructive abilities and language	PCT	PCT did not differ significantly between PD patients with impaired vs. unimpaired cognition
Pigott et al. (2015)	Longitudinal (between 2 and 6 years follow-up interval)	141 PD patients at baseline 68 PD patients were eligible for the 6-year follow-up	MCI and PDD were assessed using MDS criteria (Litvan et al., 2012; Emre et al. 2007 respectively)	Global cognitive function, executive abilities and working memory, memory, visuospatial function and language	JLOT	Visuospatial assessment was not a predictive factor of progression from normal cognition to dementia
Santangelo et al. (2015)	Longitudinal (4-year follow-up)	Baseline: 76 PD patients (25 PD-MCI; 51 PD-CN) Follow-up 1 (2-year testing): 62 PD patients Follow-up 2 (4-year testing): 55 PD patients	MCI was diagnosed using MDS criteria (Litvan et al., 2012)	Memory, attention, frontal functions, language, and visuospatial and visuoconstructive skills	Constructional Apraxia Test JLOT	Visuospatial and visuoconstructive abilities differed at baseline and between PD-MCI reverters, non-reverters and cognitively stable patients.

Stefanova et al. (2015)	Cross-sectional	111 non-demented PD patients 104 healthy subjects	MCI was diagnosed using MDS criteria (Litvan et al., 2012)	Attention and working memory, executive functions, verbal and visual memory, and language and visuospatial domains	HVOT Clock drawing	Memory and visuospatial domains were the most commonly affected, and multiple-domain MCI subtype was the most common (78%).
Johnson et al. (2016)	Longitudinal (3 to 5 years follow-up interval)	24 non-demented PD patients 39 PDD patients	Diagnosis of dementia was based on CDR (Morris et al., 1993) and DSM-IV	Memory, language, associate learning, attentional and working memory functions, visuospatial abilities, processing speed and executive functions	Block design BVRT-copy	Meaningful prodromal change-points in Block design and BVRT-copy were significant in PD patients. Declines appear linearly
Kalbe et al. (2016)	Cross-sectional	269 PD patients with MCI	Petersen (2004)	Memory, attention, executive, visuospatial and language domains	Subtests of mental rotation and spatial imagination from LPS	Visuospatial abilities differed between different subtypes of MCI, but among all cognitive domains, they only preceded language in frequency of impairment in PD patients with MCI
Lawrence et al. (2016)	Cross-sectional	45 PD-MCI patients 25 healthy subjects	MCI was diagnosed using MDS criteria (Litvan et al., 2012)	Global cognition, executive functions, attention and working memory, memory, language and visuospatial functions	JLOT HVOT	Visuospatial MCI subtype was present in 2.2% of patients. Visuospatial functions were impaired in 31.2%, and changing to a 2SD cut-off, visuospatial impairment was present in 45%.
Caspell-Garcia et al. (2017)	Longitudinal (3-year follow-up)	423 PD patients (PPMI cohort)	Cognitive impairment was assessed with MoCA, MDS criteria and site investigator's clinical diagnosis	Global cognition, memory, visuospatial function, processing speed and attention, and executive function and working memory	JLOT	There was a significant change from baseline to follow-up in visuospatial abilities (p=0.02)

In alphabetical order; BVRT: Benton Visual Retention Test; CDR: Mattis Clinical Dementia Rating scale; DSM-IV: Diagnostic and Statistic Manual of Mental Disorders IV version; FRT: Facial Recognition Test; HR: Hazard Ratio; HVOT: Hooper Visual Organization Test; JLOT: Judgment of Line Orientation test; LPS: Leistungsprüfungssystem; MCI: Mild Cognitive Impairment; MDS: Movement Disorders Society; MMSE: Mini-Mental State Examination; MoCA: Montreal Cognitive Assessment; PCT: Pentagon Copying Test; PD: Parkinson's disease; PDD: Parkinson's disease dementia; PPMI: Parkinson's Progression Markers Initiative; ROFC: Rey-Osterrieth Figure Copy test; SCOPA-COG: SCales for Outcomes of PArkinson's disease-cognition; VOSP: Visual Object and Space Perception battery; VRGIT: Visuospatial Reasoning Groningen Intelligence Test. $^{+}$ and * indicate subjects from the same PD cohort.

Spatial orientation

Spatial orientation has been widely assessed in PD patients. One of the tools most commonly used is the Judgment of Line Orientation test (JLOT). This test examines the ability to estimate angular relationships between line segments by visually matching angled line pairs (see Figure 5). It has a high construct validity, test-retest reliability and internal consistency, and practice effects have been described to be minor (Lezak et al., 2012). Moreover, it seems especially appropriate because of less influence from other cognitive processes on its performance. The JLOT has been consistently related to temporo-occipital areas with right hemisphere predominance (Benton et al., 1994; Tranel et al., 2009).

In studies of visuospatial deficits in PD patients, the JLOT has been commonly reported to be impaired (Raskin et al., 1990; Levin et al., 1991; Finton et al., 1998; Alegret et al., 2001; Uc et al., 2005; Gullett et al., 2013; Segura et al., 2014; Stirk & Foreman, 2005; Renfroe et al., 2017). Moreover, significant decreases in JLOT scores are evident in cognitively impaired PD patients (Raskin et al., 1990; Levin et al., 1991) (see Table 6).

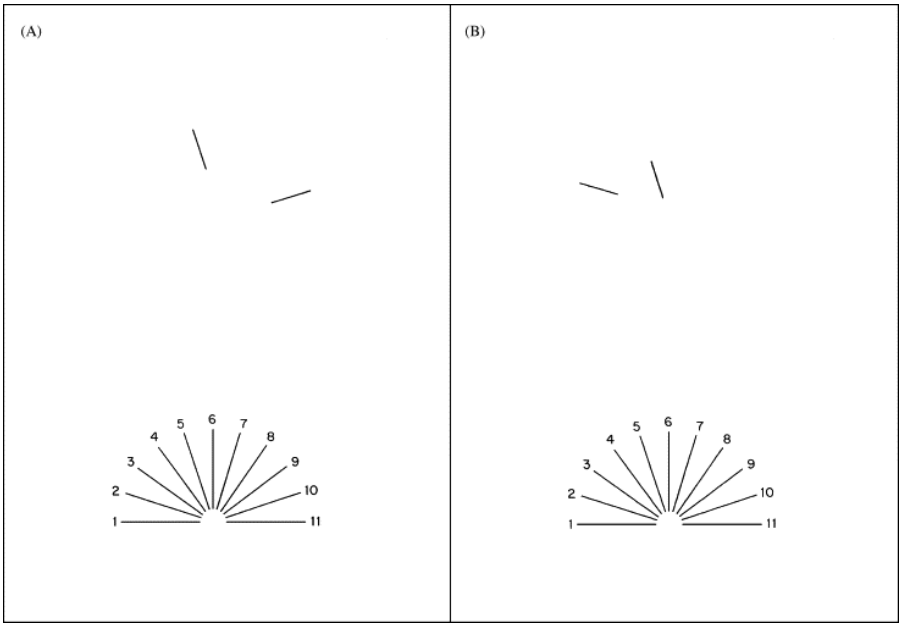

Figure 5. Reproduction of an item from JLOT. Benton, A.L., Hannay, H.J., & Varney, N.R. (1975): Visual perception of line direction in patients with unilateral brain disease. *Neurology*, 25, 907-910.

Error type analysis is an especially useful approach to study spatial processing deterioration. Finton et al. (1998), using an error system classification designed by Ska et al. (1990) (see Annex 1), reported that, although the test did not differentiate between AD and PD patients, a specific pattern of type of errors is most commonly seen in PD. PD subjects tend to mistake oblique lines by two or more spacings with or

without maintaining the initial space between the lines. Alegret et al. (2001) also found that PD patients tend to make a greater proportion of severe intraquadrant errors than controls as well as errors in horizontal lines. These reports highlight the existence of a specific visuospatial impairment associated with PD.

Regarding the use of different JLOT abbreviated forms in PD patients, Gullett et al. (2013) compared the odds-number form, the even-number form, and the two-thirds form to the full-length JLOT version. Authors reported that, next to the full form, only the two-thirds form exhibited minimally acceptable internal reliability, had the highest correlation with the full form and produced the least amount of diagnostic criteria misclassification in PD.

Spatial processing has also been assessed in PD patients with novel paradigms. Kemps et al. (2005) using Corsi blocks concurrently with visuospatial sketch pad and central executive tasks, demonstrated that the interference of the visuospatial sketch pad was a determinant of the performance only in moderate to severe stages of the disease, in agreement with previous findings stating that visuospatial impairment assessed with the JLOT is specifically found in cognitively impaired PD subjects (Raskin et al., 1990; Levin et al., 1991). In this line, Leek et al. (2014) designed two tasks to measure visuospatial navigation and visual memory, evidencing that a nonspecific deficit in sequencing cannot account for visuospatial impairment in PD. Using a virtual location task, Stirk & Foreman (2005) also demonstrated a specific deficit of spatial location abilities in PD patients, in comparison with healthy subjects and closed head injuries patients.

Mental rotation, visual transformation and visuospatial problem solving

Mental rotation, three-dimensional reasoning and visual transformation tasks have also been reported to be impaired in PD patients (Lee et al., 1998; Kerai et al., 2012) (see Figure 6). Early studies on transformation processes suggest that expedient problem-solving strategies may contribute in mental rotation tasks (Johnson, 1990). A certain number of studies propose that deficits in visuospatial problem solving share a relationship with the involvement of frontostriatal circuitry and mechanisms of working memory and attention (Hodgson et al., 2002; Amick et al., 2006; Kerai et al., 2012), but also posterior cortices (Cronin-Golomb & Braun, 1997).

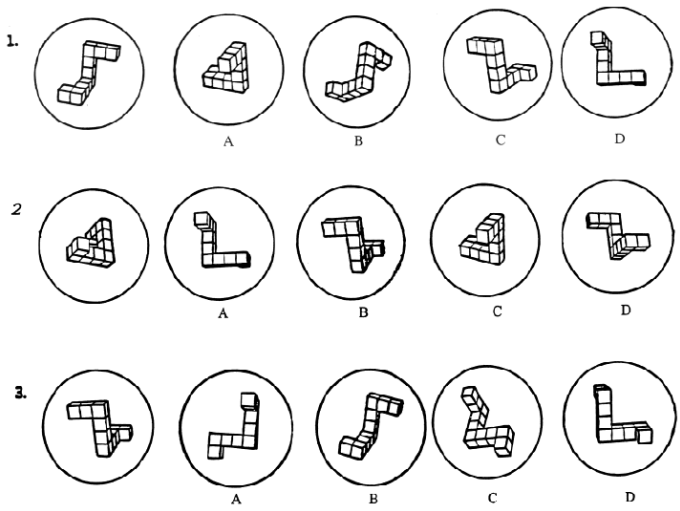

Figure 6. Extracted from Crucian et al. (2003). Reproduction of an example of the Mental Rotation Test.

On the other hand, PD male subjects are distinctively vulnerable to mental rotation deficits (Crucian et al., 2003), a fact that is perhaps related to the commonly reported superior performance in visuospatial tasks of male healthy subjects (Collaer & Nelson, 2002; Jordan et al., 2006).

VISUOPERCEPTUAL IMPAIRMENT

Face and object visual perception

One of the tools used to determine visuoperceptual functions in PD patients is the Facial Recognition Test (FRT) (Benton et al., 1994). This test examines the ability to recognize faces without involving a memory component. It consists in matching identical front views, front with side views and front views taken under different lighting conditions (Lezak et al., 2012) (see Figure 7). The FRT exhibits considerable reliability (Levin et al., 1991), and practice effects are mostly negligible (Lezak et al., 2012). Another of its strengths lies in its low sensitivity to the level of education (Benton et al., 1994). Similar to the JLOT, the FRT has right hemisphere predominance, particularly for temporal regions (Tranel et al., 2009).

In PD, a number of patients fail more on this test than on the JLOT, even those subjects who remain cognitively unimpaired (Raskin et al., 1990; Levin et al., 1991; Pereira et al., 2009; Archibald et al., 2013). Visual facial perception impairment in PD has also been described with other research paradigms (Marneweck & Hammond, 2014) (see Table 6).

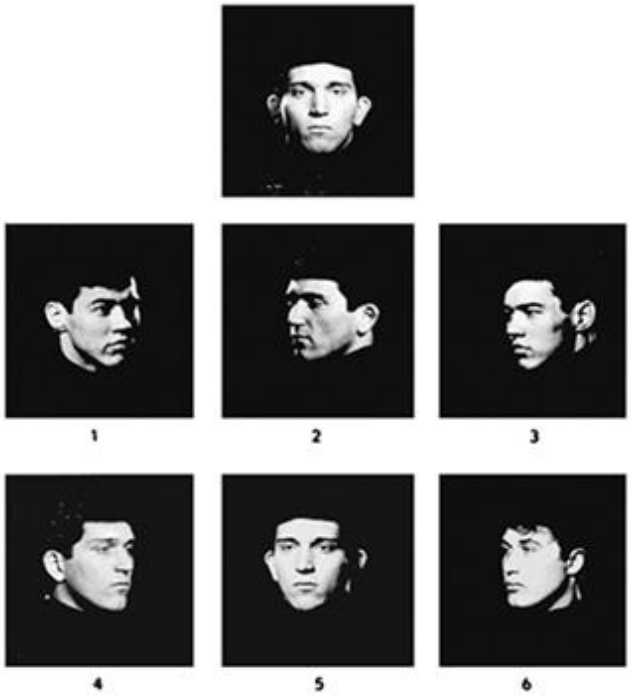

Figure 7. Reproduction of an item from FRT. Benton AL, Sivan AB, Hamsher K (1994): *Contributions to Neuropsychological Assessment. A clinical manual* (2nd ed.). New York: Oxford University Press

Similarly, another test related to visual perception, as well as spatial judgments, is the Visual Form Discrimination Test (VFDT) (Benton et al., 1994). The VFDT is a multiple-choice test that consists of a target set of stimuli and four stimulus sets among which there is one that exactly matches the initial target (Lezak et al., 2012) (see Figure 8).

Although this test may rely on somewhat more mixed functional circuitry than the FRT because of its spatial judgment component, it is a suitable test to assess visual recognition impairment in PD, since it is not affected by age, sex or education (Benton et al., 1994), and exhibits adequate consistency coefficient and sensitivity, as well as high specificity (Lezak et al., 2012). Another particular advantage of the VFDT is the possibility to classify the type of errors produced, such as rotation, distortion or peripheral misjudgments.

The VFDT has been used to assess visual perception in PD patients, demonstrating a gradual impairment of visuospatial functions in the disease (Raskin et al., 1990). Likewise, other authors have reported its impairment in non-demented PD subjects (Pereira et al., 2009; Segura et al., 2014).

Visual perception has also been assessed with different experimental tasks. Using images of scrambled versus coherent objects, cognitively mildly deteriorated PD patients evidence lower performance than cognitively preserved patients (Laatu et al., 2004). These findings have also been demonstrated with tasks

of identification of objects embedded in complex figures. Shine et al. (2015) designed a novel paradigm of misperceptions based on a bistable percept paradigm (BPP). BPP-impaired PD patients were described to make more perceptual errors, to be less accurate in perceptual judgments and to be more likely to misperceive a stimulus.

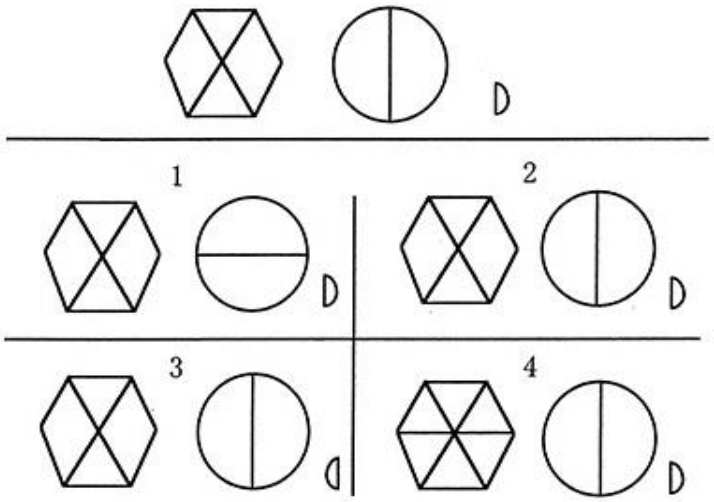

Figure 8. Reproduction of an item from VFDT. Benton AL, Sivan AB, Hamsher K (1994): *Contributions to Neuropsychological Assessment. A clinical manual* (2nd ed.). New York: Oxford University Press.

Interestingly, PD patients also show problems in categorization of visual stimuli semantically (Laatu et al., 2004). Some studies have pointed out that identification of visual objects is affected by orientation of stimuli (Arguin & Leek, 2003), especially when visual short-term memory tasks are required (Harris et al., 2008). Polarity features and shape of axes play a role in the computation of orientation-invariant shape representations; in PD, shape axes might facilitate the localization of polar features, which in turn are used by PD patients to resolve the polarity of shape representations during misoriented object recognition (Leek & Johnston, 2006).

Space and depth perception

Deficits in the perception of space and depth have also been described in PD. PD patients exhibit a left-side rightward bias in perceptual space judgments (Lee et al., 2001; Laudate et al., 2013). Regarding depth perception, stereopsis impairment is common (Sun et al., 2014; Koh et al. 2013), even in *de novo* PD subjects (Kim et al., 2011). These deficits have been related to the presence of dysfunctional basic visual perception processes, such as color vision and contrast sensitivity (Sun et al., 2014), as well as disease severity and motor impairment (Kim et al., 2011).

Motion detection

Visuoperceptual impairment in the detection of motion is also a feature of PD (Dayan et al., 2012; Jaywant et al., 2016; Kloeters et al., 2017). Deficits in perceiving biological motion are independent of motor phenotype and basic visual dysfunction, suggesting that they may arise from deficits in the perceptual integration of form and motion cues (Jaywant et al., 2016). Biological motion can also automatically lengthen perceived temporal duration independently of global configuration. Interestingly, in PD patients, this temporal dilation effect appears to be significantly reduced compared with healthy subjects (Cao et al., 2015).

VISUOCONSTRUCTIVE IMPAIRMENT

Visuconstructive impairment has been widely assessed in clinical settings by means of short screening tests, such as the clock drawing or the pentagon copying test (PCT) from MMSE (Smith, 2009; Pachana et al., 2010; Lezak et al., 2012) (see Figure 9). The PCT consists in the copy of two interlocking pentagons, respecting the angles by which the intersection is produced. According to the original scoring system (Folstein et al., 1975), it can be scored as correct when all ten angles are present and two form an intersection.

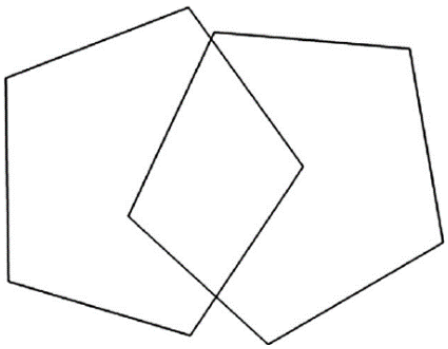

Figure 9. Reproduction of the interlocking pentagons from MMSE. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;12:189-98.

The first use of the PCT was in the context of the Bender-Gestalt figures test. It is a useful tool in discriminating dementia from normal ageing as well as between different types of dementia (Ala et al., 2001; Mosimann et al., 2004; Tiraboschi et al., 2006; Caffarra et al., 2013). However, it is important to consider the relevance of demographic factors, such as age and education, when interpreting the performance in copy tasks.

In the context of PD, the PCT has been widely used as a tool to determine general cognitive status because of its inclusion in the MMSE, as well as in separate forms, to assess visuconstructive abilities. Its utility has been highlighted in the process of differential neuropsychological diagnosis, since it is able to differentiate between distinct profiles of dementia. Cormack et al. (2004), using a scoring system designed by Bourke et al. (1995), found that the PCT is able to differentiate PD subjects from patients with AD, PDD and DLB. However, PDD and DLB patients did not differ in its performance. In this study, PCT correlated with global MMSE scores only in AD and PDD. Interestingly, longitudinal studies assessing the progression of cognitive deficits have evidenced that the PCT can track cognitive progression in PD (Williams-Gray et al., 2007; Williams-Gray et al., 2009; Williams-Gray et al., 2013; Kaul & Elble, 2014).

Some studies have aimed to compare performance and test properties between the PCT and other simple visuconstructive tests used in clinical settings to evaluate general cognitive status. Assessing PD and PDD patients, Alty et al. (2015) found that the ability to copy a wire cube was more often impaired than performance in the PCT, and that copying a wire cube significantly predicted cognitive impairment with moderate sensitivity and specificity. Conversely, recent findings have reported a limited specificity and accuracy of this item as part of the Montreal Cognitive Assessment (MoCA) (Hendershott et al., 2017). Lehrner and colleagues (2015) used the Vienna Visuo-constructional Test (VVT) in a sample of MCI, AD and PD patients, as well as healthy subjects, with a complex novel scoring system. This test includes the copy of the wire cube, interlocking pentagons, as well as the clock test. Taking these visuoconstructive tasks together, the test exhibited good reliability and was able to distinguish between healthy subjects, PD and MCI patients. Low correlations with other cognitive domains suggest that visuoconstructive functions are an independent cognitive domain (Lehrner et al., 2015). In this context, Lee et al. (2011) reported that the clock test was significantly more impaired in patients with AD or with vascular dementia than in PDD subjects. The same authors reported no changes in scores in longitudinal settings in the clock test, or in the MMSE.

Other studies have used the block design subtest from the Wechsler Adult Intelligence Scale (WAIS) (Levin et al., 1991; Uc et al., 2005). Visuoconstructive impairment on this test has been related to worsening of other cognitive domains, motor phenotype and disease severity (Uc et al., 2005), and has also been reported to differentiate between PD patients with advanced disease duration from patients with early and intermediate disease duration (Levin et al., 1991). Visuoconstructive abilities have also been studied in PD patients by means of more complex copy tests, such as the Rey-Osterrieth Copy Figure (ROCF) (Uc et al., 2005; Scarpina et al., 2016). Comparing two different scoring systems that assess executive and visuospatial functions separately in ROCF, PD patients exhibited worse performance in executive indexes (planning and neatness), but impairment in visual cognitive processes was also evident, specifically in judgment of line orientation and rotation (Scarpina et al., 2016) (see **Table 6**).

Closing-in

Individuals with PD and PDD often show a tendency to copy figures very close to the model, a phenomenon known as 'closing-in' (De Lucia et al, 2015a). Differences have been established between 'near closing-in', by which the drawn copy approaches the model without overlapping it, and 'adherent closing-in', by which the copy may surpass the original drawing. PD patients do not overlap their copy with the model (De Lucia et al., 2015a), on the other hand, PDD patients tend to show both near and adherent closing-in (De Lucia et al., 2015b) (see Figure 10).

Figure 10. Reproduced from De Lucia et al. (2015b). Effect of dual task conditions on left-to-right copying in PD-D individuals (left-hand Panels, A–C) and healthy adults (right-hand Panels, D–F): in the upper row copying in the single task condition (Panels A and D); in the middle row copying in the simple dual task condition (i.e., while counting onward; Panels B and E); in the lower row copying in the complex dual task condition (i.e., while counting backward; Panels C and F).

To date, in the context of a complex entanglement of neural mechanisms in the process of drawing (Trojano et al., 2009), there are two distinct interpretations of this phenomenon. Initial reports considered closing-in as a form of a constructional apraxia. Some authors have suggested that it might act as a strategy to compensate for a visuospatial dysfunction or visuospatial working memory deficit (Lee et al., 2004), and a strong association between closing in and visuospatial dysfunctions has been reported in AD patients (Serra et al., 2010). However, according to the 'attraction hypothesis' (McIntosh et al., 2008), closing-in phenomenon could arise from an impaired control of a default attraction of motor action towards the focus of visual attention (Kwon et al., 2002). In this same line, drawing and visuoconstructive tests have traditionally been considered as tasks that also sustain an influence of executive abilities (Cosentino et al., 2004).

The main problem of using a visuoconstructive test to assess the cognitive functions in PD is its motor component. In longitudinal studies, it is often difficult to isolate the effect of progressive motor deterioration from the cognitive decline.

In non-demented PD patients, De Lucia et al., (2015a) evidenced that closing-in errors were more common in complex figures. Although authors did not find significant differences between PD subjects who made closing-in errors and those who did not, closing-in patients scored significantly lower on frontal-executive tasks and the copy drawing test, and had higher apathy scores. Authors report that the only significant predictor of closing-in in a logistic regression analysis was the score in frontal-executive tasks; however, no measures of visuospatial and visuoperceptual impairment were assessed. Nonetheless, the association between closing-in and executive and attentional functions was posteriorly replicated in PDD patients (De Lucia et al., 2015b), suggesting that at least in part the closing-in phenomenon is related to frontal-executive dysfunction in PDD patients.

SYMBOL DIGIT MODALITIES TEST

The Symbol Digit Modalities Test (SDMT) is considered a predominantly speed-dependent test, which also relies in scanning, motor persistence, sustained attention, response speed and visuomotor coordination (Lezak et al., 2012). Furthermore, it assesses complex scanning and visual tracking, and brings out inattentiveness or imappreciation of orientation changes, especially by means of inversion errors (see Figure 11). Hence, it can also be considered as a test which can reflect the integrity of posterior cortical areas. Functional neuroimaging studies have found significant increased activation predominantly in posterior areas, specifically in the bilateral occipital cortex, cuneus, and inferior parietal regions (Forn et al., 2009).

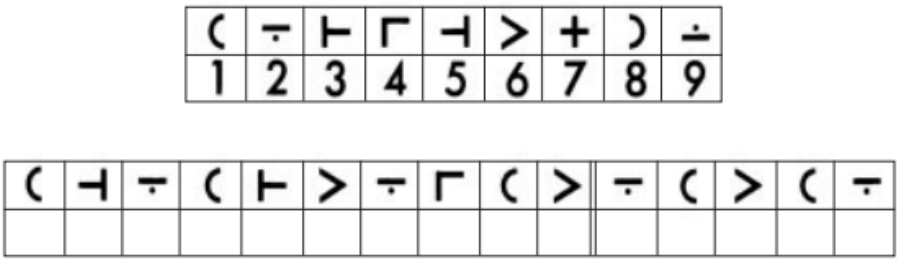

Figure 11. Key sequence and first line of the SDMT. Smith A (1982): *Symbol Digit Modalities Test*. Los Angeles, CA: Western Psychological Ser-vices.

Table 6. Findings in visuospatial, visuoperceptual and visuoconstructive functions in PD, classified according to domains

Authors (year)	Design	Sample	Test	Findings
Visuospatial				
Levin et al. (1991)	Cross-sectional	183 PD patients subdivided according to disease duration and general cognitive status: • 84 early PD patients (50 non-demented) • 64 middle duration (33 non-demented) • 35 advanced disease (24 non-demented)	NEFT HVOT JLOT	Visual cognition does not decline uniformly, but gradually deteriorates as a function of disease duration. By middle duration, demented patients experience difficulty in JLOT and HVOT, whereas in advanced stages, patients with dementia show pervasive impairment in all areas of visual cognition.
Finton et al. (1998)	Cross-sectional	21 patients with probable AD 28 patients with idiopathic PD 24 HC	JLOT	PD patients scored significantly lower than healthy subjects, but there were no significant differences between AD and PD, or between AD and HC. QO3 errors were made by a significantly greater number of PD patients.
Alegret et al. (2001)	Cross-sectional	76 PD patients 76 HC	JLOT	PD patients' total error scores differed from HC's. Visuospatial impairment correlated significantly with age, education, duration of disease and disease severity. PD patients made a greater proportion of severe intraquadrant errors (QO2, QO4), and errors in the horizontal line than HC.
Crucian et al. (2003)	Cross-sectional	23 female PD patients 28 male PD patients 28 healthy male subjects 28 healthy female subjects	MRT	Non-demented men with PD were significantly less accurate on MRT than healthy matched men. Women with PD performed similarly to matched control women, but both groups of women did not perform better than chance.
Kemps et al. (2005)	Cross-sectional	15 PD patients 15 HC	Corsi blocks task with visuospatial sketch pad and central executive concurrent tasks	PD patients performed more poorly on the Corsi blocks task with the concurrent visuospatial sketchpad task, supporting the existence of a specific visuospatial dysfunction in PD.
Uc et al. (2005)	Cross-sectional	76 PD patients with mild to moderate disease severity 161 HC	JLOT	PD subjects performed significantly worse in all measures of visual cognition. Predictor variables of cognition were UFOV and JLOT.
Gullett et al. (2013)	Cross-sectional	141 PD patients 56 HC	JLOT (versions H, OF, EF, TF)	PD group performed lower than HC on all JLOT forms. Among the short forms, TF exhibited minimally acceptable internal reliability, had the highest correlation with the full form and produced the least amount of diagnostic criteria misclassification.

Leek et al. (2014)	Cross-sectional	13 non-demented PD patients 20 HC	Two navigation tasks design for the study	PD patients were impaired in the visuospatial grid navigation task, but not in sequential number subtraction, demonstrating that a nonspecific deficit in sequencing cannot account for visuospatial impairment in PD.
Stirk & Foreman (2015)	Cross-sectional	Group 1: 9 older PD patients Group 2: 12 patients with CHI Group 3: 12 older controls (to match PD patients) Group 4: 18 younger HC (to match CHI patients)	JLOT Virtual tray of objects task Virtual flag location task	PD patients reported no navigational difficulties. JLOT exhibited significant group differences. There was a significant group effect in the virtual tray of objects tasks between HC and all patients group, but not for the virtual flag location task.
Renfroe et al. (2017)	Cross-sectional	47 PD patients	NAB JLOT	NAB and JLOT were significantly influenced by education. It is unclear whether the JLOT or Visual Discrimination subtest is superior in measuring visuospatial functioning in PD, but JLOT has superior test-retest reliability.
Visuoperceptual				
Raskin et al. (1990)	Cross-sectional	15 PD patients with impaired visual processing 13 PD patients with intact visual processing 13 patients whose performance on a task of spatial orientation was lower than their performance on a task of complex perceptual discrimination	VFDT (to assess 'basic visual perception' according to which patients were categorized) FRT (measure of 'complex perceptual discrimination')	The 'perceptually impaired group' was older at the time of testing, showed moderate cognitive deficits on the DRS and fell between the other two groups in duration of symptoms. The other two groups were younger and not demented. The group with average performance had the shortest duration of symptoms. No significant differences were observed in the patterns of predominant motor symptoms between the three groups, but differed in age at time of testing, duration of symptoms and degree of dementia.
Levin et al. (1991)	Cross-sectional	As described above	Ghent task FRT	Visual cognition does not decline uniformly, but gradually deteriorates as a function of disease duration. In the early phase of PD, demented and non-demented subjects exhibit a highly selective decline in FRT, whereas in advanced stages, patients with dementia show deep impairment in all areas of visual cognition.
Laatu et al. (2004)	Cross-sectional	28 PD patients 14 HC	Discrimination task and object detection task from CogniSpeed	Cognitively mildly deteriorated PD patients performed more poorly than HC or other PD patients in discriminating scrambled objects from real coherent objects and had more problems than HC in categorizing visual stimuli semantically.
Archibald et al. (2013)	Cross-sectional	64 non-demented PD patients 26 PDD patients 32 HC	A shape position task Overlapping figures task	Error rates were significantly higher in cognitively impaired PD subjects, their explorations strategy was less efficient, had reduced saccade amplitudes and their gaze fixation duration was longer.

Shine et al. (2012)	Cross-sectional	45 PD patients (subdivided into 23 BPP-impaired and 22 BPP-normal PD patients) 18 HC	Novel paradigm for misperceptions (BPP)	Significant effect of group on all BPP measures: • Patients classified as BPP impaired by their BPP error score were significantly less accurate at correctly identifying bistable percepts than the BPP normal patients • BPP impaired patients were significantly less accurate at correctly identifying single images than BPP normal patients • BPP impaired patients were significantly more likely to misperceive a stimulus than BPP normal patients • BPP impaired patients were significantly worse than BPP normal patients when comparing the rates of missing images.
Visuoconstructive				
Levin et al. (1991)	Cross-sectional	As described above	Block design	Visual cognition does not decline uniformly, but gradually deteriorates as a function of disease duration. By middle duration, demented patients experience difficulty mentally in block design, whereas in advanced stages, patients with dementia show pervasive impairment in all areas of visual cognition.
Cormack et al. (2004)	Cross-sectional	100 AD patients (MMSE:18.03) 50 DLB patients (MMSE: 17.13) 36 PDD patients (MMSE: 19.36) 81 PD patients (MMSE: 28.81)	PCT Copy of a spiral Copy of a three-dimensional house	PCT showed a group effect, were all differed significantly from non-demented PD patients. DLB patients perform worse than AD and PD patients on PCT, and all patients with dementia perform worse than non-demented PD subjects.
Uc et al. (2005)	Cross-sectional	As described above	Block design ROFC	PD subjects performed significantly worse in all measures of visual cognition. Impairment in visuoconstructive abilities correlated with impairment in speed of processing and attention, CS, VA and spatial perception. Increased severity of PIGD correlated significantly with motion perception and visuoconstructive abilities. Higher H&Y stage, disease severity and impaired visual attention correlated significantly with visuoconstructive impairment.
Lee et al. (2011)	Longitudinal	94 AD patients 22 VaD patients 119 PDD patients	CDT	Overall cognitive function was significantly better in the PDD group. AD exhibited the lowest CDT scores. No clear difference in the longitudinal changes on the CDT and MMSE scores were found among the three types of dementia.
Kaul & Elble (2014)	Longitudinal	144 PCT-normal PD patients 80 PCT-abnormal PD patients	PCT	Non-demented PD patients (MMSE >25) exhibited more than twice the rate of decline in MMSE score if they drew PCT incorrectly at initial examination, and they were three times as likely to reach an MMSE score <26.
Alty et al. (2015)	Cross-sectional	32 non-demented PD patients 23 PD patients with MCI 8 PDD patients	PCT Wire cube	Wire cube was copied incorrectly by a greater number of PD patients than PCT, as well as PD subjects with MCI and dementia. Incorrect PCT was not a significant predictor of cognitive impairment.

De Lucia et al. (2015[a])	Cross-sectional	100 PD patients	Copy drawing test	50% of patients made closing in errors (92% made closing-in errors in isolation, 4% adherent-closing-in in isolation and 4% shoed both near and adherent types of closing in). Closing-in errors were more frequent in more complex figures.
De Lucia et al. (2015[b])	Cross-sectional	30 PDD patients 29 HC	Copy drawing test	PD-D group showed closing in. The occurrence of the closing in phenomenon was significantly associated with the executive composite score, whereas there were no significant associations between closing in and demographic variables, general cognitive status, visuospatial short-term memory, visuoconstructive score or memory score.
Lehrner et al. (2015)	Cross-sectional	30 AD patients 18 PD patients 55 PD patients with MCI 76 HC	VVT (includes copy of clock, pentagons and cube)	There was a significant group effect, and post hoc tests showed significant differences between controls and the groups MCI and PD. AD differed from MCI, but no significant differences were found between MCI and PD, or between AD and PD. VVT significantly discriminated between healthy controls and all patients' groups, and was able to identify patients with MCI.
Scarpina et al. (2016)	Cross-sectional	30 PD patients 30 HC	ROFC	PD performed significantly lower in ROCF. PD had worse performance scored according to the BQSS (in executive indexes of planning, neatness and in the visuoconstructive skill of rotation).

In alphabetical order; AD: Alzheimer's disease; BPP: Bistable Perception Paradigm; BQSS: Boston Qualitative Scoring System; CDT: Clock Drawing Test; CHI: Closed Head Injuries; CS: Contrast Sensitivity; DLB: Dementia with Lewy bodies; DRS: Mattis Dementia Ratinc Scale; FAB: Frontal Assessment Battery; FRT: Facial Recognition Test; HC: Healthy subjects; HSD: Tukey's Honest Significant Difference; HVOT: Hooper Visual Organization Test; H&Y: Hoehn & Yahr scale; JLOT: Judgment of Line Orientation test (OF: Odds-number Form; EF: Even-number Form; TF: Two-thirds Form); MCI: Mild Cognitive Impairment; MMSE: Mini-Mental State Examination; MRT: Mental Rotation Test; NAB: Neuropsychological Assessment Battery; NEFT: Non-verbal Embedded Figures task; PD: Parkinson's disease; PDD: Parkinson's disease dementia; PIGD: Postural and Instability Gait Disorder; ROFC: Rey-Osterrieth Figure Copy; UFOV: Useful Field of View; VA: Visual Acuity, VaD: Vascular dementia; VFDT: Visual Form Discrimination test; VVT: Vienna Visuo-constructional Test.

Basic visual dysfunction

Flowers & Robertson (1995), using three-dimensional stereo vision, figure-ground discrimination and pattern perception tasks in PD patients, demonstrated that retinal effects on perception in PD occur in advanced stages of the disease and, in earlier stages, any visual dysfunction probably reflects top-down disturbances from higher levels of the cognitive behavioral system. These results are in agreement with a number of studies which evidenced that even after the contribution of poor visual resolution, overall visual perception remained impaired in PD patients (Jones & Donaldson, 1995; Uc et al., 2005).

In addition, findings that loss of contrast sensitivity occurs at specific intermediate spatial frequencies and the evidence of a stronger selectivity of deficits in horizontal gratings indicate a cortical origin as the locus for deficits in contrast sensitivity in PD, since, opposite to neurons in the retina or thalamus, the primary visual cortex is linked to orientation specificity and selectivity for different spatial frequencies (Armstrong, 2015; Weil et al., 2016).

Motor phenotype

The laterality of PD motor symptoms has been related to visuospatial impairment (Levin et al., 1991; Karadi et al., 2015; Seichepine et al., 2015). PD patients with left-sided motor symptoms and non-tremor phenotype have been found to perform more poorly in visuospatial tasks than healthy subjects and other PD patients, and their number of errors was found to correlate with the degree of motor symptom asymmetry (Karadi et al., 2015). These findings are in line with a certain number of studies, which favor a predominance of right hemisphere participation on the performance of visuospatial tasks (Kesler et al., 2004).

Regarding other aspects of the motor phenotype, freezing of gait has also been related to visuospatial, visuoperceptual and visuoconstructive impairment (Levin et al., 1991; Amboni et al., 2012; Nantel et al., 2012; Factor et al., 2014a; Kelly et al., 2015; Silveira et al., 2015).

Silveira et al., (2015) found that PD patients with freezing of gait show more impairment in visuoconstructive tasks and, although they have a similar number of freezing of gait episodes to the rest of PD subjects, the error variability in their perceptual judgment predicts the percentage of time spent in double support in narrowing conditions. These findings support the notion that sensory-perceptual deficits both prior to movement planning and during movement execution are important factors contributing to freezing of gait.

Moreover, visuospatial impairment in PD is strongly associated with postural instability (Amboni et al., 2012). Addressing measures of basic visual function, visual cognition and disease parameters, Uc et al. (2005) suggested that the most likely common substrate for gait impairment and visual inattention in PD is the degeneration of central cholinergic systems.

Conversely, visuospatial deficits, although less consistently, have also been related to tremor predominant motor symptoms (Wang et al., 2017) and fronto-executive functions have been related to the postural instability and gait disorder phenotype (Lord et al., 2014). In this context, some studies have stated that the relationship between motor phenotypes and visuospatial impairment is supported by changes in frontostriatal pathways and subcortical structures, rather than posterior cortical areas and cholinergic pathways. Sunwoo et al. (2013) related thalamic volume with visual recognition, and suggested that it could be a major contributor to the development of freezing of gait in non-demented PD patients. Unresponsive freezing of gait has also been associated with both executive and visuospatial dysfunctions, implicating a degeneration of frontostriatal pathways, while responsive freezing of gait has been related to hallucinations, suggesting involvement of posterior cortical regions (Factor et al., 2014a).

Visual hallucinations

Visual hallucinations in PD are a complex phenomenon composed of flickering lights and illusionary misconceptions, often preceding the most common manifestation, namely, stereotypical colorful images (Armstrong, 2008). Their occurrence takes place in 30-60% of PD patients (Diederich et al., 2005). In PD, visual hallucinations have been associated with ocular disturbances as well as impairment in contrast sensitivity and color vision (Diederich et al., 1998), and patients who suffer them exhibit greater deficits in object and face identification (Barnes et al., 2003; Gallagher et al., 2011). Ramirez-Ruiz et al., (2006) evidenced that PD patients with visual hallucinations differ from other PD subjects in verbal learning and visuoperceptual functions, independently of general cognitive status, disease severity and depression; and patients with a history of visual hallucinations exhibit a fast impairment of complex visual functions, together with a progressive decline in multiple cognitive domains (Ramirez-Ruiz et al., 2007). Furthermore, poor primary vision and reduced activity of the primary visual cortex (V1) appear as risk factors for hallucinations in PD patients (Armstrong, 2008).

Visual hallucinations are common especially in patients treated with levodopa and dopamine agonists, and may involve a disturbance in the regulation of the gating and filtering of external perception and internally generated visual images (Armstrong, 2008). Although visual hallucinations are neuropsychiatric dysfunctions often associated with other psychotic symptoms, Factor et al. (2014b) suggested delusions and hallucinations share a different pathogenic mechanism and possibly anatomical substrates.

Medication

Early reports in PD related cognitive performance with duration of dopaminergic medication. Studies focusing on cognitive outcomes regarding changes in medication have evidenced beneficial effects of dopaminergic medication on spatial working memory, but not visual recognition memory or visuospatial paired associated learning, deficits which may rely predominantly in posterior cortical areas (Weil et al., 2016). Nonetheless, emotional face recognition has been described to improve with levodopa (Sprengelmeyer et al., 2003), and there is evidence that supports a relationship between the presence of hallucinations and dopamine agonists (Weil et al., 2016).

On the other hand, anticholinergic drugs are commonly related to visual hallucinations and delirium in PD patients, and have a detrimental effect on visuospatial memory in early PD (Herzallah et al., 2010). Moreover, cholinesterase inhibitors are the only demonstrated medication to confer moderate clinical benefits in PDD (Emre et al., 2004).

Disease progression and evolution to dementia

Age and disease duration can interact differentially with the disease process. The subdivision of PD patients according to the degree of impairment in visual processing by Raskin et al., (1990) evidenced the existence of a specific subtype of PD, in which patients exhibit faster cognitive deterioration in shorter duration of disease symptoms, similarly to other studies (Levin et al., 1991). Levin et al. (1991) sampled all visual processing skills in PD and aimed to study their relationship with disease factors. Authors found that visual cognition does not decline uniformly, but gradually deteriorates as a function of disease duration. In the early phase of PD, demented and non-demented subjects exhibit a highly selective visuoperceptual decline on facial recognition; by intermediate disease duration, demented patients experience difficulties in mentally assembling puzzles, formulating angular judgments and identifying embedded objects and geometric figures; whereas, in advanced stages, patients with dementia show pervasive impairment in all areas of visual cognition.

According to Johnson et al. (2016), cognitive decline in PD progresses to PD-MCI, where visuospatial imagery and memory retrieval deficits manifest before eventual development of overt dementia. These findings are also in agreement with previous reports, stating that the greatest rate of progression of cognitive impairment is seen in patients with initially more severe impairment of visuospatial functions (Stepkina et al., 2010) and that visuospatial functions are severely affected in PDD (Mosimann et al., 2004; Janvin et al., 2006).

Longitudinal disease-state design studies support a prodromal dementia stage marked by early declines in working memory and visuospatial processing beginning 5 years before clinical diagnosis of PDD (Johnson et al., 2016). Furthermore, the relevance of posterior cortically-based deficits in PD has been evidenced by the finding that impairment in these cognitive functions, including visuoconstructive tasks such as the PCT from MMSE, are predictive of the subsequent emergence of PDD (Williams-Gray et al., 2007; Williams-Gray et al., 2009; Williams-Gray et al., 2013).

NEUROANATOMICAL CORRELATES OF VISUAL COGNITION IN PARKINSON'S DISEASE

Neuroanatomical-correlate studies address a fundamental question in the neural mechanisms that underlie neuropsychological deficits in diseases, providing a growing knowledge on the neurodegenerative processes in PD.

Commonly used techniques are the analysis of gray and white matter structure as well as functional brain parameters, in cross-sectional and, less commonly, longitudinal settings (see Table 7). A consistently observed finding is that visuospatial, visuoperceptual and visuoconstructive impairment in PD patients is related to the loss of integrity of posterior cortical areas (Pereira et al., 2009; Pagonabarraga et al., 2013; Filoteo et al., 2014; Segura et al., 2014; Pereira et al., 2015) (see Figure 12 and Figure 13). However, there are studies that also found associations of these deficits with anterior brain regions (Filoteo et al., 2014; Segura et al., 2014).

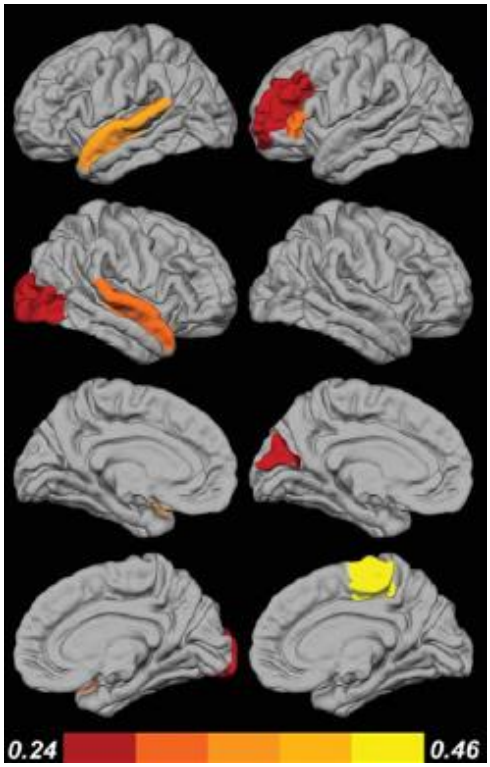

Figure 12. Modified from Filoteo et al., (2014). Correlation of regional volumes with performance in JLOT (left) and PCT (right). Color bar designates the partial correlation coefficient magnitude.

The finding of a posterior-cortical predominant dysfunction has been replicated by functional studies, using a variety of techniques, such as fludeoxyglucose positron emission tomography (FDG-PET) (Mentis et al., 2002; Ishioka et al., 2011; Garcia-Garcia et al., 2012; Nishio et al., 2017), single-photon emission computed tomography (SPECT) (Abe et al. 2003) dopamine transporter (DAT) scan (Pellechia et al., 2015) and functional MRI (fMRI) (Baggio et al., 2014; Caproni et al., 2014; Nombela et al., 2014; Baggio et al., 2015). Another approach by which the relationship between brain functional parameters and impairment in visual cognition processes has been studied is electroencephalography (EEG) slowing. Significant changes in parietal, occipital and temporal alpha/theta ratio are related to the performance in visuoconstructive tests (Eichelberger et al., 2017).

In summary, structural and functional data pointed to the involvement of bilateral posterior temporal, parietal and occipital areas. Some studies, nonetheless, observed right hemisphere predominance (Abe et al., 2003; Caproni et al., 2014; Kim et al., 2014). Finally, some findings indicated a relationship between global atrophy parameters and visuoperceptual deficits (Dalaker et al., 2009a).

White matter abnormalities have also been related to the impairment in visuospatial, visuoperceptual and visuoconstructive functions (Dalaker et al., 2009a; Pellechia et al., 2015; Theilmann et al., 2013; Goldman et al., 2017). These studies have highlighted the relevance of posterior (Goldman et al., 2017) and anterior (Theilmann et al., 2013; Pellechia et al., 2015), white matter brain regions.

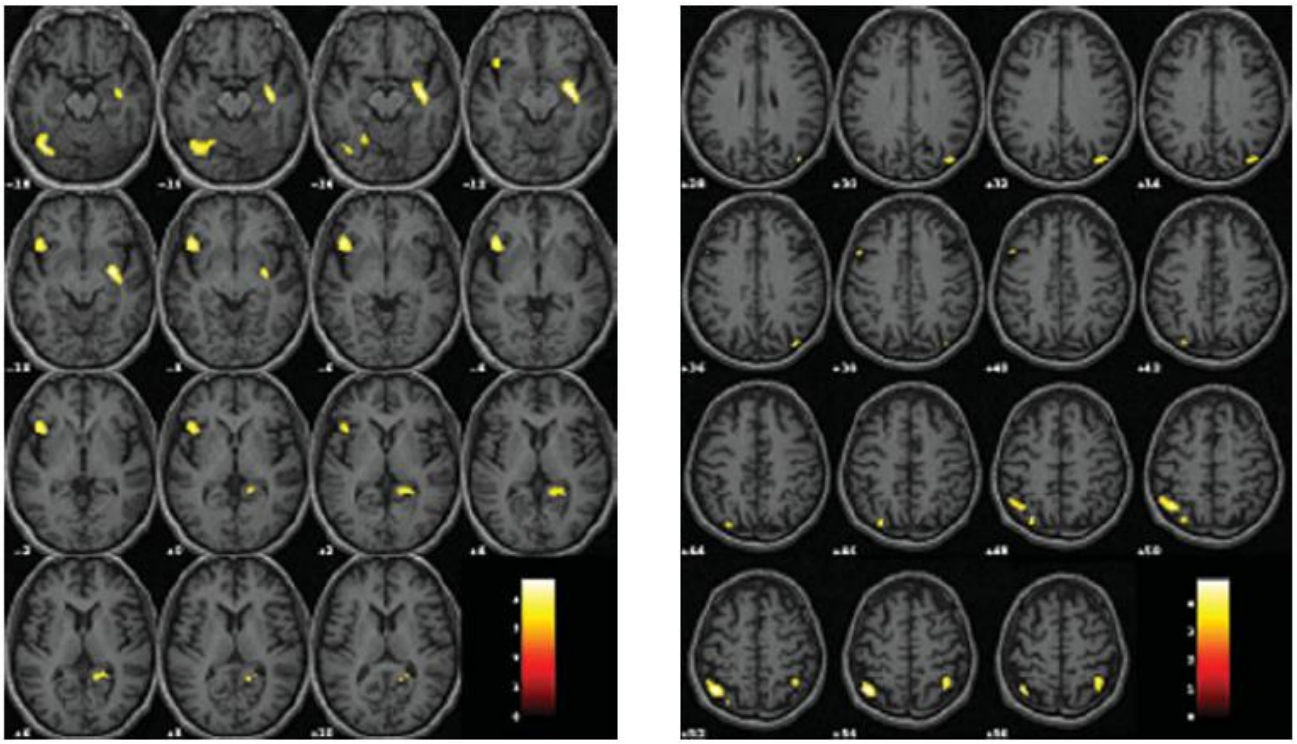

Figure 13. Reproduced from Pereira et al., (2009). Regions showing significant positive correlations with FRT (left) and VFDT (right). Colored areas correspond to gray matter reductions.

A specific relevant aspect of these findings is that the areas reported above, which share a relationship with the impairment of visual cognition processes, have been described to degenerate as cognitive function declines (Burton et al., 2004; Beyer et al., 2007; Dalaker et al., 2009b; Weintraub et al., 2011; Melzer et al., 2012; Compta et al., 2013; Nagano-Saito et al., 2014; Danti et al., 2015; Gerrits et al. 2014; Gerrits et al., 2015; Mak et al., 2014; Mak et al., 2015; Baba et al., 2017).

Table 7. Findings of neuroanatomical correlates studies in visuospatial, visuoperceptual and visuoconstructive performance in PD

Authors (year)	Correlate technique	Sample	Test	Domain	NPS findings	Neuroimaging results
Mentis et al. (2002)	FDG-PET (data were analyzed by using brain-behavior partial least squares, a voxel-based analysis)	15 non-demented PD patients	HVOT	Visuospatial	Mean score in HVOT was within the normal range	Two significant, independent topographic patterns were identified. Pattern 1 included parieto-occipito-temporal and medial temporal brain regions, and pattern 2 included the lateral frontal and anterior limbic cortex. Patterns 1 and 2 exhibited a double dissociation in their behavioral correlates: pattern 1 correlated with both visuospatial and mnemonic functioning but not with dysphoria; pattern 2 correlated with dysphoria but not with the cognitive measures ($p<0.03$).
Abe et al. (2003)	^{123}I-FP-CIT SPECT (rCBF measurement)	28 non-demented PD patients 17 HC	RPM	Visuoperceptual, visuospatial	PD patients scores were significantly lower than HC's ($p<0.05$)	There was a positive correlation between rCBF and right dorsolateral occipital and right posterior parietal cortices ($p<0.01$). Most of these regions were reported to have significantly lower rCBF in PD patients than healthy subjects.
Dalaker et al. (2009[a])	WMH volumes	155 PD patients 101 healthy subjects	VOSP (Silhouettes)	Visuoperceptual		There were significant correlations between WMH, whole brain parenchyma and lateral ventricle volumes and visuospatial z-score in PD patients ($p<0.001$).
Pereira et al. (2009)	VBM	36 non-demented PD patients 20 HC	VFDT FRT	Visuospatial, visuoperceptual	PD patients differed significantly from HC in both measures ($p<0.002$)	PD patients' performance on FRT correlated with with a GM decrease in the fusiform gyrus, parahippocampus, middle occipital gyrus and inferior frontal gyrus. VFDT correlations were seen in bilateral superior parietal lobes, superior occipital cortex, and middle frontal and inferior frontal gyri ($p<0.05$).

Ishioka et al. (2011)	FDG-PET (rCMRglc utilization at rest)	4 PD patients 24 HC	Poppelreuter's overlapping figures	Visuoperceptual	Differences between PD patients and HC were not significant, but patients had an increase in the illusory response	Illusory response negatively correlated significantly with glucose metabolism in the bilateral inferior temporal gyrus, bilateral temporo-parieto-occipital junction, bilateral inferior parietal lobule, right middle frontal gyrus and left superior temporal pole ($p<0.05$).
Garcia-Garcia et al. (2012)	FDG-PET (SPM8)	21 PD-NC 28 PD-MCI patients 19 PDD patients 20 HC	PCT	Visuoconstructive	PDD and PD-MCI patients had impairment in PCT	Visuoconstructive functions positively correlated significantly with FDG-PET uptake in large posterior bilateral occipital and parietal regions ($p<0.05$).
Pagonabarraga et al. (2013)	Cortical thickness	72 PD patients (26 PD-NC patients; 26 PD-MCI patients and 20 PDD patients) 18 HC	Clock copy	Visuoconstructive		In PDD patients, clock copy correlated with thickness in the right parahippocampal gyrus ($p<0.001$), left precuneus ($p=0.01$) and left lingual gyrus ($p=0.01$).
Theilmann et al. (2013)	DTI	25 non-demented PD patients 26 HC	JLOT	Visuospatial	Differences in JLOT were not significant between PD and HC	Poorer visuospatial ability correlated with lower FA values in the left anterior corona radiata ($p<0.05$)

Baggio et al. (2014)	fMRI	66 PD patients (subdivided into 43 PD-nonMCI and 23 PD-MCI patients) 36 HC	JLOT VFDT	Visuoperceptual, visuospatial	Scores differed significantly between the three study groups ($p<0.001$)	Regression analysis in PD patients showed a negative correlation between visuospatial and visuoperceptual measures and clustering, modularity and small-world coefficients. At a regional level, clustering, degree and betweenness centrality correlated negatively with visuospatial and visuoperceptual scores in temporal and parietal cortices, basal ganglia, thalamus and medial temporal nodes ($p<0.015$).
Caproni et al. (2014)	fMRI	11 right-handed non-demented PD patients 11 HC	Novel visual perception and spatial orientation design tasks	Visuospatial, visuoperceptual	All subjects correctly carried out both tasks and did not differ ($p>0.05$)	Compared to controls, PD patients had an over-activation of the right dorso-lateral prefrontal cortex, and bilateral posterior parietal cortex, (particularly in the right hemisphere) (*F-score* range: 2–17.95).
Filoteo et al. (2014)	Volumetric cortical thickness correlates (FreeSurfer cortical thickness ROI-based approach)	51 PD patients 39 HC	JLOT PCT	Visuospatial, visuoconstructive	Scores did not differ significantly between healthy subjects and PD patients in both measures	JLOT correlated significantly with the superior temporal gyrus and occipital cortex bilaterally. PCT had significant correlations with left frontal cortex and right posterior cingulate and occipital areas ($p<0.05$).
Kim et al. (2014)	rsFC analysis using bilateral SI seed and region-of-interest-based volumetric analysis	20 short-duration PD patients 18 longer-duration PD patients	ROFC PCT	Visuoconstructive	Groups only differed significantly in the ROFC ($p=0.001$)	There were significant correlation coefficients between the ROCF and bilateral parietal areas ($p=0.032$), regions showing altered rsFC between the collapsed PD-MCI and PD patients with normal cognition groups

Lebedev et al. (2014)	fMRI (ROI-based approach; SPM8) ^{123}I-FP-CIT SPECT	30 PD patients (PPMI cohort)	JLOT	Visuospatial		A profile with better executive performance was associated with increased dorsal fronto-parietal cortical processing and inhibited subcortical and primary sensory involvement was found, and also characterized by a relative preservation of nigrostriatal dopaminergic function (p=0.004).
Nombela et al. (2014)	fMRI	168 PD patients 85 HC	Spatial rotations task (measured latency and accuracy)	Visuospatial	Patients performed significantly worse than HC in the spatial rotations task (p<0.05)	During performance in mental rotations task, wide areas of activity in bilateral occipital, parietal and temporal regions evidenced significant changes (p<0.05)
Segura et al. (2014)	FreeSurfer (surface-based cortical thickness approach)	90 non-demented PD patients (43 PD-nonMCI patients and 47 PD-MCI patients) 32 HC	JLOT VFDT	Visuoperceptual, visuospatial	The three study groups differed significantly in both measures (p<0.001)	Performance on JLOT and VFDT was associated with medial-temporal parietal atrophy. JLOT evidenced negative correlations in the rostral middle frontal gyrus (p<0.05).
Baggio et al. (2015)	fMRI FreeSurfer (surface-based cortical thickness approach)	65 PD patients (43 PD-nonMCI and 22 PD-MCI patients) 36 HC	JLOT VFDT	Visuoperceptual, visuospatial	Scores differed significantly between the three study groups (p<0.001)	Connectivity in DMN clusters significantly correlated with visuospatial and visuoperceptual measures (p=0.004). A cortical cluster in a left lateral occipital and temporal area that significantly differed in thickness between HC and PD-MCI patients correlated with visuospatial and visuopereceptual scores (p<0.05).

Pellecchia et al. (2015)	DAT imaging, [123-I] FP-CIT SPECT	34 de-novo drug naïve PD patients (19 non-MCI PD patients and 15 PD-MCI patients)	JLOT ROCF Constructional apraxia test	Visuospatial, visuconstructive	Compared to PD-nonMCI patients, PD-MCI subjects performed worse in all tests ($p<.001$)	In PD-MCI patients, lower scores in copy task of ROCF were significantly related with the caudate ($p=0.008$).
Pereira et al. (2015)	FreeSurfer (surface-based cortical thickness approach)	123 PD patients 56 HC	JLOT Clock and cube copying subtests from MoCA	Visuospatial Visuconstructive	There were significant differences between all study groups in JLOT ($p<0.05$)	Visuospatial domain evidenced significant cortical thickness correlations with bilateral parietal areas and left temporal cortex ($p=0.001$).
Eichelberger et al. (2017)	EEG slowing	57 non-demented PD patients	ROFC Clock drawing Block design	Visuoconstructive		A significant positive correlation was established between ROCF and parietal alpha/theta ratio ($p=0.012$) and occipital alpha/theta ratio ($p=0.030$). Significant correlations were also seen between central, parietal, frontal, temporal and occipital alpha/theta ratio and clock drawing ($p<0.45$). Block design correlated significantly with alpha/theta ratio in temporal areas ($p=0.013$).
Goldman et al., (2017)	FreeSurfer (volumetric-based approach)	100 PD patients (PD-NC: 28 patients; PD-MCI: 47 patients; PDD: 25 patients	JLOT PCT Clock copy	Visuospatial, visuoconstructive	The four groups of the study differed in the visuospatial composed z-score ($p<0.0005$)	Visuospatial domain was associated with the posterior subsection of the caudate volume ($p<0.0005$).

Kim et al. (2017)	Cortical thickness Sustantia innominate volume	116 PDD patients 121 HC	PCT ROCF	Visuoconstructive	Early onset and late onset PD patients differed in the execution of both measures ($p<0.001$)	In the younger PD patients, sustantia innominata volume correlated significantly with visuoconstructive measures ($p=0.044$).
Nishio et al. (2017)	Volumetric MRI FDG-PET	67 PD patients	VOSP Facial Recognition subtest from VPTA battery Object decision subtest from BORB	Visuoperceptual		Three distinct brain–behavior correlation patterns were identified: (1) posterior cortical atrophy/hypometabolism associated with minor hallucinations/illusions and visuospatial impairment; (2) upper brainstem and thalamic atrophy/hypometabolism associated with psychosis/dysphoria and (3) frontal cortical atrophy/hypometabolism associated with non-visual cognition ($p<0.015$).

In alphabetical order; BORB: Birmingham Object Recognition Battery; DTI: Diffusion Tensor Imaging; FA: Fractional Anisotropy; fMRI: functional Magnetic Resonance Imaging; FDG-PET: 18F-fluorodeoxyglucose-positron emission tomography; FRT: Facial Recognition Test; EEG: Electroencephalography; GM: Gray matter; HC: Healthy control subjects; HVOT: Hooper Visual Organization Test; [^{123}-I] FP-CIT: N-isopropyl-p-[123I]iodoamphetamine; JLOT: Judgment of Line Orientation; MCI: Mild Cognitive Impairment; MRI: Magnetic Resonance Imaging; PCT: Pentagon Copying Test; PD: Parkinson's disease; PDD: Parkinson's disease dementia; PPMI: Parkinson's Progressive Markers Initiative; PD-NC: non-demented Parkinson's disease patients; rCMRglc: Regional cerebral metabolic rate of glucose; ROFC: Rey-Osterrieth Figure Copy; ROI: Region of Interest; rsFC: Seed-based resting-state functional connectivity; SBR: Striatal Dopamine Transporter Binding Ratios; SPECT: Single Photon Emission Computerized Tomography; SPM: Statistical Parametric Mapping; VBM: Voxel-Based Morphometry; VFDT: Visual Form Discrimination Test; VOSP: Visual Object and Space Perception battery, VPTA: Visual Perception Test for Agnosia; WMH: White Matter Hyperintensities.

CHAPTER 2.
HYPOTHESES AND OBJECTIVES

This thesis is contextualized in the study of cognitive impairment in Parkinson's disease, specifically, in the study of the neuroanatomical substrates of visual cognition impairment in PD and its evolution over time. Therefore, the general aim pursued is to describe the changes in visuospatial and visuoperceptual functions that occur in Parkinson's disease patients and their relationship with MRI parameters of neuroanatomical degeneration of cortical as well as white matter brain structures.

HYPOTHESES

(1) Visuospatial and visuoperceptual functions would be impaired in Parkinson's disease patients in comparison with matched healthy subjects.

(2) Parkinson's disease patients would show regional brain atrophy detectable by cortical thickness and white matter integrity measures.

(3) Visuospatial and visuoperceptual impairment would be reflecting the dissociable degeneration of dorsal and ventral streams involved in visual perception.

(4) The degeneration of cortical areas would exhibit a differential pattern in Parkinson's disease patients with and without mild cognitive impairment over time.

(5) The deterioration of visuospatial and visuoperceptual functions over time would be related to cortical thinning in Parkinson's disease patients.

OBJECTIVES

(1) To describe the impairment of visuospatial, visuoperceptual and visuoconstructive functions in Parkinson's disease, comparing the performance between patients and controls.

(2) To study the evolution over time of these functions using a longitudinal design.

(3) To explore the gray matter degeneration associated with Parkinson's disease through surface-based cortical thickness and global atrophy parameters, in cross-sectional as well as longitudinal designs.

(4) To analyze the white matter degeneration associated with Parkinson's disease through the assessment of white matter microstructure integrity.

(5) To study the neuroanatomical correlates of visuospatial, visuoperceptual and visuoconstructive impairment in Parkinson's disease, through surface-based cortical thickness and global atrophy parameters, in cross-sectional and longitudinal analyses, as well as white matter microstructure integrity.

CHAPTER 3.

METHODS

STUDY SAMPLES

The studies reported in this thesis were performed using a sample of healthy subjects and a sample of PD patients that were followed longitudinally as part of a project pursued at the *Laboratori de Neuroimatge* of *Facultat de Medicina* of the *Universitat de Barcelona*.

The cohort initially consisted of 121 PD patients consecutively recruited from an outpatient movement disorders clinic (*Unitat de Parkinson i Trastorns del Moviment*, *Servei de Neurologia*, *Hospital Clínic*, Barcelona) from September 2010. Fourty-one healthy subjects were recruited from the *Institut de l'Envelliment* (Barcelona) and were matched for age, sex and years of education to the patients group. This study was approved by the ethics committee of the *Universitat de Barcelona* (IRB00003099). All subjects agreed to participate voluntarily and written informed consent was obtained after full explanation of the procedures.

Inclusion criteria for participants consisted of fulfilling the diagnostic criteria for PD established by the UK PD Society Brain Bank (Daniel & Lees, 1993). Exclusion criteria consisted of: presence of dementia according to the Movement Disorder Society (MDS) criteria (Dubois et al., 2007), Hoehn and Yahr scale (H&Y) score >3, juvenile-onset PD, presence of psychiatric and/or neurologic comorbidity, low global IQ score estimated by the Vocabulary subtest of the WAIS, 3rd edition (scalar score ≤7 points), MMSE score ≤25, claustrophobia, imaging findings on MRI not compatible with PD other than mild white matter hyperintensities in the Fluid-Attenuated Inversion Recovery (FLAIR) sequence, and MRI artifacts. The final sample at the baseline assessment consisted of 92 PD patients and 36 controls. A follow-up assessment was pursued after approximately four years, with a sample of 20 healthy subjects and 44 PD patients.

Motor symptoms were assessed with the Unified Parkinson's Disease Rating Scale, motor section (UPDRS-III) (Fahn & Elton, 1987). All PD patients were taking antiparkinsonian drugs, consisting of different combinations of levodopa, COMT inhibitors, MAO inhibitors, dopamine agonists and amantadine. To standardize doses, the levodopa equivalent daily dose (Tomlinson et al., 2010) was calculated. All assessments were done while patients were under the effect of their usual medication (*on* state).

We divided the subjects into three groups: healthy subjects, PD patients without MCI, and PD patients with MCI. Expected z scores adjusted for age, sex and education for each test selected in the project and each subject were calculated based on a multiple regression analysis performed in the healthy subject group (Aarsland et al., 2009). The presence of MCI was established if the *z* score for a given test was at least 1.5 lower than the expected score in at least two tests in one cognitive domain, or in at least one test per domain in at least two domains.

NEUROPSYCHOLOGICAL ASSESSMENT

The screening test MMSE was used as a global measure of cognitive status. We used two additional grading measurements of the pentagon item: the scoring system of the Modified Mini-Mental State (3MS) (Teng & Chui, 1987), a modified MMSE grading system that provides a quantitative, wide-range scoring measurement system; and the simple scoring system used by Williams-Gray et al., (2007; 2009; 2013), modified from Ala et al. (2001).

According to the original scoring criteria, the pentagon item is considered correct if five angles are present in each pentagon and two are intersecting. Possible scores are 0 and 1. In the 3MS version, scores range from 0 to 10. Up to four points are given for each pentagon and up two points for the intersecting quadrilateral. Four points are given to each pentagon when it has five approximately equal sides, whereas three points are given if there are five sides that are unequal (>2:1). Lower scores are given when another enclosed figure is drawn (two points), or two or more lines (one point); less than two lines account for zero points. The simple scoring system used by Williams-Gray et al. (2007; 2009; 2013) grades two points to those pentagons that meet the original criteria, whereas one point is given for those that meet the 'relaxed criteria', in which there must be two figures that seem to be intersecting, at least one of them having five angles. Zero points are given to less accurate copies, *i.e.*, to those figures in which no pentagon exhibits five angles and/or there is no intersection present (see **Table 8**).

Table 8. Pentagon copying item scoring system used in the studies presented in this thesis

Original criteria from MMSE (Folstein et al., 1975)	Criteria according to 3MS (Teng & Chui, 1987)	Scoring system used by Williams-Gray et al. (2007; 2009; 2013)
To be acceptable, all 10 angles must be present and 2 must intersect Tremor and rotation are ignored	Up to 4 points for each pentagon and up to 2 points for the intersecting quadrilateral **PENTAGONS' SCORE**: 5 approximate equal sides (4 each) 5 but unequal (>2:1) sides (3 each) Other enclosed figure (2 each) 2 or more lines (1 each) Less than 2 lines (0 each) **INTERSECTION SCORE**: 4-cornered enclosure (2 points) Not 4-conrnered enclosure (1 point) No enclosure (0 points) Tremor or rotation are ignored	1) **ORIGINAL** – given 2 points: To be acceptable, all 10 angles must be present and 2 must intersect Tremor and rotation are ignored 2) **RELAXED** – given 1 point: To be acceptable, there must be two figures that seem to be intersecting. At least one of the figures must have five angles. Tremor, rotation, relative size and symmetry are ignored. Consider only lines that patient has drawn (ignore any lines from the original model that the patient may have included as part of the copy). If the patient has drawn more than one copy, grade the best copy. 0 points: less accurate copies.

In alphabetical order; 3MS: Modified Mini-Mental scoring system; MMSE: Mini-Mental State Examination.

We used a neuropsychological battery to assess cognitive functions usually impaired in PD following the MDS recommendations (Litvan et al., 2012). Attention and working memory were assessed with the Trail Making Test (TMT) (in seconds), part A (TMT A) and part B (TMT B), digit span forward and backward, and the Stroop color-word test; executive functions were evaluated with phonemic (words beginning with the letter 'p' in 1 minute) and semantic (names of animals in 1 minute) fluencies; language was assessed by the total number of correct responses in the short version of the Boston Naming Test (BNT), memory through total learning recall (sum of correct responses from trial I to trial V), and delayed recall (total recall after 20 min) through scores on Rey's Auditory Verbal Learning Test (RAVLT).

Visuospatial and visuoperceptual functions were assessed with Benton's JLOT, VFDT and FRT; we further included the SDMT as a measure representative of the visual cognition processes described above. Visuoconstructive abilities were addressed with the PCT and the clock copying test scored according to the CLOX2 system (Royall et al., 1999). These tests were further clustered to obtain a composite *z* score of each cognitive domain.

STRUCTURAL NEUROIMAGING TECHNIQUES

MRI ACQUISITION

Magnetic resonance images were acquired with a 3 Tesla scanner (MAGNETOM Trio, Siemens, Germany) from IDIBAPS located at the *Centre de Diagnòstic per la Imatge Clínic* (CDIC) of the *Hospital Clínic de Barcelona* using an 8-channel head oil.

High-resolution three-dimensional (3D) T1-weighted images acquired in the sagittal plane (repetition time [TR] = 2300 ms, echo time [TE] = 2.98 ms, inversion time [TI] = 900ms, 240 slices, field of view = 256mm; matrix size = 256 × 256; 1mm isotropic voxel and an axial FLAIR sequence (TR = 9000 ms, TE = 96 ms).

Two singleshot echo planar imaging sagittal diffusion-weighted imaging acquisitions with identical parameters (TR = 7700 ms, TE = 89ms, diffusion-encoding in 30 directions at b = 0 and 1000 s/mm2) but reversed phase-encoding direction (anterior-posterior and posterior-anterior) were obtained for each subject. These data sets were preprocessed with FSL (version 5.0.9; https://fsl.fmrib.ox.ac.uk/fsl/) tools (top-up and eddy) to correct for susceptibility-related geometric distortions, eddy current distortions, and head motion. The two preprocessed images were then averaged into a single 30-direction data set in order to increase the signal-to-noise ratio.

GRAY MATTER DEGENERATION

FreeSurfer software (version 5.1; available at http://surfer.nmr.harvard.edu) was used to obtain cortical thickness estimates as previously described (See **Chapter 1**). Comparisons between groups and regressions were assessed using a vertex-by-vertex general linear model. Different contrasts were carried out to assess differences between study groups. Regression models included whole-brain cortical thickness as an independent factor and cognitive scores as dependent factors. To avoid clusters appearing significant purely by chance (*i.e.*, false positives), Monte Carlo null-Z simulation with 10,000 iterations was applied to cortical thickness maps to provide clusterwise correction for multiple comparisons. Results were thresholded at a corrected p value of 0.05 (Hagler et al., 2006).

After processing each subject cross-sectionally, in order to perform the longitudinal analyses of the data, within-subject templates (Reuter & Fischl, 2011) and corresponding longitudinal files were created for each time point for each subject. Briefly, a template volume for each subject using information from all of their time points and an average image were created using robust, inverse, consistent registration (Reuter et al., 2010). All time points were constructed through unbiased mean images and later aligned. After

registration and creation of the templates, images from all time points were mapped to the template location and averaged, and processed with the default cross-sectional stream. The symmetrized percent change was used for longitudinal analyses of cortical thickness, and calculated as follows:

$$\text{Symmetrized percent change} = \frac{(\text{Thickness time point 2} - \text{Thickness time point 1})}{0.5 * (\text{Thickness time point 1} + \text{Thickness time point 2}) * \text{Interval between asessments}}$$

Volumetric global atrophy measures, namely, mean thickness, cortex volume, total gray matter volume and lateral ventricular system volume, were obtained automatically via whole brain segmentation procedures performed with FreeSurfer. Intracranial volume (ICV) was entered as a covariate of no interest in comparisons of global atrophy measures. Mean thickness for both hemispheres was calculated as follows:

$$\text{Mean cortical thickness} = \frac{(\text{Left hemisphere thickness} * \text{Surface area}) + (\text{Right hemisphere thickness} * \text{Surface area})}{(\text{Left hemisphere surface area} + \text{Right hemisphere surface area})}$$

WHITE MATTER DEGENERATION

Whole-brain voxelwise statistical analysis of FA was carried out using TBSS from FSL as previously described (See **Chapter 1**). Voxelwise general linear model was applied using permutation-based non-parametric testing (5,000 permutations) for FA analyses, correcting for multiple comparisons across space using familywise-error correction (FWE). Only clusters with FWE corrected $p<.05$ and extension >10 voxels were reported. The John Hopkins University (JHU) White-Matter Tractography atlas was used to obtain anatomical labels of structural regions within the significant clusters.

STATISTICAL ANALYSES

Statistical analyses of neuropsychological, demographic, clinical and MRI volumetric data variables were carried out using the statistical package SPSS-20 (2011; Armonk, NY: IBM Corp.). A longitudinal variable was created for each test used to pair neuropsychological data with the structural longitudinal measure of symmetrized percent change, and was used in all statistical and structural analyses of the study.

CHAPTER 4.

RESULTS

The studies carried out in this thesis are the following:

STUDY 1 **Structural MRI correlates of the MMSE and pentagon copying test in Parkinson's disease**

Garcia-Diaz AI, Segura B, Baggio HC, Marti MJ, Valldeoriola F, Compta Y, Vendrell P, Bargallo N, Tolosa E, Junque C. Structural MRI correlates of the MMSE and pentagon copying test in Parkinson's disease. *Parkinsonism Relat Disord* 2014; 12:1405-10. IF: 4.484 Q1 Clinical Neurology

STUDY 2 **Structural brain correlations of visuospatial and visuoperceptual tests in Parkinson's disease**

Garcia-Diaz AI, Segura B, Baggio HC, Marti MJ, Valldeoriola F, Compta Y, Bargallo N, Uribe C, Campabadal A, Abos A, Junque C. Structural Brain Correlations of Visuospatial and Visuoperceptual Tests in Parkinson's Disease. *J Int Neuropsychol Soc* 2018; 24:33-44. IF: 2.181 Q2 Psychology

STUDY 3 **Cortical thinning correlates of changes in visuospatial and visuoperceptual performance in Parkinson's disease: A 4-year follow-up**

Garcia-Diaz AI, Segura B, Baggio HC, Uribe C, Campabadal A, Abos A, Marti MJ, Valldeoriola F, Compta Y, Bargallo N, Junque C. Cortical thinning correlates of changes in visuospatial and visuoperceptual performance in Parkinson's disease: A 4-year follow-up. *Parkinsonism Relat Disord*, 2018; 46:62-8. IF: 4.484 Q1 Clinical Neurology

STUDY 1

Structural MRI correlates of the MMSE and pentagon copying test in Parkinson's disease

Garcia-Diaz AI, Segura B, Baggio HC, Marti MJ, Valldeoriola F, Compta Y, Vendrell P, Bargallo N, Tolosa E, Junque C.

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Structural MRI correlates of the MMSE and pentagon copying test in Parkinson's disease

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ABSTRACT

Background: Cognitive impairment in Parkinson's disease (PD) is common and recent studies have focused on addressing the most suitable screening tool for its assessment. MMSE is commonly used in clinical practice and longitudinal studies found a relationship between the MMSE pentagon copying item and progression to dementia, but its neuroanatomical correlates have been poorly investigated. The aim of this study is to investigate the MRI structural correlates of the global MMSE and the pentagon item scores in PD patients in the absence of dementia.
Methods: We selected a sample of 92 PD patients and 36 controls. MMSE was used as a global measure of cognitive status, and the pentagon copying test as a measure of visuospatial performance. FreeSurfer software was used to assess intergroup differences in cortical thickness (CTh) and global atrophy measures, as well as their relationship with cognitive performance.
Results: Compared to controls, patients showed significant differences in measures of global atrophy, which correlated with performance on MMSE and the pentagon item. Regional differences in CTh were seen between PD patients and controls bilaterally in the temporo-parietal-occipital region. Patients with impaired performance compared with those of normal performance also showed CTh reductions in these regions.
Conclusion: Our results suggest MMSE and the pentagon item reflect brain changes which at a regional level involve mainly posterior regions. Correlates of the pentagon item were seen in the same regions where PD patients exhibited significant thinning, and involved more areas and bigger cluster sizes than the correlates of MMSE global scores.

1. Introduction

Cognitive impairment is a frequent [1] and important non-motor symptom in Parkinson's disease (PD) [2,3], with a significant impact on quality of life [4]. Over time, approximately 80% of patients become demented [5]. The Mini-Mental State Examination (MMSE) is the cognitive screening tool most frequently used to assess global cognitive status in degenerative illnesses [6]. Rate of change of MMSE scores in PD ranged from 1.4 to 6.8 points per year [1]. However, the MMSE is not considered as a suitable screening tool to assess cognitive dysfunctions in PD, because it does not fully address executive functions [6], which is one of the domains usually impaired in this disease [2]. Therefore, other screening tests have been proposed as alternatives, such as the Montreal Cognitive Assessment (MoCA) [7].

Although the MMSE is not commonly used as a single screening tool in PD, scores below the cut-off point of 26 are used as a criterion in the identification of dementia in PD [8]. Despite the broad criticism associated with the MMSE, the pentagon item raised interest in clinical settings because of a population-based longitudinal study where it was found to be predictive of dementia in PD [1,9,10], suggesting that the dementing process is heralded by posterior cortical based cognitive deficits [1,9,10].

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Magnetic resonance imaging (MRI) volumetric research has also shown that PD patients' MMSE scores significantly correlate with measures of global atrophy such as ventricular volume [11]. The correlates with regional gray matter reductions were observed in temporo-parietal regions in voxel-based morphometry studies [12] and also involved frontal regions using cortical thickness (CTh) analyses [13]. A recent study using an ROI-based analysis in non-demented PD patients has shown that the pentagon copying test significantly correlates with volumetric decreases in cortical regions, such as right supplementary motor area, left rostral middle frontal cortex, pars triangularis and left cuneus [14]. However, to our knowledge, there are no previous studies specifically assessing the correlations between pentagon copying test and whole-brain CTh.

Therefore, the aims of this study were 1) to investigate the MRI structural correlates of the MMSE global scores and the pentagon item and 2) to identify whether impairment in the pentagon item reflects brain atrophy in non-demented PD patients.

2. Methods

2.1. Participants

The cohort of this study consisted of 121 PD patients consecutively recruited from an outpatient movement disorders clinic (Parkinson's disease and Movement Disorders Unit, Service of Neurology, Hospital Clínic, Barcelona, Spain) from September 2010 to March 2012. Forty-one healthy subjects were recruited from the *Institut de l'Envelliment* (Barcelona, Spain) and were matched for age, sex and years of education to their patients peers. This study was approved by the ethics committee of the University of Barcelona; all subjects agreed to participate voluntarily and written informed consent was obtained after full explanation of the procedures.

Inclusion criteria for participants consisted of fulfilling the diagnostic criteria for PD established by the UK PD Society Brain Bank [15]. Exclusion criteria consisted of: presence of dementia according to the Movement Disorders Society criteria [2,8], Hoehn and Yahr (H&Y) scale score >3, juvenile-onset PD, presence of psychiatric and/or neurologic comorbidity, low global IQ score estimated by the Vocabulary subtest of the Wechsler Adult Intelligence Scale, 3rd edition (Scalar score $\leq$7 points), MMSE score $\leq$25, claustrophobia, imaging findings on MRI not compatible with PD and MRI artifacts. Levodopa equivalent daily dose (LEDD) was calculated as suggested by Tomlinson et al. [16].

Ninety-two PD patients and 36 healthy volunteers were finally selected. Twelve patients and eight controls were excluded as they fulfilled criteria for dementia or other neurological disease, six PD patients for psychiatric comorbidity, one PD patient who scored higher than 3 on the H&Y scale, one PD patient who presented with juvenile-onset PD, three PD patients and one control who had low global IQ scores, two PD patients for claustrophobia, two PD patients and two controls were excluded because of missing tests used in this study and two controls and two PD patients due to MRI artefacts (demographic and clinical data of patients and healthy controls included in study sample are summarized in Table 1). Excluded patients did not differ from final PD participants in terms of demographics and clinical variables.

2.2. Cognitive status assessment

The screening test MMSE was used as a global measure of cognitive status. We used two additional grading measurements of the pentagon item: the scoring system of the Modified Mini-Mental State (3MS), a modified MMSE grading system that provides a quantitative, wide-range scoring measurement system; and the simple scoring system (SSS) used by Williams–Gray et al., because of its demonstrated value in predicting conversion to dementia in PD patients [1,9,10].

According to the original scoring criteria [17], the pentagon item is considered correct if 5 angles are present in each pentagon and 2 are intersecting. Possible scores are 0 and 1. In the 3MS version, scores range from 0 to 10. Up to 4 points are given for each pentagon and up 2 points for the intersecting quadrilateral. Four points are given to each pentagon when it has 5 approximately equal sides, whereas 3 points account for 5 sides but unequal (>2:1). Lower scores are given when another enclosed figure is drawn (2 points), or 2 or more lines (1 point); less than 2 lines account for 0 points. The simple scoring system used by Williams–Gray et al. [1,9,10] grades 2 points to those pentagons that meet the original criteria, whereas 1 point is given for those that meet the "relaxed criteria", in which there must be two figures that seem to be intersecting, at least one of them having 5 angles. Zero points are given to less accurate copies, *i.e.*, to those figures in which no pentagon exhibits 5 angles and/or there is no intersection present (see Fig. S1 for drawing and grading scores examples). For correlation analyses purposes we scored the test as 1, 2 and 3.

Table 1
Demographic and clinical data of the participants.

	Patients (n = 92)	Controls (n = 36)	t[a], χ[b]	p value
Age	64 ± 11.1	63.4 ± 10.5	0.287[a]	0.775
Sex (male/female)	37/55	19/17	0.521[b]	0.300
Education, years	10.6 ± 5.4	11.4 ± 4.3	0.750[a]	0.454
Age at onset	56 ± 12.2			
Evolution, years	8.4 ± 5.9			
H&Y	1: 21			
	1.5: 5			
	2: 47			
	2.5: 9			
	3: 10			
UPDRS-III	16.4 ± 9.3			
LEDD	803.7 ± 494.2			

UPDRS-III: Unified Parkinson's Disease Rating Scale-III; H&Y: Hoehn & Yahr; LEDD: Levodopa Equivalent Daily Dose. Values are mean ± Standard Deviation (SD).
[a] Student t test statistics.
[b] χ^2 statistics.

2.3. MRI acquisition

Magnetic resonance images were acquired with a 3T scanner (MAGNETOM Trio, Siemens, Germany). The scanning protocol included high-resolution 3-dimensional T1-weighted images acquired in the sagittal plane (TR = 2300 ms, TE = 2.98 ms, TI 900 ms, 240 slices, FOV = 256 mm; matrix size = 256 × 256; 1 mm isotropic voxel) and an axial FLAIR sequence (TR = 9000 ms, TE = 96 ms).

2.4. Cortical thickness analysis

FreeSurfer software (version 5.1; available at http://surfer.nmr.harvard.edu) was used to obtain CTh and whole brain measurements of brain atrophy. The cortical surface 3D model of CTh is created using intensity and continuity information, as described in detail by authors [18]. Independent steps are performed in the initial preprocessing of images for each subject: removal of non-brain tissue, automated Talairach transformation, intensity normalization [19], tessellation of the gray matter/white matter boundary, automated topology correction [20] and accurate surface deformation to optimally place the gray matter/white matter and gray matter/cerebrospinal fluid (CSF) boundaries [18]. The resulting representation of CTh is calculated as the distance between white and gray matter surfaces at each vertex of the reconstructed cortical mantle [19]. In our study, results for each subject were carefully visually inspected to ensure accuracy of registration, skull stripping, segmentation, and cortical surface reconstruction. Maps were smoothed using a circularly symmetric Gaussian kernel across the surface with a full width at half maximum (FWHM) of 15 mm.

Comparisons between groups and CTh correlations were assessed using vertex-by-vertex general linear model, including CTh as a dependent factor and cognitive scores as independent factors. In the PD patient group, the vertex-by-vertex general linear model was used to assess the relationship between cognitive scores and CTh. Positive and negative associations between each test were assessed using Qdec. In order to avoid clusters appearing significant purely by chance (i.e., false positives), Monte Carlo Null-Z Simulation with 10000 iterations was applied to CTh maps to provide clusterwise correction for multiple comparisons and results were thresholded at a corrected p value of 0.05 [21].

2.5. Global atrophy measures

Mean thickness for both hemispheres was calculated ((left hemisphere thickness * left hemisphere surface area) + (right hemisphere thickness * right hemisphere surface area))/(left hemisphere surface area + right hemisphere surface area)). Total gray matter and lateral ventricular volumes were obtained automatically via whole brain segmentation procedures performed with *FreeSurfer* software [22].

2.6. Statistical analyses

Statistical analyses of neuropsychological, demographic, clinical and MRI volumetric data variables were carried out using the statistical package SPSS-20 (2011; Armonk, NY: IBM Corp.). Student t tests were used to assess group differences between patients and healthy subjects in clinical and neuropsychological continuous variables (*i.e.*, MMSE and 3MS scoring system) and Chi square test was applied to assess group differences in categorical variables (*i.e.*, sex and group).

Group differences were assessed with Student t test statistics for mean thickness, and with ANCOVA including intracranial volume (ICV) as a covariate in the model for volumetric atrophy measures. We addressed the reliability of the scoring systems used with Cronbach's α.

Correlations between mean thickness and continuous variables were assessed with Pearson's r statistics and with and Spearman's ρ for categorical variables. Correlations between cognitive scores and volumetric variables were analyzed using partial Pearson's r, accounting for ICV.

Table 2
Differences between PD patients and healthy subjects in global atrophy measures and correlations between cognitive status and pentagon item and atrophy measures.

	Group differences						Correlations in PD patients					
	PD patients		Controls		*t*/F	*p*	MMSE		3MS		WG-A	
	Mean	SD	Mean	SD			*r*	*p*	*r*	*p*	ρ	*p*
Mean CTh*	2.4	0.1	2.5	0.1	2.610[a]	0.010	0.251	0.016	0.224	0.033	0.958	<0.0001
Cortical GMV**	601.55	64.2	611.62	54.3	2.027	0.157	0.189	0.075	0.279	0.008	0.185	0.082
LVV**	25.2	14.3	20.0	8.4	4.219	0.042	0.222	0.035	0.179	0.063	0.179	0.063

CTh: cortical thickness; LVV: lateral ventricular volume; GMV: gray matter volume; SD: standard deviation; MMSE: mini-mental state examination; 3MS: modified mini-mental state; WG: simple scoring system used by Williams–Gray et al. (2007–2013), modified from Ala et al. (2001). *t*: Student *t* test statistics; F: ANCOVA (ICV used as covariate); r: Pearson's *r*; ρ: Spearman's rho; a: Student *t* test statistics; *mm; **cm^3.

3. Results

Imaging analyses revealed that PD patients compared to controls had significant increases in lateral ventricle volume as well as reduction in mean CTh, but did not differ in global cortical gray matter volume (see Table 2).

Regional CTh maps showed that PD patients had thickness reductions involving lateral and medial temporo-parieto-occipital cortices bilaterally (see Fig. 1A and Supplementary Table 1 for details of the location and size of significant clusters).

MMSE scores in PD patients (29.05 ± 1.1) were significantly lower than those of the control group (29.67 ± 0.5) ($t = 4.429$, $P < 0.001$). Pentagon-copying scores according to 3MS system also differed significantly ($t = 2.136$, $P = 0.035$) between patients (9.3 ± 1.1) and healthy subjects (9.6 ± 0.5). The scoring systems we used obtained a reliability of 0.762.

3.1. Global atrophy measures in PD patients

MMSE correlated with mean CTh and lateral ventricular volume in PD patients. Mean cortical thickness and cortical gray matter volume showed significant correlations with 3MS scores. Correlations between global atrophy measures and the simple scoring system were significant for mean cortical thickness but not for lateral ventricular volume (see Supplementary Table 3).

3.2. Cortical thickness in PD patients

Patients with abnormal scores on the pentagon item according to the original criteria ($n = 15$), compared with those of normal scores ($n = 77$), had significant thickness reductions in the left superior temporal gyrus and precuneus bilaterally, as well as in the right precentral and postcentral gyri, superior parietal region and posterior cingulate cortex (see Fig. 1B and Supplementary Table 2). PD patients' MMSE scores significantly correlated with CTh in left occipital and posterior cingulate regions (see Fig. 2A and Supplementary Table 3).

Pentagon item scores according to 3MS showed significant correlations with CTh involving bilateral posterior areas, such as parietal and temporal bilateral cortex, but spreading also to anterior regions, including paracentral and medial frontal areas (see Fig. 2B and Supplementary Table 3).

The simple scoring system showed significant correlations with bilateral parietotemporal regions, including the left precuneus and right supramarginal, superior parietal, fusiform and posterior cingulate regions (see Fig. 2C and Supplementary Table 3). There were no significant correlations between structural measures and pentagon scores in control subjects. Scores in the latter group exhibited a ceiling effect.

4. Discussion

In our study, non-demented PD patients showed mean CTh decreases and ventricular enlargement. In addition, we observed cortical thinning in bilateral posterior parieto-temporal regions. Both MMSE and pentagon item scores correlated with measures of global atrophy and with regional CTh but with different extent and patterns.

MMSE scores correlated with measures of global cerebral atrophy, namely, mean cortical thickness and ventricular enlargement.

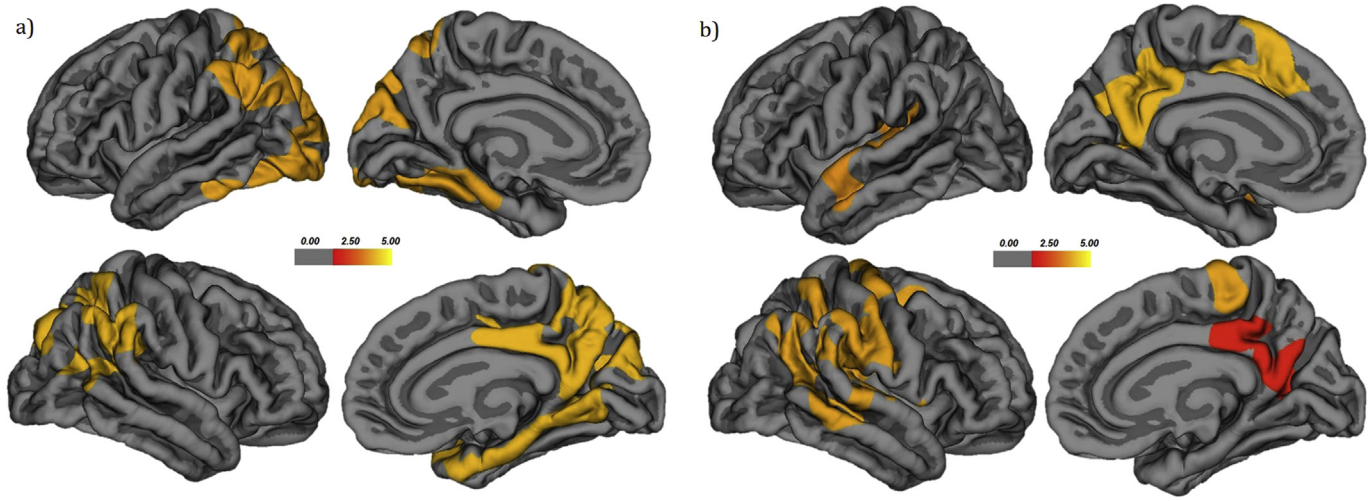

Fig. 1. CTh differences between A) patients and healthy controls (Healthy controls > PD patients) and B) patients with correct or incorrect pentagon according to the original grading criteria used in the MMSE. Monte-Carlo Null Z Simulations at corrected $p < 0.05$. Color bar indicates the level of statistical significance.

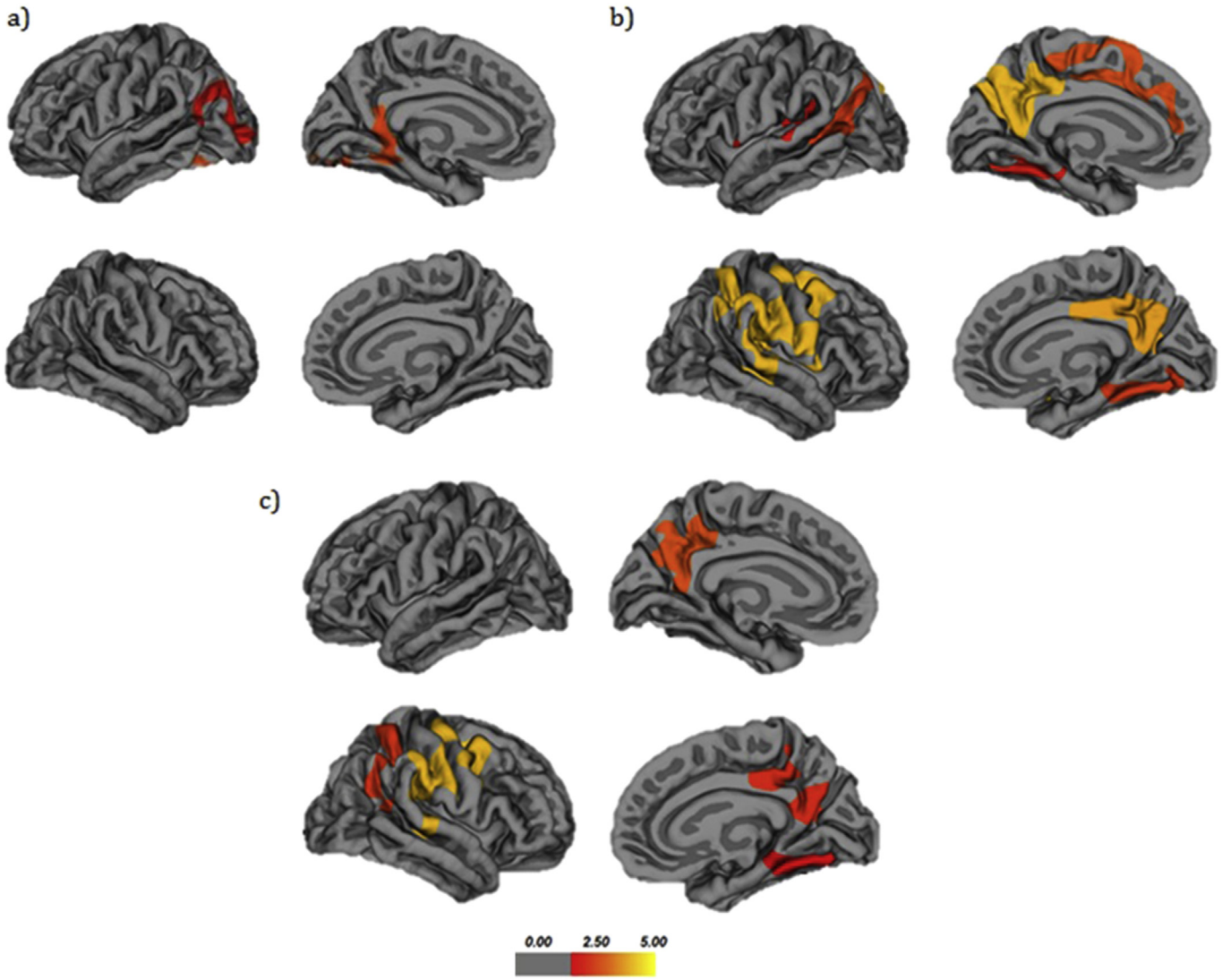

Fig. 2. CTh areas showing significant correlations in PD patients with A) MMSE, B) Pentagon item scored according to 3MS system and C) Pentagon item scored according to the simple scoring system. Monte-Carlo Null Z Simulations at $p < 0.05$. Color bar indicates the level of statistical significance.

Our results about correlations with ventricular enlargement are in agreement with previous studies that tested such relationship with samples that included cognitively impaired patients [11]. As expected, the pattern of regional correlations that we have observed was less extended than that previously reported in samples which included demented patients [13]. We only obtained significant correlations in regions limited to the left hemisphere. The left hemisphere predominance could be due to the fact that MMSE scores include several verbal items [23]. MMSE decreases in PD are probably indicating evolution to dementia. In this sense, Compta et al. [24] reported that Braak tau stages along with the parietal, cingulate, entorhinal and total cortical amyloid-B scores negatively correlated with MMSE scores ante-mortem, whereas such correlation was not found for the Lewy body score or Braak Parkinson's disease stage. Thus, there is some neuropathological evidence suggesting that MMSE decreases in PD are related to Alzheimer's-type pathology.

The scores of the pentagon copying test are also reflecting the degree of diffuse cerebral atrophy, but have a further pattern of CTh correlations involving bilateral posterior temporo-parietal regions. These results are in agreement with previous studies performed with non-demented PD patients that focused on the correlates of visuospatial and visuoperceptual functions using more complex tests, such as Benton's Visual Form Discrimination and Facial Recognition Test [25]. In demented PD, it has been reported that visuospatial functions assessed by clock copying correlated with left precuneus and lingual gyrus thickness [26]. The only previous study that reported the anatomical correlates of the pentagon item test using ROI-based analyses also found correlations in medial bilateral posterior areas but also in the left anterior regions [14]; differences in both studies may be due to the MRI analyses and the procedures used to quantify the performance of the pentagon test.

We investigated the possible differential patterns of correlations in relation to the cognitive measurements. Interestingly, the pentagon's pattern of correlations observed was very similar to CTh reductions obtained in the comparison between PD patients and controls. Previous research assessing the relevance of cognitive deficits heralded by posterior cortical changes has evidenced that these deficits act as predictors of a dementing process in PD [1,9,10], in which dementia has been said to be largely due to an age-dependent and tau-dependent posterior cortically based process,

rather than a dopaminergic dysfunction in frontostriatal networks [10]. In sum, our results indicate that the MMSE can reflect the global atrophy present in medium to long duration PD, but has poor power to detect these changes in bilateral temporo-parietal regions. In contrast, the specific regional posterior correlates of the pentagon copying test correspond to the differences in CTh between patients and controls. Our study has some limitations. There is currently no generally accepted standard for in vivo cortical thickness measurements, because in vivo reference values of cortical thickness or systematic comparison of post mortem data with an in vivo estimation are not available [27]. However, studies regarding which method best monitors cerebral involution in PD have exhibited that surface-based methods, especially CTh, are sensitive to PD-related neural degeneration [28].

Another limitation of our study is the lack of previous information about the reliability of the scoring systems used. However, Ala et al. [29], applying the original scoring system of the pentagon's item, reported high inter-raters reliability (Cronbach's α: 0.98). Finally, our results cannot be generalized to all the pre-dementia stages of PD, because our sample of patients had a relatively long duration of disease, thus they are not representative of early stages.

In summary, our study suggests that both MMSE and the pentagon item reflect global brain degeneration that at a regional level is mainly located in the posterior regions, but the pentagon copying test correlated with more areas and with bigger cluster sizes. Our data supports the utility of the pentagon's item as a tool in patient care to monitor evolution of cognitive status.

There are previous studies that have independently addressed the value of the pentagon item [1,9,10] and cortical thinning [30] as markers for cognitive decline or dementia. However, to our knowledge there are no previous studies analyzing in the same sample the predictive power of cortical thickness and pentagon's item to predict future dementia in individual patients. Future longitudinal studies are needed to address these questions.

Disclosure

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Author roles

1. Research project: A. Conception, B. Organization, C. Execution;
2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique;
3. Manuscript: A. Writing of the first draft, B. Review and Critique

Garcia-Diaz: 1C, 2A, 2B, 3A; Segura: 1B, 1C, 2A, 2B, 3B; Baggio: 1B, 1C, 2B, 2C, 3B; Marti: 1B, 1C, 2C, 3B; Valldeoriola: 1B, 1C, 2C, 3B; Compta: 1B, 1C, 2C, 3B; Vendrell: 1B, 1C, 2C, 3B; Bargallo: 1B, 1C, 2C, 3B; Tolosa: 1B, 1C, 2C, 3B; Junque: 1A, 1B, 1C, 2A, 2B, 2C, 3B;

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.parkreldis.2014.10.014.

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SUPPLEMENTARY MATERIAL

Table S1. Significant clusters showing CTh differences between PD patients and healthy subjects

	Anatomical region	Cluster size	Talairach coordenates of the maxima			Z value	Clusterwise probability
			X	Y	Z		
Left	Supramarginal	8006.70	-48.6	-48.8	37.3	-4.682	0.0001
	Fusiform	3503.77	-26.6	-51.0	-10.0	-3.536	0.0001
Right	Superior parietal	112522.39	26.8	-56.9	43.1	-4.420	0.0001

Results were corrected using family wise error correction with Monte Carlo Null-Z Simulation and thresholded at p=.05

Table S2. Significant clusters showing differences between patients with acceptable or incorrect pentagon (Acceptable >Incorrect) according to the original grading criteria

Anatomical region	Cluster size (mm^2)	Talairach coordenates of the maxima			Z value	Clusterwise probability
		X	Y	Z		
L Superior temporal	3236.85	-46.4	-31.4	5.5	-4.057	.0001
L Precuneus	4220.40	-13.9	-39.7	33.5	-3.369	.0001
R Postcentral	8607.50	26.8	-25.5	48.0	-3.493	.0001
R Superior parietal	2792.71	30.9	-39.0	40.6	-3.271	.0003
R Posterior cingulate	2165.76	5.7	-29.4	34.9	-3.001	.005
R Precentral	1515.57	47.9	5.6	27.5	-2.363	.0464

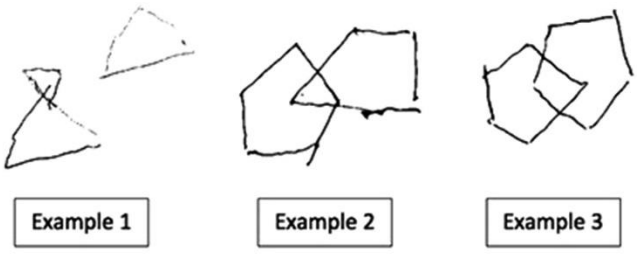
L: Left; R: Right

Table S3. Significant clusters showing correlations between cognitive scores and CTh

	Anatomical region	Cluster size (mm^2)	Talairach coordenates of the maxima			Z value	Cluster-wise probability
			X	Y	Z		
MMSE	*L Lateral occipital*	1646.00	-27.7	-83.0	4.4	2.965	.0237
	L Isthmus cingulate	2194.28	9.6	-49.9	8.5	2.365	.0034
3MS	*L Inferior parietal*	2133.70	-47.7	-61.0	12.7	4.649	.0056

	L Precuneus	3544.58	-9.3	-55.2	28.9	3.839	.0001
	L Superior temporal	1565.52	-48.2	-31.5	6.4	3.824	.0344
	L Fusiform	1700.77	-32.8	-44.6	-10.0	3.626	.0208
	L Paracentral	2292.86	-13.0	-11.9	42.2	2.810	.0208
	R Superior temporal	11309.12	50.0	-33.5	14.9	5.318	.0001
	R Fusiform	2097.70	29.0	-66.0	-3.2	3.538	.006
	R Posterior cingulate	2152.39	5.0	-30.0	38.1	3.473	.0002
Williams-Gray *et al*.	*L Precuneus*	2322.96	-7.8	-43.0	45.0	2.759	.0028
	R Supramarginal	6373.23	56.1	-23.4	35.9	3.750	.0001
	R Superior parietal	2001.60	35.4	-44.2	57.6	3.600	.0076
	R Fusiform	1502.36	29.1	-66.4	-4.1	2.589	.0477
	R Posterior cingulate	1888.19	5.5	-29.9	36.0	2.304	.0116

MMSE: Mini-Mental State Examination; 3MS: Modified Mini-Mental State; L: Left; R: Right



- Example 1:
  - Original grading criteria: Incorrect
  - 3MS: 4 points
  - Simple scoring system by Williams-Gray *et al*.: 0 points
- Example 2:
  - Original grading criteria: Incorrect
  - 3MS: 7 points
  - Simple scoring system by Williams-Gray *et al*.: 1 point
- Example 3:
  - Original grading criteria: Correct
  - 3MS: 10 points
  - Simple scoring system by Williams-Gray *et al*.: 2 points

Fig. S1. Drawing and grading scores examples of patients' pentagon copying test

STUDY 2

Structural brain correlations of visuospatial and visuoperceptual tests in Parkinson's disease

Garcia-Diaz AI, Segura B, Baggio HC, Marti MJ, Valldeoriola F, Compta Y, Bargallo N, Uribe C, Campabadal A, Abos A, Junque C.

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Structural Brain Correlations of Visuospatial and Visuoperceptual Tests in Parkinson's Disease

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Abstract

Background: Diagnosis of mild cognitive impairment in Parkinson's disease (PD) is relevant because it is a marker for evolution to dementia. However, the selection of suitable tests to evaluate separate cognitive domains in mild cognitive impairment related to PD remains an open question. The current work aims to investigate the neuroanatomical correlates of several visuospatial/visuoperceptual tests using the same sample and a multimodal MRI approach. **Methods:** The study included 36 PD patients and 20 healthy subjects matched for age, sex, and education. The visuospatial/visuoperceptual tests selected were: Pentagon Copying Test (PCT), Judgment of Line Orientation Test (JLOT), Visual Form Discrimination Test (VFDT), Facial Recognition Test (FRT), Symbol Digit Modalities Test (SMDT), and clock copying task (CLOX2). FreeSurfer was used to assess cortical thickness, and tract-based spatial statistics was used for fractional anisotropy analysis. **Results:** Lower performance in the PCT, JLOT, and SDMT was associated with extensive cortical thickness reductions in lateral parietal and temporal regions. VFDT and CLOX2 did not show this common pattern and correlated with more limited medial occipito-temporal and occipito-parietal regions. Performance in all visuospatial/visuoperceptual tests correlated with fractional anisotropy in the corpus callosum. **Conclusions:** Our findings show that JLOT, SDMT, and PCT, in addition to differentiating patients from controls, are suitable visuospatial/visuoperceptual tests to reflect cortical thinning in lateral temporo-parietal regions in PD patients. We did not observe the dissociation between dorsal and ventral streams that was expected according to the neuropsychological classification of visuospatial and visuoperceptual tests. (*JINS*, 2018, *24*, 33–44)

Keywords: Degenerative disorders, Cortical thickness, Diffusion tensor imaging, Mild cognitive impairment, Neuropsychological testing

INTRODUCTION

Cognitive decline is a common non-motor manifestation of Parkinson's disease (PD) that may start early in the course of the disease (Aarsland, Brønnick, Larsen, Tysnes, & Alves, 2009), and progresses to mild cognitive impairment (MCI) and eventually to dementia in the majority of patients (Aarsland, Andersen, Larsen, Lolk, & Kragh-Sørensen, 2003; Hely Morris, Reid, & Trafficante, 2005).

MCI in PD (PD-MCI) has been defined by the Movement Disorder Society Task Force (MDSTF) as a cognitive decline that is more severe than expected for age but with preserved functional activities (Litvan et al., 2012). According to the MDSTF guidelines, the diagnosis of PD-MCI is mainly supported by performance in five cognitive domains: attention and working memory; executive; language; memory; and visuospatial and visuoperceptual (VS/VP) functions. Among these suggested cognitive domains, visuospatial deficits have recently received particular attention because they cannot be explained by the dopaminergic imbalances seen in PD.

It is well known that several deficits in visual functions are present in different stages of PD from prodromal to dementia.

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In the initial stages of the degenerative process, changes in visual acuity, contrast sensitivity, and color perception have been described. An accurate assessment of these visual functions could be useful in differentiating parkinsonian symptoms (Armstrong, 2015; Weil et al., 2016). In later stages, visuospatial deficits emerge and have been associated with incident dementia in longitudinal population-based studies (Williams-Gray, Foltynie, Brayne, Robbins, & Barker, 2007; Williams-Gray et al., 2009, 2013).

Several neuropsychological tests have been suggested by the MDSTF to assess the cognitive domains stated above. This proposal assumes that the tests included in a given domain are equivalent, and, therefore, share common but not necessarily identical brain substrates.

Previous studies have addressed this issue in regards to VS/VP functions, looking for the structural correlates of several neuropsychological tests including the Facial Recognition Test (FRT), the Visual Form Discrimination Test (VFDT) (Pereira et al., 2009; Segura et al., 2014), the Judgment of Line Orientation Test (JLOT) (Filoteo, Reed, Litvan, & Harrington, 2014; Segura et al., 2014), the Pentagon Copying Test (PCT) from the Mini-Mental State Examination (MMSE) (Filoteo et al., 2014; Garcia-Diaz et al., 2014), and the clock drawing and copying tests (Pagonabarraga et al., 2013). The results obtained are discrepant probably due to the different MRI approaches, including voxel-based (Pereira et al., 2009), volumetric (Filoteo et al., 2014), and cortical thickness measures (Garcia-Diaz et al., 2014; Segura et al., 2014), as well as to heterogeneity in the PD samples used. In this context, there emerges the necessity to study the specific neuroanatomical correlates of VS/VP functions in the same sample, using common neuropsychological tests. For these purposes, we used cortical thickness as well as white matter fractional anisotropy to study five tasks classically defined as VS/VP tests (VFDT, FRT, JLOT, PCT, and the clock copying task), as well as Symbol Digit Modalities Test (SDMT), previously defined as a processing speed and attention test, but highly dependent on VS/VP processing (Lezak, Howieson, Bigler, & Tranel, 2012). A study on functional neuroimaging correlates using the oral version of the SDMT, such as that used in our study, found significant increased activation predominantly in posterior areas, specifically in the bilateral occipital cortex, cuneus, and inferior parietal regions (Forn et al., 2009).

METHODS

Participants

The cohort of this study was recruited from an outpatient movement disorders clinic (Parkinson's Disease and Movement Disorders Unit, Service of Neurology, Hospital Clínic, Barcelona, Spain), and healthy subjects were recruited from the *Institut de l'Envelliment* (Barcelona, Spain). The current sample consisted of 20 healthy controls (HC) and 36 PD patients assessed between 2013 and 2015.

Inclusion criteria for patients consisted on fulfilling the diagnostic criteria for PD established by the UK PD Society Brain Bank (Daniel & Lees, 1993). Exclusion criteria for all subjects were as follows: presence of dementia according to the Movement Disorders Society criteria (Dubois et al., 2007) and clinical assessment performed by a neurologist (M.J.M., F.V., Y.C.), Hoehn and Yahr scale score >3, young-onset PD, presence of psychiatric and/or neurologic comorbidity, low global IQ score estimated by the Vocabulary subtest of the Wechsler Adult Intelligence Scale (WAIS) 3rd edition (scalar score ≤7 points), MMSE score ≤25, claustrophobia, imaging findings on MRI not compatible with PD other than mild white matter hyperintensities in the FLAIR sequence, and MRI artifacts.

Motor symptoms were assessed with the Unified Parkinson's Disease Rating Scale, motor section (UPDRS-III) (Fahn & Elton, 1987). All PD patients were taking antiparkinsonian drugs, consisting of different combinations of L-DOPA, cathecol-O-methyltransferase inhibitors, monoamine oxidase inhibitors, dopamine agonists, and amantadine. To standardize doses, the L-DOPA equivalent daily dose (Tomlinson et al., 2010) was calculated. All assessments were done while patients were under the effect of their usual medication (*on* state).

In line with the MDSTF recommendations (Litvan et al., 2012), we assessed five cognitive domains. Attention and working memory were assessed with the Trail Making Test (TMT) (in seconds), part A (TMT A) and part B (TMT B); Digit Span Forward and Backward; the Stroop Color-Word Test and SDMT. Executive functions were evaluated with phonemic (words beginning with the letter "p" in 1 min) and semantic (animals in 1 min) fluencies. Language was assessed by the total number of correct responses in the short version of the Boston Naming Test. Memory through total learning recall (sum of correct responses from trial I to trial V), and delayed recall (total recall after 20 min) through scores on Rey's Auditory Verbal Learning Test (RAVLT). VS/VP functions were assessed with JLOT and VFDT (see Segura et al., 2014 for the detailed protocol). This battery is recommended by the MDSTF to evaluate cognitive functions in PD and is able to detect MCI in PD (level I or level II criteria for PD-MCI, except for language, for which a single measure was used) (Litvan et al., 2012).

We divided the subjects into three groups: HC, PD patients without MCI (PD-NC), and PD patients with MCI (PD-MCI). Expected *Z* scores adjusted for age, sex, and education for each test and each subject were calculated based on a multiple regression analysis performed in the HC group (Aarsland et al., 2009). As in previous studies (Baggio et al., 2014; Segura et al., 2014), the presence of MCI was established if the *Z* score for a given test was at least 1.5 lower than the expected score in at least two tests in one domain, or in at least one test per domain in at least two domains.

Written informed consent was obtained from all study participants after full explanation of the procedures. The study was approved by the institutional Ethics Committee from the University of Barcelona (IRB00003099).

VS/VP Assessment

The following tests were used based on their potential involvement on VS/VP functions as described in previous studies: PCT from the MMSE scored according to the Modified Mini-Mental State criteria (3MS), as described in Garcia-Diaz et al., 2014; JLOT; VFDT; FRT; the clock copying task scored according to the CLOX2 criteria (Royall, Cordes, & Polk, 1998); and SDMT (oral version) (Forn et al., 2009; Lezak et al., 2012).

MRI Acquisition

Magnetic resonance images were acquired with a 3 Tesla scanner (MAGNETOM Trio, Siemens, Germany). The scanning protocol included high-resolution three-dimensional (3D) T1-weighted images acquired in the sagittal plane (repetition time [TR] = 2300 ms, echo time [TE] = 2.98 ms, inversion time [TI] = 900 ms, 240 slices, field of view = 256 mm; matrix size = 256 × 256; 1mm isotropic voxel and an axial FLAIR sequence (TR = 9000 ms, TE = 96 ms). Two single-shot echo planar imaging sagittal diffusion-weighted imaging acquisitions with identical parameters (TR = 7700 ms, TE = 89 ms, diffusion-encoding in 30 directions at b = 0 and 1000 s/mm^2) but reversed phase-encoding direction (anterior–posterior and posterior–anterior) were obtained for each subject. These data sets were preprocessed with FSL (version 5.0.9; https://fsl.fmrib.ox.ac.uk/fsl/) tools (*topup* and *eddy*) to correct for susceptibility-related geometric distortions, eddy current distortions, and head motion. The two preprocessed images were then averaged into a single 30-direction data set, so as to increase the signal-to-noise ratio.

Cortical Thickness Analysis

FreeSurfer software (version 5.1; available at http://surfer.nmr.harvard.edu) was used to obtain cortical thickness as previously described (Garcia-Diaz et al., 2014; Segura et al., 2014;). Comparisons between groups and regressions were assessed using a vertex-by-vertex general linear model. Different contrasts were carried out to assess differences between all study subgroups (HC *vs*. all PD patients; HC *vs*. PD-NC; HC *vs*. PD-MCI; and PD-NC *vs*. PD-MCI). Regression models included whole-brain cortical thickness as an independent factor and cognitive scores as dependent factors. To avoid clusters appearing significant purely by chance (i.e., false positives), Monte Carlo null-Z simulation with 10,000 iterations was applied to cortical thickness maps to provide clusterwise correction for multiple comparisons. Results were thresholded at a corrected p value of 0.05 (Hagler, Saygin, & Sereno, 2006).

Tract-Based Spatial Statistics Analysis

Whole-brain voxelwise statistical analysis of fractional anisotropy (FA) was carried out using tract-based spatial statistics (TBSS) from FSL (Smith et al., 2006). FA images were initially created by fitting a tensor model to the averaged motion-corrected diffusion data using DTIFIT from FDT, and then brain-extracted using BET (Smith, 2002). Mean FA images were created and thinned to obtain mean FA skeletons which represent the centers of all tracts common to the group. Each subject's aligned FA data were projected onto this skeleton and the resulting data fed into voxelwise cross-subject statistics. Voxelwise general linear model was applied using permutation-based non-parametric testing (5000 permutations) for FA analyses, correcting for multiple comparisons across space using familywise-error correction (FWE). Only clusters with FWE-corrected $p < .05$ and extension >10 voxels are reported. The JHU White-Matter Tractography Atlas was used to obtain anatomical labels of structural regions within the significant clusters.

Statistical Analyses

Statistical analyses of demographic, neuropsychological, and structural data variables were carried out using the statistical package SPSS-20 (2011; Armonk, NY: IBM Corp.). Student's t tests were used to assess group differences between PD-NC and PD-MCI. One-factor analyses of variance were used to address differences among HC, PD-NC, and PD-MCI, and Bonferroni correction was used to perform *post hoc* tests. Pearson's chi-squared tests were applied to assess contingencies between qualitative variables. To report the effect sizes of group differences, we used Cohen's d (small $d = 0.2$, medium $d = 0.5$ and large $d = 0.8$).

RESULTS

Neuropsychological Performance

Demographic and clinical data of the participants are summarized in Table 1. No significant differences were found between study groups in age, sex, education, or clinical variables associated with PD.

Neuropsychological results are summarized in Table 2. We found significant differences in VS/VP measures between HC, PD-NC, and PD-MCI. The effect size for these differences was medium to large when the PD-MCI group was compared with their healthy peers and with PD patients without MCI (see Table 2). We did not find differences between groups in VFDT or CLOX2 performance. PCT, SDMT, and FRT showed moderate to large effect sizes when comparing PD-MCI and HC, whereas JLOT and PCT showed moderate effect sizes in the comparison between PD-MCI and PD-NC. SDMT *post hoc* testing for the comparison between PD-NC and PD-MCI did not survive Bonferroni correction (corrected $p = .058$; see Table 2).

Cortical Thickness Comparison Between Groups

Imaging analyses revealed significant cortical thickness reductions in PD patients compared with healthy subjects in bilateral occipital and posterior parietal, left medial temporo-occipital, and in left frontal regions. The contrast between healthy subjects and PD-NC patients did not show significant differences. The PD-MCI group evidenced a widespread bilateral posterior–anterior pattern of cortical degeneration in

Table 1. Demographic and clinical data of the participants

	HC ($n = 20$)	PD ($n = 36$)	t^a, χ^b	PD-NC ($n = 26$)	PD-MCI ($n = 10$)	t^a, χ^b, F^c
Age	69.15 ± 7.94	64.37 ± 9.97	1.855[a]	63.58 ± 9.88	66.30 ± 10.99	1.973[c]
Sex (male/female)	11/9	28/8	2.782[b]	20/6	8/3	3.188[b]
Education (years)	11.35 ± 4.43	12.39 ± 5.83	0.701[a]	13.23 ± 5.32	11.30 ± 6.91	0.880[c]
Age at onset		54.06 ± 11.11		54.18 ± 10.41	53.80 ± 13.11	0.089[a]
Disease duration		10.342 ± 6.01		9.42 ± 3.99	11.90 ± 8.66	0.870[a]
UDPRS-III		17.53 ± 10.83		17.60 ± 11.35	17.00 ± 8.49	0.071[a]
H&Y		2.07 ± 0.73		1.92 ± 0.52	3.00 ± 1.41	−1.072[a]
LEDD		767.63 ± 461.53		743.15 ± 416.84	904.70 ± 576.21	0.935[a]

Note. Disease duration: duration of motor symptoms, in years; H&Y: Hoehn & Yahr; LEDD: Levodopa equivalent daily dose. Values are: mean ± standard deviation.
[a]Student's *t* test statistics.
[b]Pearson's chi-square statistics.
[c]One-factor analyses of variance. No significant differences were found between study groups in age, sex, education, or clinical variables associated with PD.

comparison with the other study groups. The clusters of cortical thinning in PD-MCI were more extended when compared with healthy subjects (see Figure 1; Table 3).

DTI Comparison Between Groups

DTI analysis revealed significant differences between study groups in FA (see Figure 2), located in the right posterior corpus callosum (coordinates of cluster maximum: X = 12, Y = −31, Z = 25; $p = .017$).

Correlations Between VS/VP Tests and Cortical Thickness in PD Patients

VS/VP measures showed significant cortical thickness correlations in PD patients. The PCT correlated significantly with cortical thickness in the left lateral occipital cortex and lingual gyrus, and in bilateral temporo-parietal areas involving medial regions, such as fusiform and parahippocampal gyri, left isthmus of cingulate gyrus, and precuneus, as well as in bilateral dorsal regions, specifically superior temporal and supramarginal gyri. In addition, the PCT also correlated with thickness in anterior regions including right caudal middle frontal gyrus, bilateral precentral regions, and left anterior cingulate and superior frontal gyri.

The JLOT showed significant correlates with thickness in left lateral occipital cortex and lingual gyrus, with bilateral medial regions including left fusiform and parahippocampal gyri, bilateral precuneus, and isthmus of cingulate gyrus, as well as anterior cingulate thickness. In addition, JLOT correlated with dorsal regions including bilateral superior temporal gyrus, bilateral supramarginal gyrus, and right insula.

The SDMT correlated significantly with bilateral medial and dorsal temporo-parietal regions, including bilateral fusiform and parahippocampal gyri, bilateral precuneus, superior

Table 2. Group comparison of VS/VP performance between HC, PD-NC, and PD-MCI

	Mean ± *SD*				Effect size (Cohen's *d*)		
	HC ($n = 20$)	PD-NC ($n = 26$)	PD-MCI ($n = 10$)	F (p)	HC vs PD-NC	PD-NC vs PD-MCI	HC vs PD-MCI
PCT	9.55 ± 0.69	9.65 ± 0.80	8.00 ± 3.27	4.689 (.013)		0.693*	0.656*
JLOT	24.95 ± 3.83	25.15 ± 4.05	20.30 ± 8.88	3.459 (.036)		0.703*	
VFDT	29.50 ± 2.69	29.54 ± 2.61	27.20 ± 5.33	2.085 (.134)			
FRT	23.40 ± 1.79	22.31 ± 2.24	20.67 ± 3.32	4.472 (.016)			1.024*
SDMT	46.90 ± 10.26	45.23 ± 12.80	32.60 ± 22.04	3.879 (.029)		0.701**	0.832*
CLOX2	14.45 ± 1.10	14.08 ± 1.02	13.70 ± 1.42	1.569 (.218)			

Note. PCT: Pentagon Copying Test scored according to the Modified Mini-Mental State criteria; CLOX2: Clock copying task scored according to CLOX2 criteria (Royall et al., 1998). F corresponds to one-factor analysis of variance.
*Significant *post-hoc* analyses ($p < .05$).
**SDMT post-hoc analysis $p = 0.058$ between PD-NC and PD-MCI.

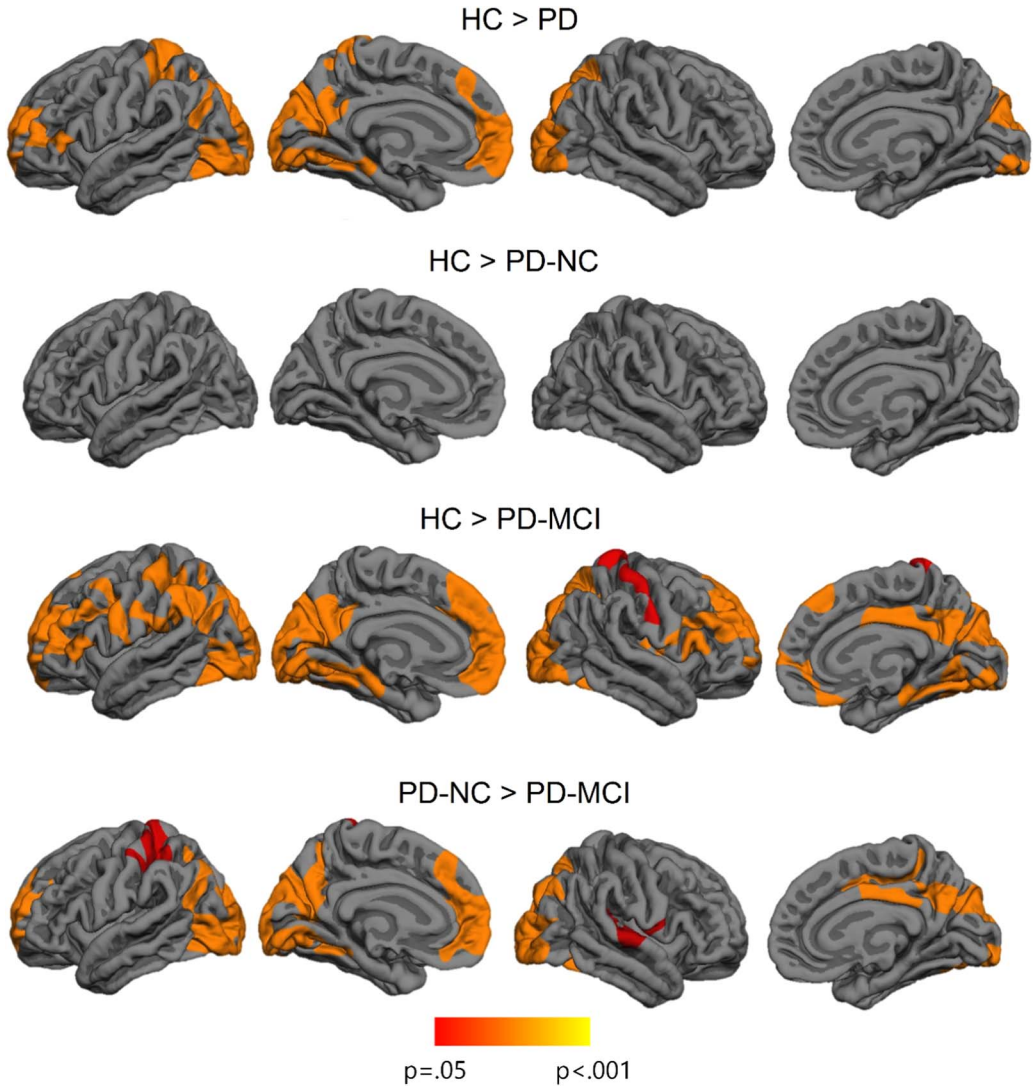

Fig. 1. Vertex-wise cortical thickness differences between study groups. The scale bar shows *p*-values.

temporal gyri, and right supramarginal and postcentral regions. Moreover, this task correlated with an anterior medial region corresponding to the left anterior cingulate. SDMT did not correlate with cortical thickness in occipital regions except for the left lingual gyrus.

VFDT scores significantly correlated with an isolated cluster that extended to the left lingual and fusiform gyrus, whereas CLOX2 test correlated with bilateral precuneus and isthmus of cingulate gyrus.

Finally, there were no significant correlations between cortical thickness and FRT performance (see Figure 3; Table 4). Considering the specific role of fusiform regions in facial recognition (Haxby et al., 2001), we performed complementary intergroup and correlation analyses between FRT scores and mean fusiform gyrus cortical thickness (as defined by the Desikan-Killiany atlas) (Desikan et al., 2006). Significant intergroup effects were observed for both left fusiform ($F = 4.064$; $p = .023$) and right fusiform ($F = 3.700$; $p = .031$), and *post hoc* analyses showed that thickness was significantly reduced in PD-MCI compared with HC (left fusiform $p = .023$; right fusiform $p = .043$). Results of correlation analyses, however, were not statistically significant (left fusiform: $r = 0.244$, $p = .157$; right fusiform: $r = 0.240$, $p = .164$).

In healthy subjects, SDMT and PCT showed a significant one-tailed cluster correlation with the left fusiform gyrus ($p < .001$), and PCT correlated significantly with right inferior parietal ($p = .0001$), lingual ($p = .032$), and inferior temporal regions ($p = .033$).

Correlations Between VS/VP Tests and DTI Measures in PD Patients

TBSS correlation analyses revealed significant results in PD patients. All the tests studied showed significant correlations between their scores and FA values. Significant correlation in all tests included the corpus callosum, bilateral forceps minor, uncinate fasciculus, inferior fronto-occipital fasciculus, forceps major, and inferior longitudinal fasciculus. Qualitatively, among all tests, SDMT

Table 3. Significant clusters showing cortical thickness differences between HC, PD-NC, and PD-MCI.

Cluster anatomical annotation	Cluster size (mm^2)	Talairach coordinates of the maxima			Z value	Clusterwise p value
		X	Y	Z		
HC > PD patients						
Left cuneus	14727.79	−20.1	−66.5	50.3	6.995	.0001
Left superior frontal	4682.70	−12.1	51.0	7.7	4.153	.0001
Right superior parietal	6752.04	−20.1	−55.1	50.3	3.839	.0001
HC > PD-MCI						
Left cuneus	29222.76	−13.0	−74.0	17.8	5.917	.0001
Left precuneus	1604.28	−15.1	−45.7	66.6	2.736	.0211
Right lateral occipital	12847.31	34.3	−90.5	−11.2	4.170	.0001
Right postcentral	2436.08	48.3	−16.8	49.2	3.429	.0018
Right superior frontal	7319.17	25.3	10.6	45.0	3.277	.0001
PD-NC > PD-MCI						
Left cuneus	13406.63	−20.1	−66.5	12.9	7.654	.0001
Left superior frontal	4552.57	−12.1	51.0	7.7	4.662	.0001
Left superior frontal	1475.63	−10.7	2.1	44.7	3.849	.0348
Left superior parietal	2278.55	−20.3	−40.9	60.7	3.813	.0023
Right lateral occipital	9933.19	26.8	−97.2	−10.5	4.119	.0001
Right postcentral	2221.82	53.3	−9.4	12.3	2.620	.0039

Note. Results were corrected using FWE correction with Monte Carlo null-Z simulation and thresholded at $p \leq 0.05$.

showed the most extensive correlations (see Figure 4; Table 5). In healthy subjects, there were no significant correlations between neuropsychological measures and FA values.

DISCUSSION

In this study, we investigated the brain correlates of six VS/VP tests used in the diagnosis of PD-MCI in the same population, using measures from two MRI modalities: cortical thickness and FA. We evidenced specific neuroanatomical correlates of these tasks in the same sample.

Not all neuropsychological tests achieved statistical significance in the group comparisons. We found significant differences among groups for all tests except for the VFDT and CLOX2. Specifically, we observed significant differences between PD-MCI and HC in PCT, FRT and SDMT performance, whereas MCI and non-MCI patients showed differences in PCT and JLOT scores. Effect sizes were medium for all tests except for the FRT, which was large in the comparison between HC and PD-MCI.

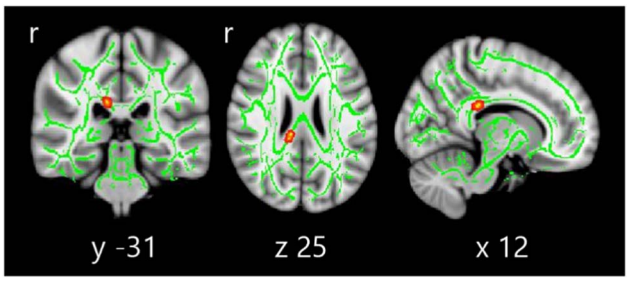

Fig. 2. Tract-based spatial statistics differences between HC, PD-NC, and PD-MCI. Voxelwise group differences are marked in warm colors. Results are overlaid on the white matter skeleton (green) and displayed over the sagittal, coronal, and axial sections of the MNI standard brain at $p \leq .05$ FWE-corrected. *Post hoc* analyses were significant in all group comparisons ($p < .001$).

The MDSTF guidelines on PD-MCI recommends using Benton's JLOT, Hooper Visual Organization, and Royall's CLOX2 to assess visuospatial functions, especially the first two tasks because of their low reliance on motor ability. We suggest that the FRT also merits consideration for the neuropsychological assessment of specific visuoperceptual functions in PD patients. Levin et al. (1991) administered six visuospatial tests to a sample of 183 patients and concluded that, in the early phases of PD, demented and non-demented patients exhibit a marked decline in FRT performance, while the impairment in JLOT performance was observed only when dementia patients were considered. Moreover, FRT has been shown to be impaired in PD with hallucinations (Ramirez-Ruiz et al., 2007).

Surprisingly, performance in the CLOX2 was similar in all groups, whereas other brief screening tests such as the PCT demonstrated significant differences between PD-MCI and the other groups, with medium effect sizes. The CLOX2 test has been reported as a useful tool in the diagnosis of dementia, but it has shown low sensitivity to detect subjects with MCI (Forti, Olivelli, Rietti, Maltoni, & Ravaglia, 2010). Regarding the VFD, a significant effect of dementia diagnosis and time of evolution has been reported (Levin et al., 1991). In our study, the exclusion of patients with dementia might, therefore, explain the lack of significant group differences in these tests.

The CLOX2 seems to be less sensitive to PD visuospatial impairment than PCT, perhaps because the former represents

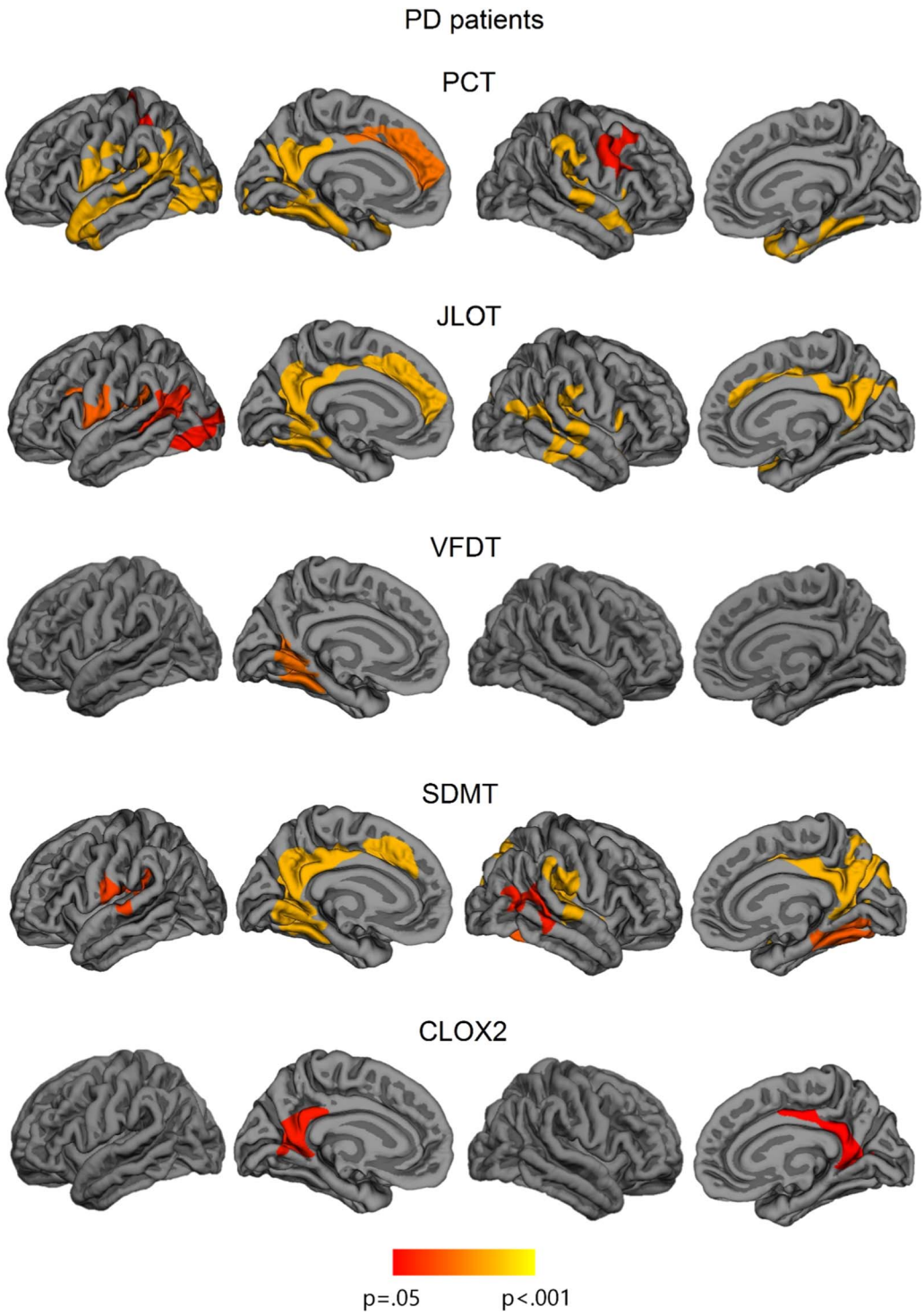

Fig. 3. Vertex-wise cortical thickness correlations with neuropsychological measures in all sample of PD patients. The scale bar shows *p*-values. PCT: Pentagon Copying Test scored according to the Modified Mini-Mental State criteria; CLOX2: Clock copying task scored according to CLOX2 criteria (Royall et al., 1998).

a more abstract and complex task. In addition, CLOX2 is influenced by semantic memory and executive functions (Cosentino, Jefferson, Chute, Kaplan, & Libon, 2004), and this association could help to compensate the VS/VP impairment in a non-demented sample. In addition, relevant longitudinal population-based studies have stated the usefulness of PCT as an incident dementia marker, probably reflecting atrophy in posterior cortical regions (Williams-Gray et al., 2007, 2009, 2013).

The patterns of cerebral correlations obtained for the VS/VP tests were also different. Lower performance in the PCT, JLOT, and SDMT were associated with cortical thickness reductions in parietal and temporal regions. The VFDT and the CLOX2, on the other hand, did not show this common pattern of

Table 4. Significant clusters showing cortical thickness correlations with VS/VP measures in the whole sample of PD patients

	Cluster anatomical annotation	Cluster size (mm^2)	Talairach coordinates of the maxima			Z value	Clusterwise p value
			X	Y	Z		
PCT	Left precuneus	17110.87	−19.2	−56.9	17.5	4.981	0.0001
	Left superior frontal	2575.12	−12.0	44.3	5.9	3.515	0.0009
	Left superior parietal	1601.59	−33.4	−40.0	45.4	3.115	0.0308
	Right parahippocampal	6518.98	35.5	−35.3	−9.3	6.452	0.0001
	Right caudal middle frontal	1795.26	40.4	2.0	34.1	3.129	0.0239
JLOT	Left precuneus	7435.32	−18.8	−56.3	19.2	5.698	0.0001
	Left supramarginal	1977.87	−53.4	−51.4	20.8	4.182	0.0134
	Left precentral	2601.05	−47.7	4.0	13.2	3.283	0.0018
	Left lateral occipital	1770.66	−43.6	−72.4	−3.8	3.175	0.0240
	Right isthmus cingulate	3518.33	4.8	−46.8	24.4	4.262	0.0001
	Right insula	6355.79	40.1	−23.8	0.5	3.869	0.0001
VFDT	Left precuneus	2768.33	−17.7	−56.6	14.9	4.087	0.0009
SDMT	Left precuneus	7252.65	−17.1	−55.3	18.6	5.803	0.0001
	Left superior temporal	2248.37	−40.0	35.8	10.4	2.857	0.0042
	Right isthmus cingulate	4888.68	5.1	−47.2	23.8	4.828	0.0001
	Right superior temporal	4119.17	44.9	−20.9	1.2	4.223	0.0001
	Right lingual	2490.76	27.3	−44.5	−3.2	4.202	0.0022
	Right banks of superior temporal sulcus	1889.24	45.8	−39.2	12.8	2.991	0.0178
CLOX2	Left precuneus	1865.08	−26.6	−61.4	7.5	2.829	0.0176
	Right isthmus cingulate	1621.63	21.9	−50.4	7.4	3.628	0.04310

Note. PCT: Pentagon Copying Test scored according to the Modified Mini-Mental State criteria; CLOX2: Clock copying task scored according to the CLOX2 criteria (Royall et al., 1998). Results were corrected using FWE correction with Monte Carlo null-Z simulation and thresholded at $P \leq 0.05$.

correlations, and only showed spatially limited correlations with medial regions. The results obtained in the current work for the JLOT and the VFDT were similar to those obtained in our previous study assessing a larger sample (Segura et al., 2014). In that study, we studied the cortical correlates of different neuropsychological tests but we did not focus on the VS/VP domain using a neuroimaging multimodal approach. There we observed that the VFDT only correlated with cortical thickness in the right superior temporal and lingual gyri, whereas performance in the JLOT correlated with thickness in the bilateral fusiform gyri and the precuneus, as well as in the right superior temporal gyrus (Segura et al., 2014).

These results are partially in agreement with those obtained by Filoteo et al. (2014), using volumetric brain measures of specific regions of interest (ROIs), who reported significant correlations between JLOT performance and bilateral superior temporal and right lateral occipital cortices. Using voxel-based morphometry, Pereira et al. (2009) reported a positive association between VFDT performance and gray matter volumes in the fusiform gyrus, parahippocampus, middle occipital gyrus, and inferior frontal gyrus, as well as between FRT and ventral occipito-temporal cortex volume. In the present study, however, we did not find significant neuroanatomical correlates for the FRT.

Using ROI analyses, we found that PD patients and controls differed in the mean cortical thickness of the fusiform gyri and in the performance of FRT, but we did not observe significant correlations between both variables. In fact, this method is not sensitive enough to delimitate the fusiform face area (FFA) and precludes the identification of fine brain-behavior correlates. In normal subjects, the role of FFA regions in face perception was well detected by classical early fMRI studies (Haxby et al., 2001), and also by recent MRI techniques using retinotopic mapping analyses (Sangupta et al., 2016). The use of a functional MRI paradigm could have identified this specific ROI (Sengupta et al., 2016) and facilitated the correlational study between cortical atrophy and FRT performance.

The results of voxel-based morphometry and cortical thickness studies are not directly comparable because these measures are not equivalent (Pereira et al., 2012). Furthermore, the threshold for statistical significance also differed between these studies. Some previously reported results should be interpreted with caution as they were not corrected for multiple comparisons (Filoteo et al., 2014).

The PCT and the CLOX2 are both brief screening tasks that assess visuospatial functions. However, the neuroanatomical correlates of these tests are not similar. Worse performance in the PCT is related to thinning in extended medial and lateral parietal and temporal cortices, whereas performance in the CLOX2 only showed specific correlations with posterior cingulate and precuneus thickness. Pagonabarraga et al. (2013) also reported that clock-copying abilities correlated with cortical thickness in the precuneus. Different neuroanatomical correlates of these screening tools might reflect heterogeneity in the underlying deficits, or differences in sensitivity of the tests. In this sense, the PCT might more strongly reflect the impact of neurodegeneration on the visual processing system.

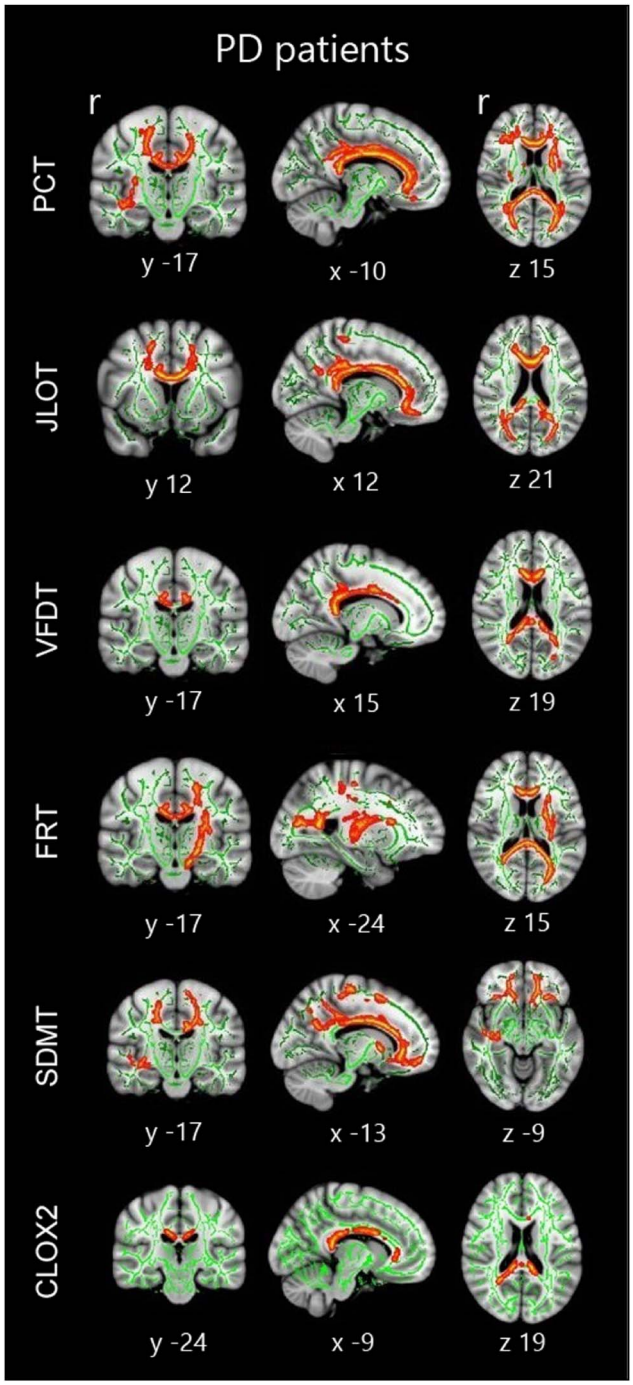

Fig. 4. Tract-based spatial statistics correlations in the whole sample of PD patients. Significant group correlations are marked in warm colors. Results are overlaid on the white matter skeleton (green) and displayed over the sagittal, coronal and axial sections of the MNI standard brain at $p < .05$ FWE-corrected. Image shows significant clusters >10 voxels. PCT: Pentagon Copying Test scored according to the Modified Mini-Mental State criteria; CLOX2: Clock copying task scored according to the CLOX2 criteria (Royall et al., 1998).

According to the classical model of complex visual processing (Haxby et al., 1991; Mishkin, Ungerleider, & Macko, 1983), the dorsal pathway, also called the "where" stream, is an occipito-parietal network involved in the processing of spatial information. In turn, the ventral pathway, also known as the "what" stream, is an occipito-temporal network involved in processing individual items such as faces, objects, colors, or words. According to this dissociation, we would expect to observe dorsal parietal correlates for the JLOT, CLOX2, and PCT; medial occipito-temporal correlates for the FRT; and mixed patterns for both VFDT and SDMT. However, the actual picture appears to be more complex, as there are some evidences of a trifurcation of the dorsal stream beyond the parietal cortex: the *parieto-medial temporal*, *parieto-premotor,* and the *parieto-prefrontal* pathways (Kravitz, Saleem, Baker, & Mishkin, 2011). It has been suggested that these three pathways interact with the ventral stream, and that a major point of convergence and perceptual integration is within the medial temporal lobe (see Kravitz et al., 2011 for a review).

Moreover, a recent meta-analysis on the functional MRI studies of normal subjects performing tasks specific to the "what" and "where" streams has identified specific regions according to stimulus type, and also several conjunctive regions in medial and lateral temporal cortices (Deng et al., 2016). The lack of retinotopic mapping in our sample hinders the interpretations about higher visual processing regions related to the visual tests. However, within this context, we could speculate that our results agree with the relevance of this area of interactions between pathways, given that we observed cortical thickness reductions in the medial temporal lobe related to all the studied tests, including the tasks putatively considered as visuospatial. In addition, several authors have shown reciprocal connections not only between structures such as the basal ganglia, subthalamic nucleus, and frontal cortex, but also the parietal cortex, a factor seemingly important when studying visuoperceptual functions.

White matter alterations can also play a role in cognitive impairment in PD (Hattori et al., 2012). The group comparison performed in our study showed that PD-NC and PD-MCI subjects differed in several cortical regions, but FA decreases were scarce. The modest results could be explained because DTI analyses were performed using the widely-adopted method TBSS; this method is more restrictive than whole brain voxel-wise group comparisons and projects the data onto an alignment-invariant tract representation. This approach, which initially improves the sensitivity, objectivity, and interpretability of analysis of multi-subject diffusion imaging studies, could be less sensitive to detect voxels further from tract centers or regions centered between two skeleton points (Zalesky, 2011; see Bach et al., 2014; Schwarz et al., 2014). Moreover, white matter hyperintensities and other FA-reducing abnormalities, common in elderly subjects, are also particularly problematic (Jones & Cercignani, 2010).

On the other hand, correlation analyses showed that the loss of corpus callosum integrity is related to lower cognitive performance in all VS/VP tests assessed. In addition, we also observed significant correlations in regions of the inferior fronto-occipital fasciculus. These associative fibers connect relevant regions involved in both VS/VP functions.

Table 5. Significant clusters showing tract-based spatial statistics correlations with neuropsychological measures in PD patients in MNI standard anatomical coordinates

	Voxels	*p* value at maximum	x, y, z coordinates	Hemisphere	Anatomical labels
PCT	28469	0.015	5, 24, 13	Right	Genu of corpus callosum/forceps minor
JLOT	36106	0.012	25, 34,4	Right	Inferior fronto-occipital fasciculus, uncinate fasciculus and anterior thalamic radiation
VFDT	3839	0.040	17, –41, 7	Right	Splenium of corpus callosum/forceps major
FRT	8140	0.022	12, –42, 17	Right	Splenium of corpus callosum/forceps major
	2442	0.041	–20, –4,10	Left	Posterior limb of internal capsule
SDMT	67610	0.003	9, 32, –19	Right	Forceps minor/uncinated fasciculus
CLOX2	1524	0.045	–14, –41, 8	Left	Forceps major
	93	0.049	–10, 28, –3	Left	Forceps minor

Note. PCT: Pentagon Copying Test scored according to the Modified Mini-Mental State criteria; CLOX2: Clock copying task scored according to the CLOX2 criteria (Royall et al., 1998). Table shows significant clusters >10 voxels at $p < .05$ FWE-corrected.

In this study, we focused on the neuroanatomical correlates of VS/VP functions in PD. The relatively regional degeneration of cortical structures is a factor partially explaining cognitive impairment. However, there are other functional contributors to this impairment. The dopaminergic dysfunctions affecting the basal-ganglia-thalamic-cortical dysfunctions could be in part responsible for VS/VP deficits in PD, especially considering that there are reciprocal connections not only between structures such as the basal ganglia, subthalamic nucleus and the frontal cortex, but also the parietal cortex (Seger, 2013).

On the other hand, recent evidence has revealed the contribution of functional connectivity impairment to VS/VP impairment in PD. Graph-theoretical analyses of functional networks obtained with resting-state functional MRI showed that network modularity partially explains VS/VP deficits (Baggio et al., 2014). Moreover, increased connectivity between the default mode network and both medial and lateral occipito-parietal regions in PD-MCI subjects have been shown in association with worse VS/VP performance (Baggio et al., 2015). Finally, given that our study focused on non-demented PD patients, the occurrence of a functional compensation phenomenon should be taken into consideration. This phenomenon could justify weaker structural correlates observed for several tests.

One possible limitation of our study is that, despite the inclusion of a variety of tests in the main cognitive domains defined in recent guidelines (attention and working memory, executive functions, memory, and visuospatial and visuoperceptual functions) (Litvan et al., 2012), we did not include the same number of tests in each cognitive domain, and language was assessed only with the Boston Naming Test. This may have biased the pattern of cognitive deficits present in the PD-MCI group.

Another limitation of this study was the fact that lower-level visual functions were not formally assessed. PD patients may have visual deficits that range from loss of visual acuity to complex visuoperceptual deficits. The primary visual deficits are associated with retinal dysfunctions, while the visuoperceptual deficits could be explained by the progressive degeneration of posterior brain regions (Weil et al., 2016). In our study, visual acuity was evaluated by clinical interview and review of the clinical record data of patients. The systematic assessment of visual acuity would allow us to study the contribution of this variable in the performance of complex VS/VP tests.

In summary, we found that impaired performance in the JLOT, SDMT, and PCT is related to a common pattern of cortical thinning, as well as microstructural white matter abnormalities. VFDT, CLOX2, and FRT showed less consistent and more limited results. Our findings suggest that JLOT, SDMT, and PCT are suitable tests to assess a common cognitive domain, sustained by a neuroanatomical correlate coincident with the VS/VP streams based on structural neuroimaging techniques. Further studies using longitudinal designs might be useful to shed light on the neural substrate of changes in VS/VP performance and its impact on the neurodegenerative process in PD.

The established anatomical pattern of correlation between cortical thickness measures and performance in VS/VP tests, as well as the involvement of white matter fasciculi connecting cortical regions, suggests the utility of these tests as tools to identify cognitive decline in the VS/VP domain, as well as the underlying brain network degeneration in PD.

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STUDY 3

Cortical thinning correlates of changes in visuospatial and visuoperceptual performance in Parkinson's disease: A 4-year follow-up

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Cortical thinning correlates of changes in visuospatial and visuoperceptual performance in Parkinson's disease: A 4-year follow-up

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ABSTRACT

Background: Growing evidence highlights the relevance of posterior cortically-based cognitive deficits in Parkinson's disease (PD) as possible biomarkers of the evolution to dementia. Cross-sectional correlational studies have established a relationship between the degree of atrophy in posterior brain regions and visuospatial and visuoperceptual (VS/VP) impairment. The aim of this study is to address the progressive cortical thinning correlates of VS/VP performance in PD.

Methods: Forty-four PD patients and 20 matched healthy subjects were included in this study and followed for 4 years. Tests used to assess VS/VP functions included were: Benton's Judgement of Line Orientation (JLOT), Facial Recognition (FRT), and Visual Form Discrimination (VFDT) Tests; Symbol Digit Modalities Test (SDMT); and the Pentagon Copying Test (PCT). Structural magnetic resonance imaging data and FreeSurfer were used to evaluate cortical thinning evolution.

Results: PD patients with normal cognition (PD-NC) and PD patients with mild cognitive impairment (PD-MCI) differed significantly in the progression of cortical thinning in posterior regions. In PD-MCI patients, the change in VS/VP functions assessed by PCT, JLOT, FRT, and SMDT correlated with the symmetrized percent change of cortical thinning of occipital, parietal, and temporal regions. In PD-NC patients, we also observed a correlation between changes in FRT and thinning in parieto-occipital regions.

Conclusion: In this study, we establish the neuroanatomical substrate of progressive changes in VS/VP performance in PD patients with and without MCI. In agreement with cross-sectional data, VS/VP changes over time are related to cortical thinning in posterior regions.

1. Introduction

Parkinson's disease (PD) is a heterogeneous neurodegenerative disorder that manifests with a wide range of nonmotor symptoms. Recent initiatives have aimed to depict the features and evolution of cognitive decline in PD [1–4].

Impairment in specific cognitive domains has been associated with a differential risk of cognitive decline. While executive functions are widely recognized to be impaired in PD even at early disease stages [1,5,6], interest in the role of posterior cortically-based functions as biomarkers of the cognitive evolution to dementia (PDD) has increased [1,7,8].

Several cross-sectional structural MRI correlational studies have established a relationship between the degeneration of posterior

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brain regions and cognitive impairment [9–12]. Specifically, previous studies by our group showed that visuospatial and visuoperceptual (VS/VP) tests are suitable to reflect cortical thinning in lateral temporo-parietal regions in PD patients [13,14].

Longitudinal studies have assessed structural gray matter differences over time in PD [15,16], and the progression of cognitive impairment has been related to degeneration of several cortical regions, including bilateral frontal and temporoparietal areas [16–18]. Progressive atrophy in widespread brain regions, such as the bilateral temporal and right occipital medial lobes, left superior frontal gyrus, and inferior parietal cortex, has been related to worsening in measures of global cognition [17,18]. Also, volumetric studies have associated the decline in executive functions with mainly bilateral frontal areas [19,20]. However, to the best of our knowledge, the relationship between the impairment of specific VS/VP functions and cortical thinning over time has yet to be studied. The aims of this study are (1) to address differential progressive gray matter loss between PD patients and healthy controls (HC), as well as (2) to investigate the changes over time in VS/VP functions in PD patients grouped according to cognitive status and their relationship with progressive cortical degeneration.

2. Methods

2.1. Participants

The cohort of this study was recruited from an outpatient movement disorders clinic (Parkinson's Disease and Movement Disorders Unit, Service of Neurology, Hospital Clínic, Barcelona, Spain), and HC were recruited from Institut de l'Envelliment (Barcelona, Spain). All participants are part of an ongoing longitudinal study, composed of 121 PD patients and 48 healthy subjects in the initial screening phase. Both groups were matched for age, sex, and years of education.

Inclusion criteria for participants consisted of fulfilling the diagnostic criteria for PD established by the UK PD Society Brain Bank [21]. Exclusion criteria consisted of: presence of dementia according to the Movement Disorder Society criteria [22], Hoehn and Yahr scale (H&Y) score >3, juvenile-onset PD, presence of psychiatric and/or neurologic comorbidity, low global IQ score estimated by the Vocabulary subtest of the Wechsler Adult Intelligence Scale, 3rd edition (scalar score ≤7 points), Mini-Mental State Examination (MMSE) score ≤25, claustrophobia, imaging findings on MRI not compatible with PD other than mild white matter hyperintensities in the FLAIR sequence, and MRI artifacts. The final sample at the baseline assessment consisted of 92 PD patients and 36 controls. A follow-up assessment was pursued after approximately four years (see Table 1), with a sample of 20 HC and 44 PD patients. Only subjects with baseline and follow-up assessments were included in this study (see Supplementary Fig. 1).

Motor symptoms were assessed with the Unified Parkinson's Disease Rating Scale, motor section (UPDRS-III). All PD patients were taking antiparkinsonian drugs, consisting of different combinations of L-DOPA, cathecol-O-methyltransferase inhibitors, monoamine oxidase inhibitors, dopamine agonists, and amantadine. In order to standardize doses, the L-DOPA equivalent daily dose (LEDD) [23] was calculated. All assessments were done while patients were under the effect of their usual medication ("on" state).

In line with the PD-MCI Movement Disorder Society Task Force (MDSTF) recommendations [24], we assessed five cognitive domains as previously described [12]. We divided the subjects into three groups: HC, PD patients without MCI (PD-NC), and PD patients with MCI (PD-MCI) at baseline. Expected z scores adjusted for age, sex, and education for each test and each subject were calculated based on a multiple regression analysis performed in the HC group [3]. As in previous studies [12,25], the presence of MCI was established if the z score for a given test was at least 1.5 lower than the expected score in at least two tests in one domain, or in at least one test per domain in at least two domains.

Written informed consent was obtained from all study participants after full explanation of the procedures. The study was approved by the institutional Ethics Committee from the University of Barcelona (IRB00003099).

2.2. Visuospatial and visuoperceptual assessment

All participants underwent a comprehensive neuropsychological assessment with VS/VP tests usually employed to evaluate the cognitive status of PD patients. The battery of tests chosen in this study is the same as that used in a previous cross-sectional study that addressed the neuroanatomical correlates of VS/VP deficits in PD [14]. The tests included were the pentagon copying test (PCT) from the MMSE, scored according to the Modified Mini-Mental State criteria (3MS); Benton's Judgment of Line Orientation test (JLOT), Visual Form Discrimination test (VFDT), and Facial Recognition test (FRT); and Symbol Digits Modalities test (SDMT).

2.3. MRI acquisition

Magnetic resonance images (MRI) were acquired with a 3T scanner (MAGNETOM Trio, Siemens, Germany) at baseline and follow-up. The scanning protocol included high-resolution 3-dimensional T1-weighted images acquired in the sagittal plane (TR = 2300 ms, TE = 2.98 ms, TI = 900 ms, 240 slices, FOV = 256 mm; matrix size = 256 × 256; 1 mm isotropic voxel and an axial FLAIR sequence (TR = 9000 ms, TE = 96 ms).

2.4. Longitudinal cortical thickness

FreeSurfer software (version 5.1; available at http://surfer.nmr.harvard.edu) was used to obtain structural measures as previously described [13]. After processing each subject cross-sectionally, in order to perform the longitudinal analyses of the data, within-subject templates [26] and corresponding longitudinal files were created for each time point for each subject. Briefly, a template volume for each subject using information from all of their time points and an average image were created using robust, inverse, consistent registration [27]. All time points were constructed through unbiased mean images and later aligned. After registration and creation of the templates, images from all time points are mapped to the template location and averaged, and processed with the default cross-sectional stream. The symmetrized percent change was used for longitudinal analyses of cortical thickness: [(Thickness at time point 1 − Thickness at time point 2)/Interval between assessments)]/[0.5*(Thickness at time point 1 + Thickness at time point 2)].

Comparisons between groups and regressions were assessed using vertex-by-vertex general linear models. Multiple contrasts were carried out to assess differences between all study subgroups (HC vs. all PD patients; HC vs. PD-NC; HC vs. PD-MCI; and PD-NC vs. PD-MCI). Regression models included symmetrized percent change as an independent factor and cognitive scores as dependent factors. In order to avoid clusters appearing significant purely by chance (i.e., false positives), Monte Carlo null-Z simulation with 10,000 iterations was applied to cortical thickness maps to provide clusterwise correction for multiple comparisons. Results were thresholded at a corrected p value of 0.05.

Table 1
Demographic and clinical data of the participants at baseline.

	HC (n = 20)	PD-NC (n = 28)	PD-MCI (n = 16)	F, x^2, t, U
Interval (years)	3.90 ± 0.32	3.89 ± 0.41	3.94 ± 0.59	0.065[a]
Age	65.50 ± 8.00	59.50 ± 9.58	64.63 ± 9.67	3.010[a]
Sex (male/female)	10/10	20/8	10/6	2.286[b]
Education	11.10 ± 4.13	12.96 ± 4.87	11.25 ± 5.94	1.045[a]
MMSE	29.75 ± 0.44	29.54 ± 0.69	28.69 ± 1.54	6.481[a]*
Evolution (years)		6.50 ± 3.87	8.03 ± 6.73	−0.814[c]
Age at onset		53.00 ± 10.21	56.91 ± 12.22	−1.136[c]
LEDD		700.79 ± 470.61	675.63 ± 535.21	0.162[c]
Dopamine agonists		17/28 (60.71%)	9/16 (56.25%)	1.206[b]
UPDRS-III		13.93 ± 9.19	11.75 ± 11.01	185.000[d]
H&Y		1: 11	1: 6	219.000[d]
		1,5: 1	2: 8	
		2: 12	2.5: 1	
		2,5: 2	3: 1	
		3:2		

HC: Healthy controls; PD-NC: Parkinson's disease patients without mild cognitive impairment; PD-MCI: Parkinson's disease patients with mild cognitive impairment; MMSE: Mini-Mental State Examination; LEDD: Levodopa Equivalent Daily Dose; UPDRS-III: Unified Parkinson's disease Rating Scale; H&Y: Hoehn and Yahr scale. Values are presented as mean ± standard deviation.
*significant at $p < 0.01$.
[a] F ANOVA statistics.
[b] Pearson's χ^2 statistics.
[c] Student *t*-test statistics.
[d] Mann-Whitney U statistics.

2.5. Global atrophy measures

Gray matter and lateral ventricular volumes were obtained automatically via whole brain segmentation procedures performed with FreeSurfer (version 5.1; available at http://surfer.nmr.harvard.edu). Intracranial volume (ICV) was entered as a covariate of no interest in comparisons of global atrophy measures. Mean thickness for both hemispheres was calculated as follows: [(left hemisphere thickness * left hemisphere surface area) + (right hemisphere thickness * right hemisphere surface area)]/(left hemisphere surface area + right hemisphere surface area).

2.6. Statistical analyses

Statistical analyses of neuropsychological, demographic, clinical, and MRI volumetric data variables were carried out using the statistical package SPSS-20 (2011; Armonk, NY: IBM Corp.). For the baseline analysis of demographic variables, Student *t* tests, ANOVA, Pearson's χ^2 statistics, and Mann-Whitney's U were used as appropriate.

A longitudinal variable was created for each test used to pair neuropsychological data with the structural longitudinal measure of symmetrized percent change, and was used in all statistical and structural analyses of the study.

For longitudinal clinical, neuropsychological, and structural variables, repeated measures general linear model was used to assess group differences over time in quantitative variables; and post-hoc tests were performed using Bonferroni correction for multiple comparisons. To address group and time effects in qualitative variables, Kruskal-Wallis H, Friedman's F, or Pearson's χ^2 statistics were used as appropriate.

3. Results

3.1. Sociodemographic and clinical data

Demographic and clinical data of the participants at baseline are summarized in Table 1. No significant differences were found between study groups in age, sex, education, clinical variables associated with PD, or the interval between assessments. The characteristics of the subjects who remained as study participants and those who dropped out are summarized in Supplementary Table 1.

The longitudinal evolution of clinical variables in all PD patients is summarized in Supplementary Table 2. Medication and motor measures showed no significant progression in this follow-up period, and did not differ between PD-NC subjects and patients with impaired cognition. MMSE showed significant group differences at baseline as well as group and time effects in the longitudinal analysis.

The progression of the detailed neuropsychological evaluation can be found in Table 2 and Supplementary Table 3. Aside from VS/VP measures, significant group-by-time interactions were seen in tests of attention and working memory. At follow-up, 17 patients remained as PD-NC (60.71%), 9 remained as PD-MCI (56.25%), 5 PD-MCI patients reverted to PD-NC (31.25%), 11 PD-NC patients progressed to PD-MCI (39.29%) and 2 PD-MCI patients fulfilled criteria for PDD (3.1%).

3.2. Visuospatial and visuoperceptual performance

All VS/VP tests showed significant group differences (see Table 2). Significant time and group-by-time interaction effects were observed for the SDMT. Post-hoc analyses evidenced that differences were found between HC and PD-MCI in all contrasts.

PCT differed between groups at baseline and follow-up when scored according to the original MMSE criteria ($\chi^2 = 12.800$, $p = 0.002$; $\chi^2 = 8.957$, $p = 0.011$ respectively) as well as according to Williams-Gray et al. criteria [1,7,8] ($\chi^2 = 9.295$, $p = 0.010$; $\chi^2 = 8.987$, $p = 0.011$ respectively); however, no significant time effects were observed for any groups.

3.3. MRI evolution

Imaging analyses revealed that, compared with PD-NC patients, PD-MCI patients exhibited significantly greater progressive cortical thinning in left lateral occipital and inferior parietal regions, and in right medial temporal regions (see Fig. 1 and Supplementary Table 4). Cortical thinning differences between HC and PD-NC, and between HC and all PD patients, were not significant.

Table 2
Group comparison of VS/VP performance between healthy subjects, PD patients without MCI, and PD patients with MCI.

	HC		PD-NC		PD-MCI		F (Group)	F (Time)	F (Group by time)	Post-hoc *P*
	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up				
PCT	9.70 ± 0.48	9.65 ± 0.59	9.79 ± 0.57	9.64 ± 0.68	9.19 ± 1.11	8.56 ± 2.73	4.428 (p = 0.016)	2.749 (p = 0.102)	1.022 (p = 0.366)	HC/PD-MCI: 0.047
JLOT	23.80 ± 2.91	25.00 ± 3.45	24.07 ± 3.81	25.21 ± 3.24	21.06 ± 5.74	19.56 ± 8.27	6.311 (p = 0.003)	0.292 (p = 0.591)	2.597 (p = 0.083)	HC/PD-MCI: 0.013
VFDT	30.00 ± 2.25	29.40 ± 2.26	29.54 ± 2.25	29.64 ± 2.53	26.88 ± 3.52	27.81 ± 4.20	6.028 (p = 0.004)	0.130 (p = 0.720)	1.024 (p = 0.365)	HC/PD-MCI: 0.008
FRT	22.70 ± 1.92	22.85 ± 1.87	22.14 ± 2.48	21.79 ± 2.73	20.44 ± 3.39	20.07 ± 3.26	4.992 (p = 0.010)	0.447 (p = 0.506)	0.346 (p = 0.709)	HC/PD-MCI: 0.008
SDMT	44.67 ± 8.40	46.90 ± 7.51	48.54 ± 10.61	43.75 ± 12.68	36.38 ± 18.91	31.31 ± 19.87	5.109 (p = 0.009)	7.552 (p = 0.008)	6.574 (p = 0.003)	HC/PD-MCI: 0.029

HC: Healthy controls; PD-NC: Parkinson's disease patients without mild cognitive impairment; PD-MCI: Parkinson's disease patients with mild cognitive impairment. PCT: Pentagon Copying Test; JLOT: Judgment of Line Orientation Test; VFDT: Visual Form Discrimination Test; FRT: Facial Recognition Test; SDMT: Symbol Digit Modalities Test. Values are presented as mean ± standard deviation.

Group comparison of global MRI atrophy parameters evidenced that mean thickness differed between groups and had a time effect (F(Group) = 7.711; p = 0.001; F(Time) = 9.891, p = 0.003; Post-hoc *P*: PD-MCI vs HC = 0.001; PD-MCI vs PD-NC = 0.016), whereas the increase in the volume of the lateral ventricular system achieved statistical significance for time and the interaction between group and time (F(Time): 88.596; p < 0.0001; F(GroupxTime) = 4.745; p = 0.012) (see Supplementary Fig. 2).

3.4. Cortical thickness correlates of visuospatial and visuoperceptual changes

Whole-brain imaging analyses showed significant correlations between changes in VS/VP measures and cortical thinning over time. In the PD-NC group, FRT also correlated with cortical thinning in the left lateral occipital area.

In PD-MCI patients, changes in PCT scores over time showed a significant cluster in the left entorhinal region that involved the middle and inferior temporal gyri, the medial temporal pole, and the parahippocampal, fusiform, lingual, and lateral occipital cortices. JLOT was significantly related to cortical atrophy in clusters located in the left insula, inferior and superior temporal areas, and the right fusiform gyrus, which extended to the left temporal pole, entorhinal, fusiform, and lingual cortices. FRT scores correlated significantly with cortical thinning in the left lingual gyrus. SDMT showed significant correlations with reductions in the left superior temporal, parahippocampal and lingual, as well as the right parahippocampal cortices (see Fig. 2, Supplementary Table 5). This pattern of anatomical correlates was maintained when only subjects with sustained cognitive diagnosis at follow-up were included in the analysis (see Supplementary Fig. 3).

We performed complementary analyses to study the cross-sectional correlates of the tests used in this study and we observed a pattern of posterior atrophy more pronounced in PD-MCI patients (see Supplementary Figs. 4a and 4b and Supplementary Table 6). We analyzed the association between cortical thinning over time and the significant longitudinal differences found in neuropsychological measures relative to other cognitive domains. In PD-NC patients, the Stroop colors test correlated significantly with left superior parietal and frontal regions. In PD-MCI patients, a non-specific widespread pattern of anterior and posterior regions correlated bilaterally with TMT-A and Stroop colors tests (see Supplementary Fig. 5 and Supplementary Table 7).

4. Discussion

In the present study, we aimed to investigate the longitudinal differences in cortical thinning between PD patients and healthy subjects, as well as the relationship between the progressive loss of VS/VP functions and the cortical degeneration underlying these changes in PD patients, grouped according to their cognitive status using the Movement Disorder Society Task Force criteria.

Our results evidence that all the neuropsychological tests with a posterior cortically-based component used in this work are sensitive to detect VS/VP impairment in MCI patients. However, among the five VS/VP tests used, only the SDMT showed a significant time effect as well as a significant group-by-time interaction, indicating that it may be useful for the evaluation of progressive cognitive impairment in PD. Previous research in PD cognitive deterioration has also described the progressive decline of visuospatial and visuoconstructive functions [1,4,7,8,28,29]. In longitudinal studies, an important issue is the distinction between cognitive and motor deficits, as there are several VS/VP tests, such as the clock drawing, the pentagon test drawing or the block design, that have a strong motor component. By contrast, in the SDMT, the motor component is very low, mainly involving eye tracking. It thus seems to be a suitable test for PD follow-up studies. In agreement with our

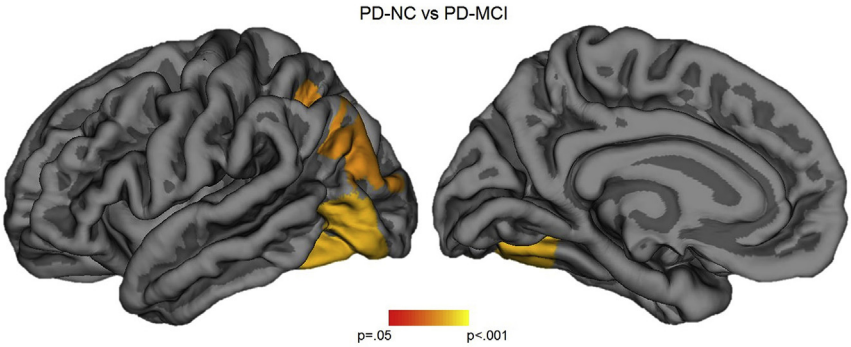

Fig. 1. Vertex-wise symmetrized percent change in cortical thickness differences between study groups. The scale bar shows *P* values. PD-NC: Parkinson's disease patients without mild cognitive impairment; PD-MCI: Parkinson's disease patients with mild cognitive impairment.

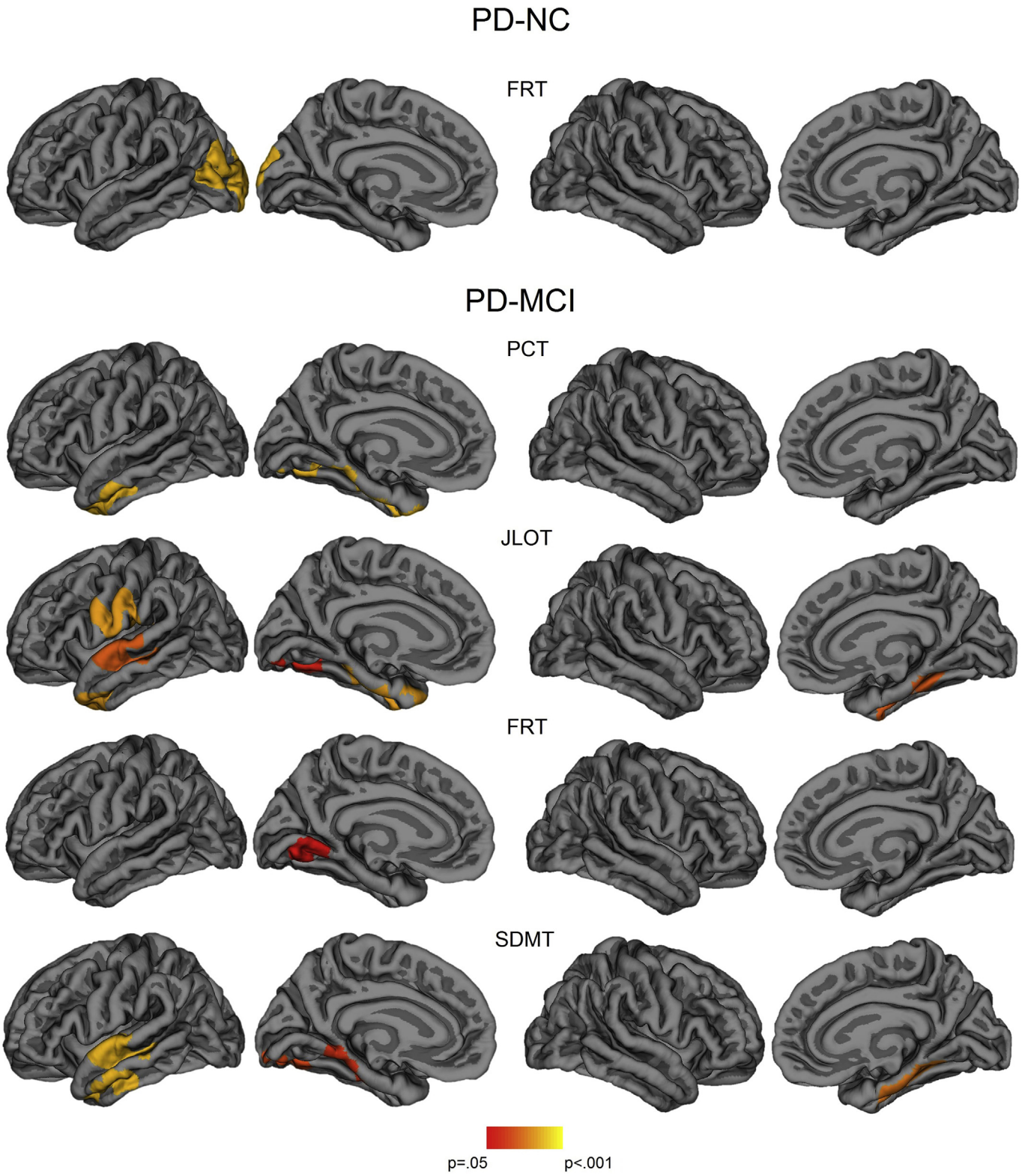

Fig. 2. Vertex-wise symmetrized percent change in cortical thickness correlations with VS/VP measures in PD patients. The scale bar shows *P* values. PD-NC: Parkinson's disease patients without mild cognitive impairment; PD-MCI: Parkinson's disease patients with mild cognitive impairment; FRT: Facial Recognition Test; SDMT: Symbol Digit Modalities Test; PCT: Pentagon Copying Test; JLOT: Judgment of Line Orientation Test.

findings, a 3-year multi-center follow-up of a large sample of PD patients, using short versions of the JLOT and the SDMT, found statistically significant effects for both tests, but the differences were stronger for the SDMT [29].

In our previous cross-sectional studies, we demonstrated a relationship between visuospatial and visuoperceptual

performance and cortical thickness in bilateral temporo-parietal-occipital areas, and widespread posterior-anterior white matter microstructure alterations [13,14]. Interestingly, in the present study, we have established a relationship between the progressive worsening in VS/VP performance and bilateral degeneration of posterior cortical regions. In PD-MCI patients, PCT, JLOT, FRT, and SDMT evidenced significant correlates with temporal, occipital, and parietal cortices. In PD-NC we also observed a relationship between decreases in FRT scores and the rate of thinning in the occipito-parietal cortex. We highlight the emergence of specific neuroanatomical correlates in PD-MCI patients, in absence of a significant time effect in neuropsychological performance for most VS/VP tests. This finding reflects that, although performance in these tests did not change significantly over time at the group level, there was a variable progressive loss of visuospatial and visuoperceptual functions in some PD patients that was explained by the variability in thinning of specific posterior cortical brain regions. This notion is supported by the finding that PD-MCI patients exhibited extensive progressive reductions in posterior parieto-temporal cortical regions in comparison with their cognitively unimpaired PD patient peers, which is in agreement with recent findings using the same technique in large study samples [17,18].

The neurobiological basis for cognitive dysfunction in PD is unclear, and several factors have been implicated, including loss of dopaminergic, noradrenergic, serotonergic, and cholinergic projections to limbic and cortical areas, as well as AD-type pathology [30]. Enhanced α-synuclein pathology, together with lysosomal deficits, have been linked to poor cognitive evolution in PD patients [31]. Functional cross-sectional studies with dopamine tracers and metabolic parameters have established the relevance of posterior regions in cognitive decline in PD [32,33], as well as the relationship between visuospatial impairment, posterior cortical regions, predominant α-synucleinopathy, and worse cognitive evolution [34,35].

The strengths of our study are that we applied validated criteria and tests to determine cognitive diagnoses [24], established a considerable follow-up interval, used a sensitive technique to identify regional gray matter changes associated with PD [36], and used the same MRI scanner, avoiding the variability of multi-center data. Our study is limited by the size of the sample due to the considerable attrition, which could in turn affect the results observed. However, cross-sectional as well as large-scale longitudinal studies of other groups are in line with our current findings [11,17,18]. In our study, mean group ages could appear as relatively low considering the epidemiological data of PD patents. This might be due to the exclusion of demented PD patients, who tend to be older. In fact, the mean age of our sample is similar to those in the abovementioned studies that also focused on non-demented PD patients using larger cohorts [17,18].

In conclusion, the present study establishes the neuroanatomical substrate of the progressive deterioration of visuospatial and visuoperceptual performance in PD patients with and without mild cognitive impairment. This study reinforces previous findings on the differential progression of atrophy in patients with MCI, thus supporting the validity of this construct. These findings give evidence to the notion that the progression of posterior-cortically based cognitive tests is indicative of progressive cortical thinning in posterior brain regions.

Disclosure

Authors AIGD, BS, HCB, CU, AC, AA, MJM, FV, NB and CJ report no disclosure. YC has received funding, research support and/or honoraria in the last 5 years from Union Chimique Belge (UCB pharma), Lundbeck, Medtronic, Abbvie, Novartis, GSK, Boehringer, Pfizer, Merz, Piramal Imaging and Esteve.

Author roles

1. Research project: A. Conception, B. Organization, C. Execution; 2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique; 3. Manuscript: A. Writing of the first draft, B. Review and Critique.

Garcia-Diaz: 1C, 2A, 2B, 3A; Segura: 1B, 1C, 2A, 2B, 3B; Uribe: 1C; Campabadal: 1C; Abos: 1C; Baggio: 1B, 1C, 2B, 2C, 3B; Marti: 1B, 1C, 2C, 3B; Valldeoriola: 1B, 1C, 2C, 3B; Compta: 1B, 1C, 2C, 3B; Bargallo: 1B, 1C, 2C,3B; Junque: 1A, 1B, 1C, 2A, 2B, 2C, 3B.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.parkreldis.2017.11.003.

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SUPPLEMENTARY TABLES

Supplementary Table 1. Sociodemographic and clinical data of PD subjects that participated in the study and those who dropped out after baseline assessment

	Study PD participants (n=44)	Dropped out (n=48)	T, χ^2, U
Age	61.68 ± 9.93	66.08 ± 11.79	-1.927 (p=0.057)[a]
Sex (male/female)	30/14	25/23	2.474 (p=0.116)[b]
Education	12.07 ± 5.58	9.27 ± 4.84	2.575 (p=0.012)[a]
LEDD	691.64 ± 489.02	889.09 ± 482.90	-2.083 (p=0.040)[a]
UPDRS-III	14.41 ± 9.40	20.44 ± 11.52	386.000 (p=0.019)[c]
H&Y	1.60 ± 0.65	2.00 ± 0.65	421.000 (p=0.016)[c]
Age at onset	54.71 ± 10.88	57.28 ± 13.30	-0.995 (p=0.322)[a]
Evolution	7.33 ± 5.34	9.35 ± 6.28	-1.658 (p=0.101)[a]
MMSE	29.16 ± 1.24	28.96 ± 0.99	0.863 (p=0.390)[a]
MCI	13	11	0.778 (p=0.438)[b]
Hallucinations	7	12	1.158 (p=0.282)[b]
BDI	8.33 ± 5.39	13.43 ± 5.87	-4.051 (p<0.001)[a]
AES	11.68 ± 7.06	14.66 ± 7.85	-1.805 (p=0.075)[a]
JLOT	22.75 ± 4.77	20.57 ± 4.85	2.156 (p=0.034)[a]
VFDT	28.66 ± 2.92	27.02 ± 3.83	2.293 (p=0.024)[a]
FRT	21.32 ± 3.06	21.00 ± 2.44	0.551 (p=0.583)[a]
PCT 3MS	9.52 ± 0.88	9.09 ± 1.30	1.871 (p=0.065)[a]
PCT Original (incorrect)	5	10	1.622 (p=0.203)[b]
Attention and working memory	0.18 ± 0.61	0.47 ± 0.78	-1.790 (p=0.078)[a]
Executive functions	-0.24 ± 1.10	-0.71 ± 0.99	2.107 (p=0.038)[a]
Memory	-0.46 ± 1.36	-1.16 ± 1.44	2.347 (p=0.021)[a]
Language	0.05 ± 0.90	-0.51 ± 1.21	2.474 (p=0.015)[a]
Visuospatial and visuoperceptual	-0.37 ± 0.94	-0.88 ± 1.06	2.368 (p=0.020)[a]

PD: Parkinson's disease patients; LEDD: Levodopa Equivalent Daily Dose; UPDRS-III: Unified Parkinson's disease Rating Scale; H&Y: Hoehn & Yahr; MMSE: Mini-Mental State Examination; MCI: Mild Cognitive Impairment; BDI: Beck Depression Inventory: AES: Apathy Evaluation Scale; JLOT: Judgment of Line Orientation test; VFDT: Visual Form Discrimination test; FRT: Facial Recognition Test; PCT: Pentagon Copying Test; 3MS: Modified Mini-Mental State. Values are presented as mean ± standard deviation. [a]: Student t test statistics; [b]: Pearson's χ^2 statistics; [c]: Mann-Whitney U statistics.

Supplementary Table 2. Progression of clinical variables in PD participants

	Baseline			Follow-up			F (Group)	F (Time)	F (Group by time)
	HC	PD-NC	PD-MCI	HC	PD-NC	PD-MCI			
MMSE	29.75 ± 0.44	29.54 ± 0.69	28.69 ± 1.54	29.30 ± 0.87	29.14 ± 0.97	27.56 ± 3.41	6.421*	11.116*	1.289
LEDD		700.79 ± 470.61	675.63 ± 535.21		720.48 ±	693.28 ± 481.07	0.044	0.068	0.989
UPDRS-III		13.93 ± 9.19	11.75 ± 11.01		17.79 ± 9.03	17.40 ± 12.70	31.036[d] 14.605[d]	366.333[d] 106.205[d]	
H&Y		1: 11 1,5: 1 2: 12 2,5: 2 3:2	1: 6 2: 8 2.5: 1 3: 1		1: 3 2: 14 3: 11	1: 3 2: 5 3: 7 4: 1	0.718[d] 3.111[d]	8.527[d] 9.257[d]	

HC: Healthy controls; PD-NC: Parkinson's disease patients without mild cognitive impairment; PD-MCI: Parkinson's disease patients with mild cognitive impairment; GxT: Group by time interaction; MMSE: Mini-Mental State Examination; LEDD: Levodopa Equivalent Daily Dose, UPDRS-III: Unified Parkinson's disease Rating Scale; H&Y: Hoehn & Yahr. *Significant at p<0.01.

Supplementary Table 3. Group comparison of neuropsychological performance between healthy subjects, PD patients without MCI, and PD patients with MCI

	HC		PD-NC		PD-MCI		F (Group)	F (Time)	F (Group by time)
	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up			
TMT A	38.42 ± 13.95	36.63 ± 11.75	33.19 ± 10.10	44.42 ± 19.84	42.60 ± 19.69	49.60 ± 17.95	6.900 (p=0.002)	9.965 (p=0.002)	3.871[a] (p=0.026)
TMT B	88.58 ± 27.94	94.00 ± 50.51	80.65 ± 18.80	104.73 ± 53.02	90.60 ± 48.13	190.20 ± 220.31	6.025 (p=0.004)	14.137 (p<0.001)	4.248[a,b] (p=0.019)
DS For-ward	5.58 ± 1.47	5.26 ± 1.45	6.12 ± 1.21	5.54 ± 1.42	5.80 ± 1.48	5.60 ± 1.27	0.931 (p=0.400)	3.181 (p=0.079)	0.878 (p=0.421)
DS Back-wards	4.16 ± 1.30	4.32 ± 1.20	4.65 ± 0.94	4.69 ± 1.29	4.30 ± 1.16	4.10 ± 1.10	4.126 (p=0.021)	0.627 (p=0.432)	1.563[b] (p=0.218)
Stroop words	100.95 ± 13.71	95.47 ± 12.07	102.50 ± 15.57	92.85 ± 15.01	77.00 ± 19.98	78.50 ± 18.25	13.544 (p<0.001)	10.624 (p=0.002)	1.393[a,b] (p=0.256)
Stroop colors	62.05 ± 16.99	62.89 ± 11.03	66.50 ± 11.93	61.46 ± 10.59	54.80 ± 12.29	48.70 ± 13.80	7.589 (p=0.001)	7.353 (p=0.009)	3.263[a,b] (p=0.045)
Stroop W-C	37.47 ± 11.44	36.11 ± 10.17	41.73 ± 11.05	38.04 ± 9.28	35.20 ± 12.23	28.60 ± 12.94	4.361 (p=0.017)	25.019 (p<0.001)	2.845[b] (p=0.066)
Phonemic fluency	15.47 ± 4.44	15.53 ± 4.94	18.35 ± 5.31	15.73 ± 4.62	13.70 ± 6.24	15.40 ± 6.93	4.534 (p=0.015)	1.070 (p=0.305)	1.916[b] (p=0.156)
Semantic fluency	19.74 ± 2.92	18.79 ± 3.63	20.62 ± 5.10	17.73 ± 6.10	18.20 ± 5.47	16.80 ± 3.74	3.129 (p=0.051)	16.454 (p<0.001)	1.521 (p=0.227)
BNT	13.63 ± 1.01	13.84 ± 0.96	13.69 ± 1.05	13.77 ± 1.14	13.70 ± 1.06	13.70 ± 1.06	0.520 (p=0.597)	0.835 (p=0.364)	0.643 (p=0.529)
RAVLT Total	43.26 ± 5.15	47.47 ± 6.96	46.73 ± 7.94	47.46 ± 8.59	37.10 ± 6.26	41.30 ± 8.10	13.837 (p<0.001)	4.526 (p=0.037)	1.989[a] (p=0.146)
RAVLT Recall	8.74 ± 1.79	10.05 ± 2.61	9.27 ± 2.49	9.69 ± 2.94	6.40 ± 1.96	6.80 ± 3.01	14.182 (p<0.001)	0.395 (p=0.0532)	2.619[a] (p=0.081)

HC: Healthy controls, PD-NC: Parkinson's disease patients without mild cognitive impairment; PD-MCI: Parkinson's disease patients with mild cognitive impairment; TMT: Trail Making Test; DS: Digit Span; Stroop W-C: Stroop Words-Colors test; BNT: Boston Naming Test; RAVLT: Rey Auditory Verbal Learning Test. Values are presented as mean ± standard deviation. [a]: Significant post-hoc contrasts between HC and PD-MCI at p<0.01. [b]: Significant post-hoc contrasts between PD-NC and PD-MCI at p<0.05.

Supplementary Table 4. Significant clusters showing cortical thickness differences over time between PD patients without MCI and PD patients with MCI

Cluster anatomical annotation	Cluster size (mm^2)	Talairach coordinates of the maxima			Z value	Clusterwise probability
		X	Y	Z		
PD-NC vs PD-MCI						
Left lateral occipital	2505.31	-41.9	-78.3	-2.8	3.440	0.00010
Left inferior parietal	2013.90	-40.7	-64.8	30.6	2.333	0.00030

PD-NC: Parkinson's disease patients without mild cognitive impairment; PD-MCI: Parkinson's disease patients with mild cognitive impairment.

Supplementary Table 5. Significant clusters showing cortical thickness correlations over time with VS/VP measures in PD patients without MCI and PD patients with MCI

	Cluster anatomical annotation	Cluster size (mm^2)	Talairach coordinates of the maxima			Z value	Clusterwise probability
			X	Y	Z		
PD-NC	**FRT**						
	Left lateral occipital	3027.57	-19.9	-94.5	8.0	3.766	0.00010
PD-MCI	**PCT**						
	Left entorhinal	3430.28	-32.1	-16.9	-24.3	4.734	0.00010
	JLOT						
	Left insula	1873.12	-37.5	-19.2	20.0	5.084	0.00020
	Left inferior temporal	1927.49	-37.7	1.7	-31.5	4.705	0.00020
	Left fusiform	1053.63	-29.5	-69.5	-5.6	4.571	0.01660
	Left superior temporal	1475.99	-56.0	-13.6	-5.1	3.490	0.00160
	Right fusiform	1475.55	35.1	-43.2	-9.6	4.136	0.00180
	FRT						
	Left lingual	1054.57	-13.1	-56.8	2.5	3.264	0.02880
	SDMT						
	Left superior temporal	2779.89	-53.5	-13.6	-6.6	4.351	0.00010
	Left parahippocampal	1182.41	-31.7	-24.3	-18.5	3.920	0.00770
	Left lingual	1311.56	-14.0	-85.3	-4.2	3.761	0.00360
	Right parahippocampal	1651.06	31.9	-22.5	-20.4	4.158	0.00070

PD-NC: Parkinson's disease patients without mild cognitive impairment; PD-MCI: Parkinson's disease patients with mild cognitive impairment; FRT: Facial Recognition Test; PCT: Pentagon Copying Test; JLOT: Judgment of Line Orientation test; SDMT: Symbol Digit Modalities Test.

Supplementary Table 6. Significant clusters showing cross-sectional cortical thickness correlations with VS/VP measures in PD patients without MCI and PD patients with MCI at baseline and follow-up assessments

	Cluster anatomical annotation	Cluster size (mm^2)	Talairach coordinates of the maxima			Z value	Clusterwise probability
			X	Y	Z		
Baseline							
PD-NC	**JLOT**						
	Right superior parietal	2602.51	19.5	-60.4	42.7	2.804	0.01350
	SDMT						
	Left fusiform	2026.16	-38.8	-62.4	-3.5	2.189	0.05090
	Right fusfirom	6744.71	40-4	.50.3	-10.0	3.032	0.00020
PD-MCI	**PCT**						
	Left precentral	1528.65	-23.8	-20.9	51.2	4.799	0.01690
	Right superior temporal	2004.66	65-2	-20.3	4.3	2.668	0.03130
	JLOT						
	Left superior temporal	2324.53	-48.7	-17.4	-9.9	3.793	0.00760
	Left precentral	2039.85	-23.6	-26.2	48.9	4.422	0.01840
	Left fusiform	1764.37	-26.1	-79.1	-3.8	3.439	0.04110
	Right precentral	5038.47	27.6	-25.0	46.2	3.819	0.00020
	Right precuneus	2017.40	11.9	-51.5	14.2	3.876	0.03000
	Right superior temporal	1936.40	46.6	-25.3	-1.2	5.428	0.03780
	FRT						
	Left middle temporal	3327.92	-62.3	-18.1	-13.4	4.158	0.00020
	SDMT						
	Left precentral	3347.49	-22.7	-23.5	48.7	4.047	0.00020
	Left inferior parietal	2978.70	-48.0	-61.4	10.4	3.777	0.00070
	Left isthmus cingulate	2458.70	-9.1	-54.0	11.4	4.488	0.00430
	Left fusiform	1890.21	-27.0	-77.2	-2.3	2.682	0.02840
	Right superior temporal	5620.20	57.0	-17.0	-1.2	3.927	0.00020
	Right precentral	2594.66	25.3	-23.3	46.3	3.742	0.00020

Follow-up							
PD-NC	**PCT**						
	Left superior temporal	2765.13	-42.7	-3.0	-18.3	2.856	0.01320
	JLOT						
	Right lateral occipital	2510.83	18.7	-95.5	-6.3	2.649	0.02230
	FRT						
	Left precuneus	3939.25	-20.8	-60.9	12.3	3.947	0.00050
	Right cuneus	7475.92	8.7	-82.4	24.4	2.948	0.00020
	SDMT						
	Left precuneus	4138.70	-21.3	-60.7	17.5	3.381	0.00020
PD-MCI	**PCT**						
	Left middle temporal	3196.58	-51.3	-26.0	-9.4	5.016	0.00150
	Left parahippocampal	3141.48	-22.4	-38.6	-8.0	3.072	0.00200
	JLOT						
	Left bankssts	6566.60	-48.9	-39.5	5.5	3.308	0.00020
	Left fusiform	2971.92	-31.6	-42.9	-11.9	3.020	0.00310
	Left precuneus	2309.59	-9.1	-56.5	18.0	2.939	0.01960
	Right superior temporal	5655.28	46.2	4.2	-18.6	3.430	0.00020
	Right parahippocampal	5118.58	24.3	-41.3	-5.1	4.188	0.00020
	Right caudal middle frontal	3236.30	39.8	2.7	34.9	4.450	0.00300
	FRT						
	Left middle temporal	1989.50	-48.1	-3.4	-27.5	2.832	0.04150
	SDMT						
	Left inferior parietal	7774.24	-50.1	-61.2	12.5	3.701	0.00020
	Left fusiform	3399.89	-40.3	-54.6	-4.8	3.234	0.00100
	Left precuneus	2266.55	-23.6	-56.2	8.9	3.355	0.02190
	Right superior temporal	6331.24	46.3	1.7	-17.8	4.620	0.00020

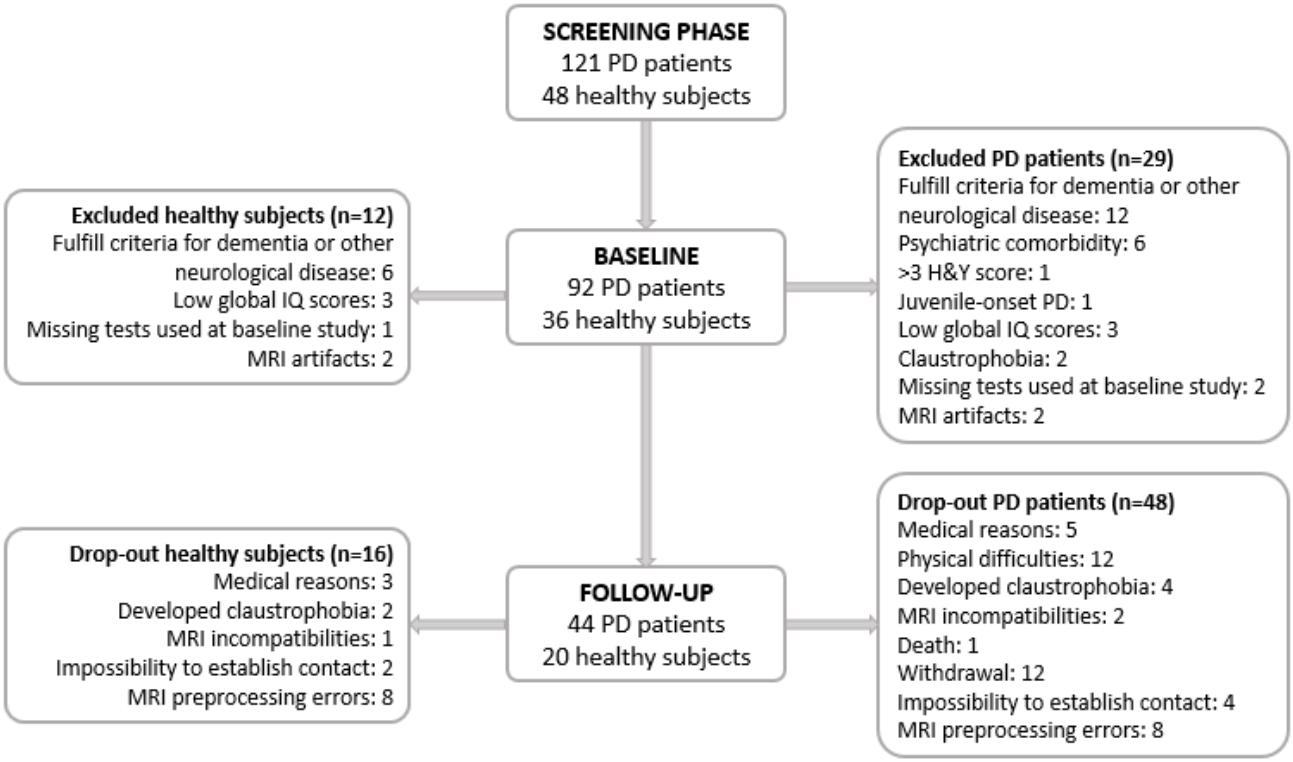
PD-NC: Parkinson's disease patients without mild cognitive impairment; PD-MCI: Parkinson's disease patients with mild cognitive impairment; JLOT: Judgment of Line Orientation test; SDMT: Symbol Digit Modalities Test; PCT: Pentagon Copying Test; FRT: Facial Recognition Test.

Supplementary Table 7. Significant clusters showing cortical thickness correlations over time with neuropsychological measures in PD patients without MCI and PD patients with MCI

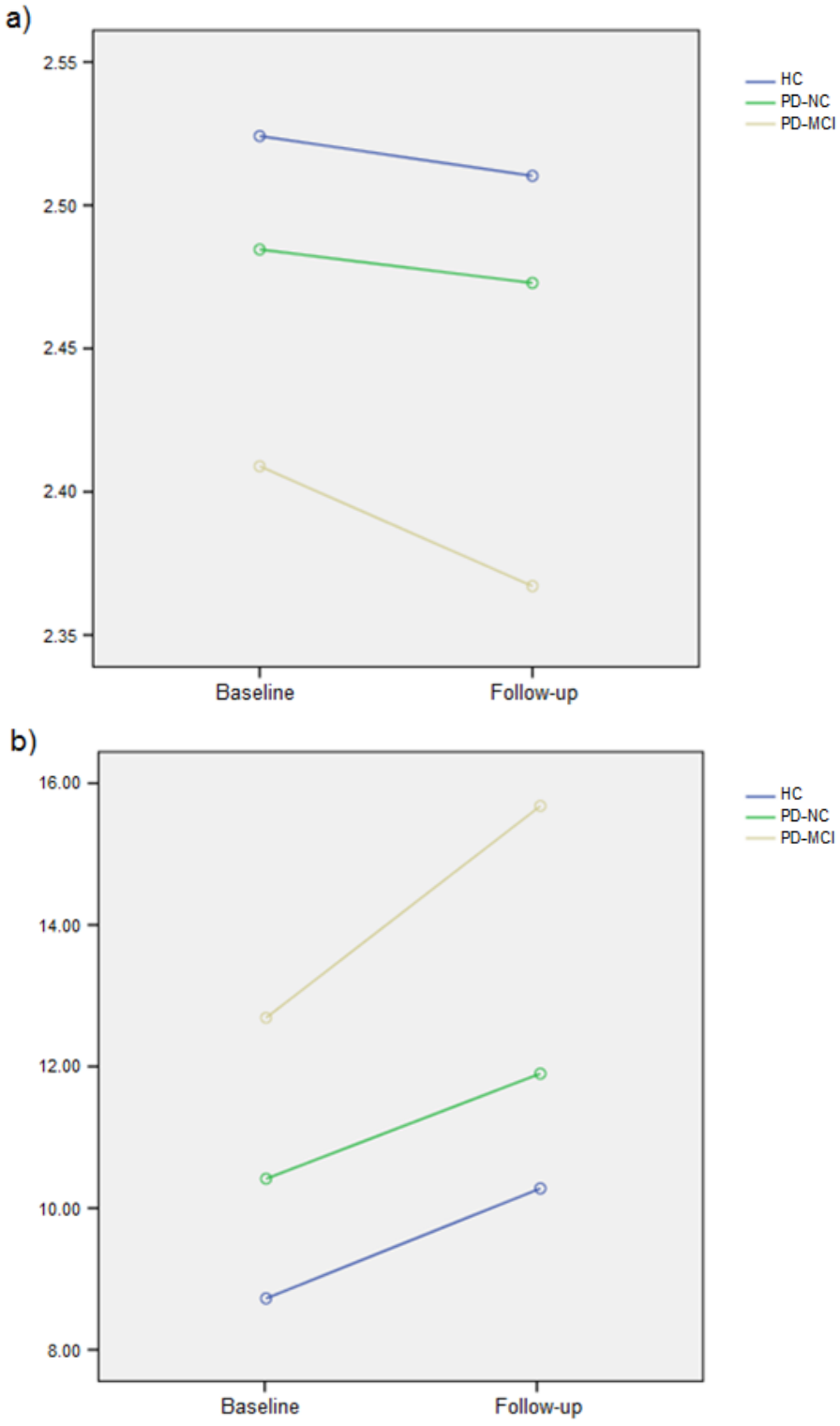
	Cluster anatomical annotation	Cluster size (mm^2)	Talairach coordinates of the maxima			Z value	Clusterwise probability
			X	Y	Z		
PD-NC	**Stroop colors test**						
	Left superior frontal	1397.49	-9.0	30.6	48.6	3.390	0.04230
	Left superior parietal	1380.02	-17.7	-76.4	34.6	2.253	0.04450
PD-MCI	**TMT-A**						
	Left parahippocampal	23479.36	-32.0	-25.0	-17.3	-5.626	<0.00001
	Left lateral occipital	2288.44	-39.1	-83.7	2.8	-4.640	0.00070
	Left inferior parietal	2092.69	-31.3	-68.0	40.0	-2.677	0.00050
	Right superior temporal	4174.33	51.2	6.8	-13.3	-4.111	0.00020
	Right superior frontal	3023.02	13.3	15.6	34.1	-4.092	0.00020
	Right lateral occipital	2021.06	41.0	-69.1	4.6	-4.244	0.00200
	Right lingual	1851.08	28.1	-49.3	-2.0	-3.457	0.00480
	Stroop colors test						
	Left supramarginal	14221.99	-57.0	-25.0	18.5	6.435	0.00020
	Left pericalcarine	4167.83	-16.4	-73.9	12.8	3.409	0.00020
	Left inferior parietal	1744.34	-42.3	-67.2	24.2	3.487	0.00660
	Left lateral occipital	1267.06	-33.5	-85.4	-0.6	3.655	0.04410
	Right paracentral	5438.37	16.0	-20.6	36.8	5.442	0.00020
	Right parahippocampal	2506.54	32.8	-22.8	-19.1	4.769	0.00020
	Right lateral occipital	2373.49	39.8	-67.2	3.4	3.294	0.00040

PD-NC: Parkinson's disease patients without mild cognitive impairment; PD-MCI: Parkinson's disease patients with mild cognitive impairment; TMT-A: Trail Making Test part A.

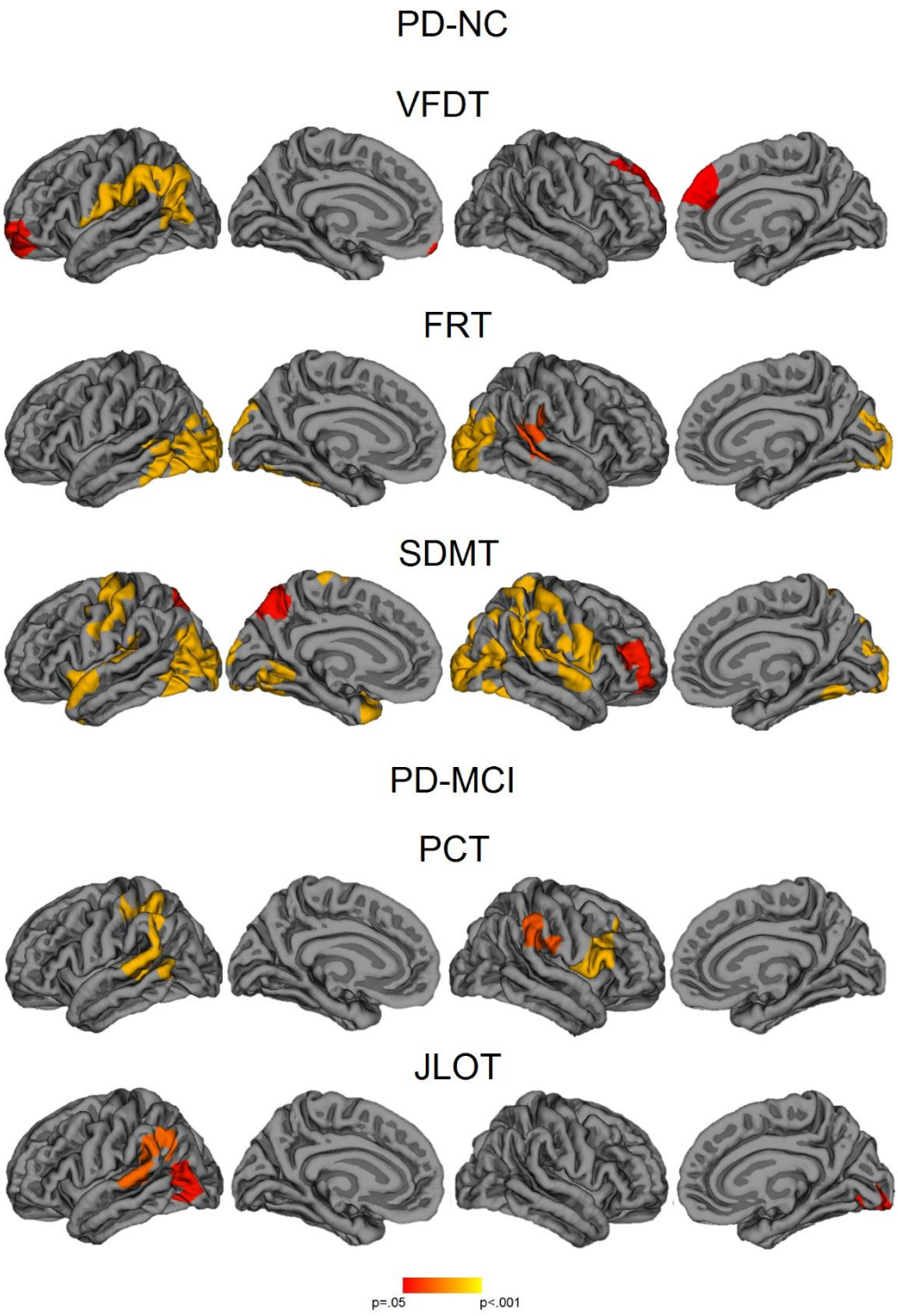
SUPPLEMENTARY FIGURES



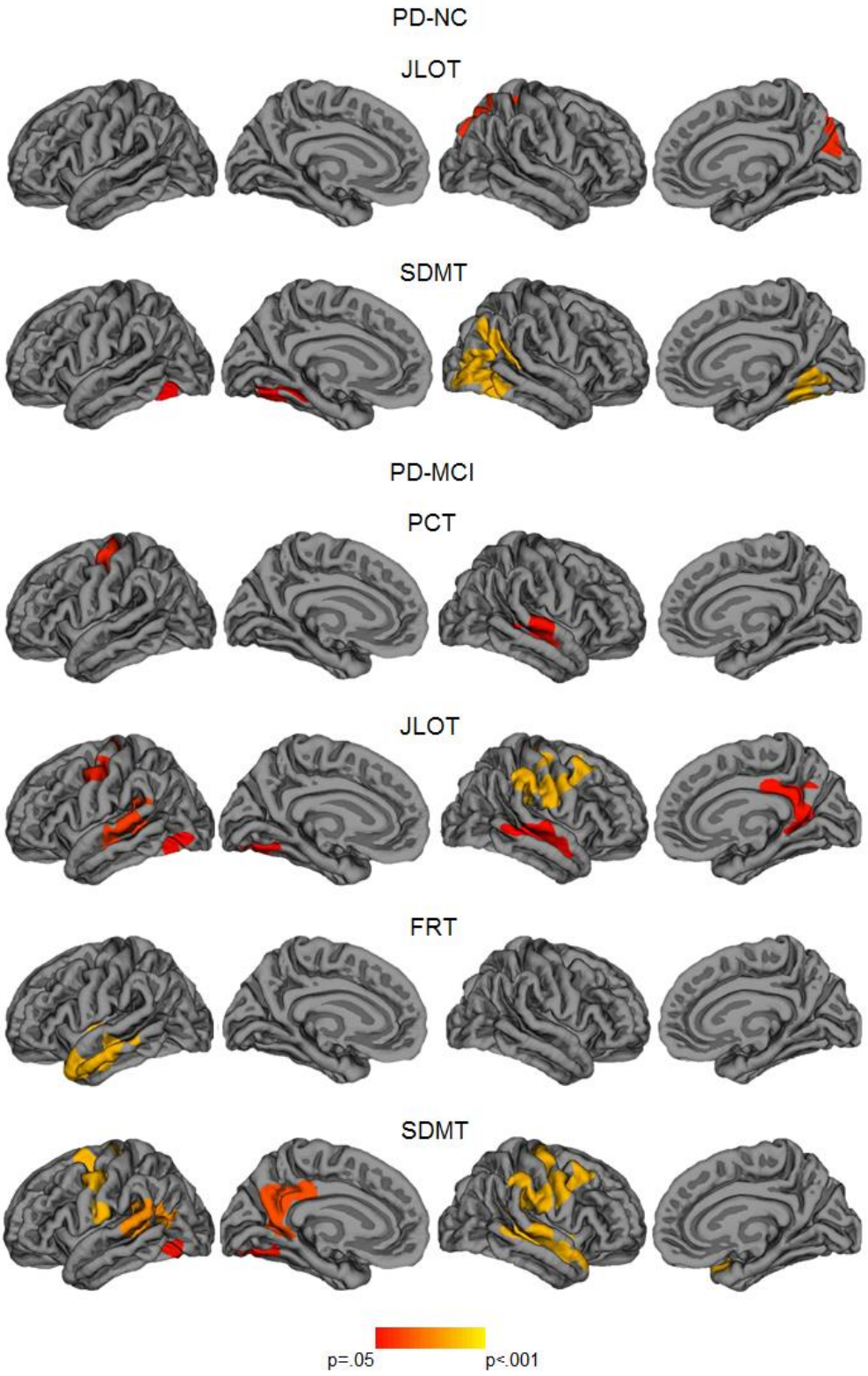
Supplementary Figure 1. Flowchart summarizing sample evolution from screening phase to follow-up. PD: Parkinson's disease; HC: Healthy controls; H&Y: Hoehn and Yahr.



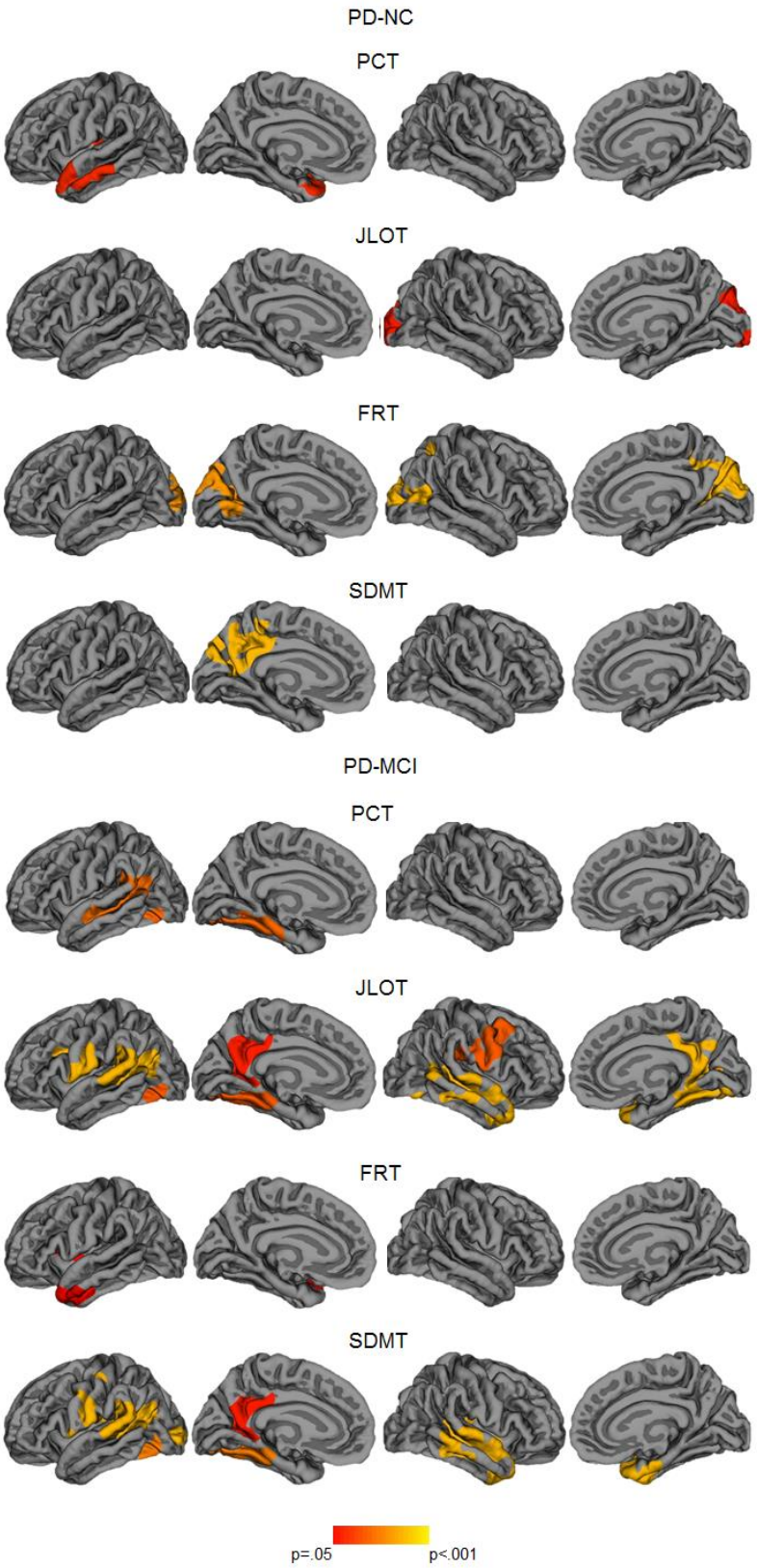
Supplementary Figure 2. a) Mean Thickness (mm) and b) LVS (cm^3) estimated marginal means at baseline and follow-up in study groups. HC: Healthy controls; PD-NC: Parkinson's disease patients without mild cognitive impairment; PD-MCI: Parkinson's disease patients with mild cognitive impairment.



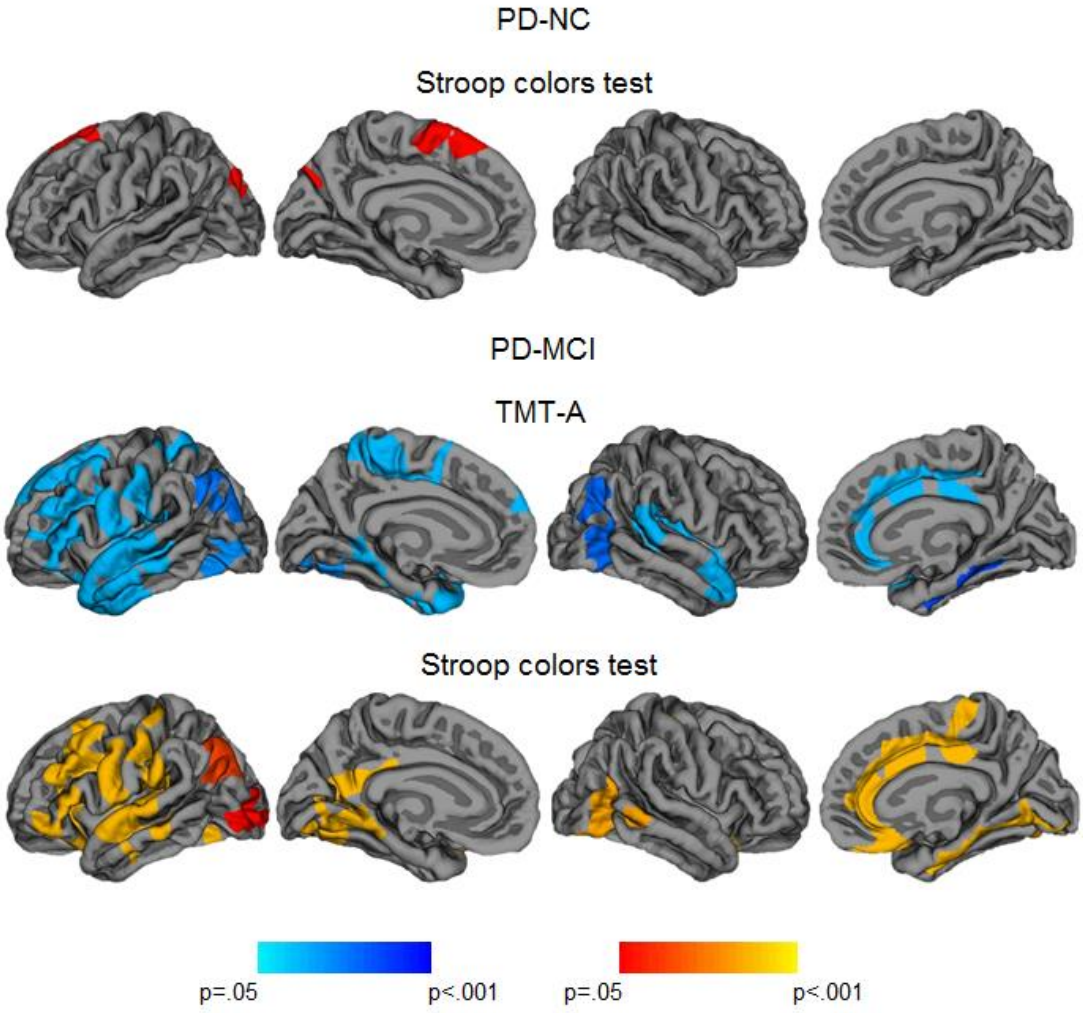
Supplementary Figure 3. Vertex-wise symmetrized percent change in cortical thickness one-tail correlations with neuropsychological measures in PD-NC and PD-MCI selected subjects who sustained cognitive diagnosis at follow-up. The scale bar shows *P* values. PD-NC: Parkinson's disease patients without mild cognitive impairment; VFDT: Visual Form Discrimination Test; FRT: Facial Recognition Test; SDMT: Symbol Digit Modalities Test; PD-MCI: Parkinson's disease patients with mild cognitive impairment; PCT: Pentagon copying test; JLOT: Judgment of Line Orientation Test.



Supplementary Figure 4a. Vertex-wise cortical thickness one-tail correlations with VS/VP measures in PD patients at baseline. The scale bar shows *P* values. PD-NC: Parkinson's disease patients without mild cognitive impairment; PD-MCI: Parkinson's disease patients with mild cognitive impairment; JLOT: Judgment of Line Orientation Test; SDMT: Symbol Digit Modalities Test; PCT: Pentagon Copying Test; FRT: Facial Recognition Test.



Supplementary Figure 4b. Vertex-wise cortical thickness one-tail correlations with VS/VP measures in PD patients at follow-up. The scale bar shows *P* values. PD-NC: Parkinson's disease patients without mild cognitive impairment; PD-MCI: Parkinson's disease patients with mild cognitive impairment; PCT: Pentagon Copying Test; JLOT: Judgment of Line Orientation Test; FRT: Facial Recognition Test; SDMT: Symbol Digit Modalities Test.



Supplementary Figure 5. Vertex-wise symmetrized percent change in cortical thickness one-tail correlations with neuropsychological measures in PD patients. The scale bar shows *P* values; warmth scale represents positive correlations; cold scale represents negative correlations. PD-NC: Parkinson's disease patients without mild cognitive impairment; PD-MCI: Parkinson's disease patients with mild cognitive impairment; TMT-A: Trail Making Test part A.

CHAPTER 5.

GENERAL DISCUSSION

This thesis was performed aiming to characterize the visuospatial and visuoperceptual impairment and the neuroanatomical changes that occur in PD. In order to address these aims, we have used a number of well-validated and recognized neuropsychological tests representative of posterior cortically-based functions, together with state-of-the-art neuroimaging techniques for the analysis of gray and white matter changes.

GENERAL COGNITIVE STATUS MEASURES

Neuropsychological deficits in PD have been studied with increasing frequency and complexity, since growing evidence highlights the relevance of cognitive impairment as an important non-motor symptom in the evolution to dementia, as well as reduced quality of life and poor outcome in PD patients.

PD-related cognitive impairment was classically regarded as a subcortical dementia (Elizan et al., 1986). The cognitive deficits seen were considered to be secondary to fronto-striatal circuitry dysfunction. Nonetheless, it has commonly been characterized from an AD-type cognitive impairment perspective. In this line, MCI diagnosis in PD was initially developed in terms of amnestic symptomatology (Petersen et al., 1999), and the assessment of general cognitive status has been widely performed in clinical as well as research settings with the use of tests developed for AD screening, such as the MMSE. However, several large-scale studies have raised concerns about the use of the MMSE in PD, since PD patients with normal scores in this test can suffer a varied range of cognitive deficits (Mamikonyan et al., 2009), and dementia (Burdick et al., 2014). It has been widely stated that the MMSE exhibits low sensitivity to detect cognitive impairment (Riedel et al., 2008; Hoops et al., 2009; Burdick et al., 2014), and can evidence floor ef-

fects in subjects with severe cognitive impairment and ceiling effects in subjects with MCI (Wind et al., 1997). Conversely, MMSE has been described to correlate with neuropathological stages described by Braak et al. (2003) (Braak et al., 2005), and with tau and β-amyloid obtained from cerebrospinal fluid (CSF) (Compta et al., 2011). Similarly, neuroimaging studies have evidenced a correlation between cortical thickness in a disease stage modelling and MMSE scores (Zarei et al., 2013).

In the first study included in this thesis, we explored MMSE scores in a large sample of PD patients as well as their relationship with structural measures of gray matter degeneration. PD patients exhibited MMSE scores that were within what is considered to be the normal range, but that were nonetheless significantly lower than healthy subjects' scores. Mean cortical thickness and lateral ventricular system volumes correlated significantly with MMSE values, whereas surface-based cortical thickness analyses only showed a correlation located in a left inferior occipitotemporal area.

The left ventral predominance of the MMSE neuroanatomical correlates in PD patients seen in our study, together with the cortical correlates of Braak's stages of tau and β-amyloid neuropathology previously reported (Compta et al., 2011), suggests that the ability of the MMSE to detect brain degeneration in PD is especially related to AD-type neuropathology. Therefore, although global MMSE score might hold a certain relationship with PD disease stages, it is not sensitive for the type of cognitive deterioration most commonly seen in PD. Nonetheless, a subtest of the MMSE, the pentagon copying item, seems to be more directly related to PD cognitive decline, since recent studies have reported that its impairment reflects greater decline in total MMSE scores in non-demented PD patients (Kaul & Elble, 2014). Interestingly, the PCT was identified in a large longitudinal study as an independent prognostic marker of the evolution to dementia in PD (Williams-Gray et al., 2007; Williams-Gray et al., 2009; Williams-Gray et al., 2013). In our first study, PD patients exhibited significantly lower PCT scores than healthy subjects using the 3MS, a simple scoring system that seems suitable for use in clinical settings.

In our second study, we divided the PD patient sample according to the presence or absence of MCI, evidencing that the differences seen between healthy subjects and PD patients were explained by the lower scores of the PD-MCI group. Interestingly, the effect sizes of these contrasts were especially large when comparing patients with normal cognition to PD-MCI patients. In our third study, using a repeated-measures linear regression model, differences appeared significant only for the comparison between healthy subjects and PD-MCI patients. These results suggest that the PCT could be a suitable test to detect cognitive impairment in PD patients who develop MCI in contrast to those who remain cognitively stable.

As a visuoconstructive test, impairment in the PCT is considered to be representative of predominantly posterior cortically-based dysfunction. Few published studies, however, focused on its neuroanatomical

substrate in PD. A structural neuroimaging study using a volumetric region of interest- (ROI) based approach and a novel scoring system reported that PCT scores correlated significantly with left frontal and cuneus regions, and the right medial occipital cortex (Filoteo et al., 2014). In our first study, patients with impaired PCT performance (*i.e.*, scored according to the original MMSE grading system) exhibited significant thickness reductions in bilateral posterior regions involving the precuneus, and superior temporal, parietal and posterior cingulate cortices. Similarly, in our first and second studies, cortical thickness analyses with the 3MS scoring system revealed a predominantly posterior pattern of correlates that involved bilateral temporo-parietal and posterior cingulate regions, in agreement with metabolic studies (Garcia-Garcia et al., 2012). Differences between our findings and those seen in the previously reported study could be due to the techniques used to detect cortical degeneration and to the scoring systems applied. Using DTI, we found that white matter tracts correlates were located in widespread posterior and anterior areas, suggesting the involvement of several brain regions, not only those related to the posterior cortex.

In our third study, using a longitudinal design, we saw that the neuroanatomical correlates described above were only maintained in PD-MCI patients. Taken together, these findings give support to the hypothesis that cortical degeneration contributes to the neuropsychological impairment revealed through abnormal PCT performance, described in previous studies that did not include MRI data (Cormack et al., 2004; Williams-Gray et al., 2007; Williams-Gray et al., 2009; Williams-Gray et al., 2013; Yu et al., 2012; Kaul & Elble, 2014). Moreover, the finding that, over time, only PD-MCI patients exhibit significant correlates between PCT scores and cortical thinning in posterior brain regions suggests a relationship that may be specific to cognitively-impaired PD patients.

Another item that is commonly used in general cognitive status tests and as a screening tool for cognitive impairment itself in PD is the clock copying test. Impairment of clock copying ability in PD has been described in cross-sectional (Stefanova et al., 2015) as well as longitudinal reports (Muslimović et al., 2009; Broeders et al, 2013), but some studies have also found no evidence of changes over time (Lee et al., 2011). In our second study, clock copying performance scored according to the CLOX2 (Royall et al., 1999) showed no significant differences between healthy subjects, PD patients without cognitive impairment and PD patients with MCI. Our MRI analyses revealed a relationship between CLOX2 and bilateral cortical thickness in precuneus and right posterior cingulate in PD patients, as well as medial white matter microstructure involvement. These results are partially in agreement with previous studies reporting clock copy cortical correlates in PDD, which highlighted the involvement of the right parahippocampal and the left lingual gyri (Pagonabarraga et al., 2013).

The absence of differences between healthy subjects, PD patients with normal cognition and PD-MCI patients seen in our second study, together with the reported neuroanatomical correlates, would further favor the use of PCT rather than clock copying as a screening tool in PD patients.

VISUOSPATIAL AND VISUOPERCEPTUAL IMPAIRMENT

Impairment of visuospatial and visuoperceptual functions has been an important matter of study since the early description of cognitive dysfunction in PD. In spite of the disparity of results, it seems clear that visuospatial and visuoperceptual impairment is common in PD; can occur early in the disease course, independently of other cognitive deficits as well as basic visual deficits; and holds an important relationship with certain disease variables, such as disease severity, motor phenotype, visual hallucinations, medication, disease progression and prospective outcome.

Nonetheless, in many neuropsychological as well as some neuroimaging studies, visual cognition deficits have been approached broadly without specification of visual processing subspecializations. In the studies presented in this thesis, we have aimed to study visual cognition deficits bearing this divergence of processes. To address visuospatial functions, we have used the JLOT, a test widely described as strictly representative of spatial orientation (Lezak et al., 2012). This test is recommended by the MDS guidelines to detect visuospatial dysfunctions (Litvan et al., 2012). In agreement with previous reports, in our second study, we found significant differences between healthy subjects, PD patients with normal cognition and PD patients without MCI in JLOT scores. Interestingly, the effect size of these differences was especially high between the two PD patient subgroups. This finding is in agreement with previous reports showing that impairment of spatial orientation is seen in more advanced stages of the disease and in PD patients with worse cognitive performance (Raskin et al., 1990; Levin et al., 1991; Stirk & Foreman, 2015). In our third study, using a repeated-measures linear regression model, in line with our previous findings, we found that healthy subjects differed significantly from PD-MCI in JLOT scores, but not from PD patients without MCI. Given these findings, the JLOT could be considered as a suitable test to address visuospatial functions in PD patients. However, these functions would appear to be impaired more commonly in PD patients with more advanced disease stages and worse cognitive performance.

To date, studies have reached an incredibly detailed description of the highly specialized visuospatial anatomical projections in the human cortex. Visuospatial functions have been widely related to the dorsal 'where/how' stream (Ungerleider & Mishkin, 1982; Milner & Goodale, 2008), that further develops into a parieto-prefrontal pathway devoted to spatial working memory, a parieto-premotor pathway related to spatial navigation, and a parieto-medial temporal pathway, which is implicated in spatial navigation and complex spatial processing (Kravitz et al., 2011). Hypothetically, performance in the JLOT could be considered to be especially related to the integrity of the parieto-premotor and parieto-medial temporal pathways, which are broadly related to dorsal regions of the premotor cortex, the ventral and medial portions of the intraparietal area, the medial superior temporal region, the parahippocampal formation and the posterior cingulate and retrosplenial cortices. In our second study, we reported the neuroanatomical correlates of JLOT performance in PD patients. We found that JLOT scores were related to predominant-

ly posterior regions involving bilateral medial and superior temporal sulci, ventral parietal, posterior cingulate and medial anterior regions, as well as left fusiform and lingual gyri. Conversely, white matter microstructure involvement was located in widespread anterior and posterior tracts. In our third study, in agreement with the neuropsychological results obtained, we found no significant relationship between changes over time in JLOT scores and cortical thinning in PD patients without MCI, whereas PD-MCI patients showed significant correlations between cortical thinning in bilateral superior and medial temporal sulci, the temporal pole and lingual and fusiform gyri, as well as left ventral parietal regions. In agreement with our findings, previous reports addressing the neuroanatomical correlates (Pereira et al., 2009; Filoteo et al., 2014; Segura et al., 2014) as well as functional neuroimaging studies (Mentis et al., 2002; Baggio et al., 2014; Nombela et al., 2014) of strictly visuospatial functions in PD have stated a relationship with atrophy in predominantly parieto-temporal regions. However, the implication of other brain regions, such as the lateral occipital cortex (Filoteo et al., 2014) and the right frontal pole (Segura et al., 2014), has also been described.

To address the impairment of visuoperceptual functions in PD we used the FRT, a neuropsychological test equally described to be representative of visuoperceptual performance because it involves the perception of faces but not their position in space (Lezak et al., 2012). Previous neuropsychological studies have reported impaired FRT performance in PD patients (Raskin et al., 1990; Levin et al., 1991; Galtier et al., 2014), and some have stated that these deficits, in contrast to visuospatial impairment, appear early in the disease course (Levin et al., 1991). In our second study, we reported significant FRT score differences between healthy subjects, PD patients with normal cognition and PD-MCI patients. The effect size for these differences was especially high for the comparison between healthy subjects and the PD-MCI group. In our third study, using a repeated-measures linear regression model, significant differences were only found between healthy subjects and PD-MCI patients. These findings stand in contrast to those previously reported, since controls and PD patients with normal cognition appear to have similar scores in visuoperceptual measures. Interestingly, in our studies, we have seen a similar relationship between visuospatial and visuoperceptual measures and clinical disease variables, such as age at disease onset and functional status (see Annex 2). In our second study, we reported an absence of neuroanatomical correlates for the FRT. In our third study, on the other hand, PD patients with normal cognition showed a significant relationship between changes in FRT scores and cortical thinning in the left lateral occipital cortex. Additionally, PD-MCI patients exhibited a significant correlate located in the left lingual gyrus. Conversely, in our second study we reported that FRT correlated significantly with white matter microstructure integrity loss in widespread tracts. Previous cross-sectional neuroanatomical as well as functional neuroimaging studies have reported an implication of the occipital cortex and the lingual gyrus in visuospatial impairment (Abe et al., 2003; Ishioka et al., 2011; Pereira et al., 2009; Nishio et al., 2017).

Moreover, other brain regions have been related to these deficits, such as the fusiform gyrus, parahippocampus, and inferior frontal gyrus (Pereira et al., 2009).

We further addressed visual perception and spatial judgments in PD with the use of VFDT, a test that involves the perception of geometric shapes as well as their position in space. In a cross-sectional design, we found no significant differences between healthy subjects, PD patients with normal cognition and PD-MCI patients; however, using a repeated-measures linear regression model, we observed that PD patients with MCI differed significantly from healthy subjects in VFDT scores. Cross-sectional neuroanatomical correlates were limited to the left precuneus and white matter microstructure alteration in the corpus callosum. Our findings are in contrast with those seen in previous studies reporting a relationship with bilateral temporo-parietal regions (Pereira et al., 2009; Baggio et al., 2014; Segura et al., 2014), the superior occipital cortex and middle and inferior frontal gyri (Pereira et al., 2009).

Lastly, we included the SDMT among the tests used in our studies, because of its properties in measuring the appreciation of changes in orientation and visuomotor working memory, as well as its reported relationship with posterior cortical regions (Forn et al., 2009). In our second study, we found that performance in the SDMT was significant different between PD-MCI patients, PD patients with normal cognition and healthy subjects. In our third study, in agreement with previous longitudinal reports (Caspell-Garcia et al., 2017), we found that deterioration in SDMT differed significantly between PD-MCI subjects and controls. Cross-sectional correlational studies evidenced a significant relationship with predominantly posterior regions, involving bilateral temporo-parietal areas and the precuneus, and widespread alteration of white matter microstructure. Evolution of SDMT scores revealed significant correlates with cortical thinning in bilateral superior and medial temporal regions.

Although a certain overlap between the described neuroanatomical cortical regions involved in the subspecialized projections of visuospatial and visuoperceptual functions and the reported cortical thinning correlates can be seen, we cannot assume the existence of a complete dissociation of these functions and projections in PD patients measured with these tests. Interestingly, we have also seen that visuospatial and visuoperceptual tests exhibit high intercorrelations in PD patients, but not in healthy subjects (see Annex 2). This fact could be due to several reasons, to name a few, to the possibility that other cognitive processes interfere in the tests' performance or the existence of specific mechanisms occurring in PD, or that the neuroanatomical abnormalities in regions not reported to be specifically related to these projections could take place concomitantly. Moreover, these regions could be acting more as parts of a complex visual processing network (de Haan & Cowey, 2011; Kravitz et al., 2013), in which certain brain areas might be holding a distinctly relevant role in this network organization.

The absence of a significant group-by-time interaction in the performance of certain tests, in contrast to the neuroanatomical correlates previously described, suggests the existence of a structural degeneration specific of a subgroup of PD patients, which might not evolve linearly, since variability in the evolution of neuropsychological scores appears to be enough to account for the emergence of specific neuroanatomical correlates in a longitudinal basis. Similarly, the existence of functional compensations and reorganization in activity patterns could in turn be affecting the relationship between anatomical measures and visuospatial and visuoperceptual performance in PD. Previous functional studies that have addressed the changes occurring in PD found that PD-MCI patients exhibit significant changes in resting state connectivity, connectivity reductions predominantly in long-range connections and an increase in local interconnectedness that are significantly related to performance in visuospatial and visuoperceptual tests (Baggio et al., 2014; Baggio et al., 2015). These findings may indicate that functional changes occur prior to structural degeneration.

Some correlational studies have also approached the neuroanatomical correlates of tests considered relative to other cognitive domains. Although findings from cross-sectional reports suggest the absence of a clear divergence of correlational patterns and, instead, a certain overlap between the areas related to specific tests (Pereira et al., 2014; Segura et al., 2014), the executive domain seems to involve more extensive regions of the anterior cortex. However, to further understand the relationship between these cognitive deficits and neuroanatomical degeneration, longitudinal approaches would be more suitable. Volumetric studies associated the decline in executive functions with bilateral frontal regions (Lee et al., 2014; Wen et al., 2015); Nonetheless, to date, there are no reports available regarding the direct relationship between the evolution of surface-based cortical thickness and other neuropsychological domains in PD. In our third study, we reported that changes in Stroop color-word test scores correlated significantly with cortical thinning in dorsal anterior regions in PD patients without MCI, and in widespread posterior and anterior areas in PD-MCI patients. Similarly, changes in TMT-A scores correlated significantly with a widespread pattern of cortical thinning in PD-MCI patients. This finding is in contrast with the predominantly posterior longitudinal correlates of SDMT, which appear to share a certain similarity with the pattern reported above for visuospatial performance.

The tests suggested in the guidelines for the diagnosis of MCI in PD should have robust psychometric properties, but also need to be chosen based on their neuroanatomical and neurofunctional substrates, similar to the procedures followed in other neurodegenerative diseases (Sorbi et al., 2012). This more elaborate strategy for test selection could help reduce excessively time-consuming neuropsychological batteries that, while useful in research, do not appear to be suitable for a clinical setting. Under this perspective, our findings could be considered as relevant information for the selection of tests to be incorporated in the neuropsychological battery designed for the diagnosis of PD-MCI.

STRUCTURAL DEGENERATION IN PARKINSON'S DISEASE

We have also aimed to describe the structural degeneration that PD encompasses in gray matter structures and white matter tracts. In all the studies presented in this thesis, we have evidenced that PD patients exhibit signs of increased brain atrophy through neuroimaging measures, namely, mean cortical thickness, cortex volume and lateral ventricular system volume, with regards to healthy subjects. These signs of atrophy are especially marked in patients who fulfill criteria for MCI (see also **Annex 2**), who also exhibit a significantly more pronounced rate of atrophy over time.

The vertex-wise surface-based approaches used in our studies contributed to understand which areas were mostly implicated in these differences. In our first study, we found that PD patients differed from healthy subjects in cortical thickness of bilateral posterior regions, involving extensive parieto-temporal areas, the precuneus and the lateral occipital cortex. We further analyzed the structural gray matter differences between PD patients, subdivided according to cognitive status, and healthy subjects. In our second study, we showed that PD patients with normal cognition did not have significant differences compared with healthy subjects. However, PD-MCI patients exhibited an extensive pattern of cortical thickness reductions that involved widespread bilateral posterior temporo-parietal regions, as well as anterior cortices. These results suggest that the differences previously seen between PD patients and healthy subjects are mainly explained by the cortical degeneration of PD patients with MCI. In our third study, we aimed to analyze the differences in cortical thinning over time in PD. Importantly, we only found significant differences in cortical thinning between the two PD patient groups, located in parieto-temporal cortices. This result could be due to the possible natural evolution of the sample of healthy subjects. Nonetheless, it seems clear that a differential structural gray matter substrate can be found between PD patients without MCI and those diagnosed with MCI. In agreement with previous cortical thickness studies, the gray matter pattern of degeneration commonly described to emerge in PD is related to the involvement of posterior cortices, especially in those patients with MCI (Pagonabarraga et al., 2013; Zarei et al., 2013; Pereira et al., 2014; Segura et al., 2014; Uribe et al., 2016). Albeit the considerable shortage of studies of longitudinal cortical changes in PD, previous findings with large cohorts also evidenced the involvement of posterior brain regions (Hanganu et al. 2014; Mak et al., 2015).

Interestingly, some reports have suggested the existence of loss of white matter integrity detected by DTI prior to gray matter involvement in PD (Hattori et al., 2012; Agosta et al., 2014; Duncan et al., 2016). These results are in contrast with those described in our second study, in which white matter differences between healthy subjects, PD patients with normal cognition and PD patients with MCI were limited to an area of the posterior corpus callosum. Of note, these studies also used TBSS to address white matter microstructure integrity, but gray matter atrophy was assessed with VBM analyses. Surface-based cortical thickness measures reportedly have a higher sensitivity to detect subtle changes in cortical gray mat-

ter (Fischl & Dale, 2000). Therefore, the absence of differences in cortical structures could be due to the techniques used. Furthermore, in some of these studies, cognitive impairment was not assessed according to the MDS criteria (Hattori et al., 2012). Further longitudinal multimodal studies using state-of-the-art neuroimaging techniques could shed light on the development of these changes.

CONCLUDING REMARKS

Overall, our results demonstrate that visual cognition is clearly impaired in PD, and the tests commonly used in its neuropsychological assessment are suitable tools, since they reflect gray and white matter degenerative changes. Thus, cognitive decline in PD has detectable brain structural bases.

Furthermore, our results may have translational implications regarding clinical practice. The relationship between the progression of visuospatial and visuoperceptual functions in PD and thinning of posterior temporo-parietal and occipital cortices could contribute to validate the use of these tests in clinical trials, with the aim of monitoring clinical interventions regarding the progression of cortical degeneration in PD.

The short period of follow-up of patients was a limitation of the studies included in this thesis, because it precluded the detection of the predictive value each test might have to detect conversion to dementia. In the future, the combination of structural and functional MRI data may help to characterize subtle changes, which may be valuable tools for the therapies addressed to stop or slow the degenerative process in PD.

CHAPTER 6.

CONCLUSIONS

Through the studies included in this thesis, we can conclude that:

1) Parkinson's disease patients exhibit impairment in visuospatial, visuoperceptual and visuoconstructive functions, which is more pronounced in patients with mild cognitive impairment. Among the tests selected for this assessment, Pentagon Copying and Symbol Digit Modalities tests are the most suitable to be used in clinical practice because they showed the ability to differentiate between patients and controls, and between Parkinson's disease patients with and without mild cognitive impairment.

2) Parkinson's disease involves brain atrophy detectable by global and regional MRI volumetric measures, and patients classified as having mild cognitive impairment exhibit more prominent atrophy than those with normal cognition. Brain atrophy in Parkinson's disease with mild cognitive impairment mainly involves temporo-parietal cortical regions.

3) In agreement with the gray matter reductions observed, Parkinson's disease patients show white matter microstructural changes in the posterior corpus callosum.

4) Tests measuring visuospatial, visuoperceptual and visuoconstructive functions had differential patterns of gray matter correlates, but always involving regions of lateral and medial posterior cortices. However, we did not observe the dissociation between dorsal and ventral streams that would be expected according to the neuropsychological classification of visuospatial and visuoperceptual tests.

5) Visuospatial, visuoperceptual and visuoconstructive impairment is related to diffuse abnormalities of white matter microstructure, involving intra- and interhemispheric regions.

6) In comparison with Parkinson's disease patients without mild cognitive impairment, cognitively impaired subjects show cortical thinning over time in temporo-parieto-occipital regions.

7) The progression of cortical thinning in bilateral posterior regions explains the decline in visuospatial, visuoperceptual and visuoconstructive functions.

ABSTRACT

Parkinson's disease is a common neurodegenerative disorder that manifests with a wide range of non-motor symptoms. Among them, cognitive impairment is present in a high proportion of patients, having a great impact on quality of life and prospective outcome. Initiatives have aimed to describe the features of cognitive impairment in Parkinson's disease and, although findings are not conclusive, the visuospatial and visuoperceptual neuropsychological domain can be impaired early in the disease course, and these deficits sustain a relationship with disease severity and progression. Moreover, posterior cortically-based deficits are prognostic markers of the emergence of dementia in Parkinson's disease. Hence, their early identification is an important undertaking in clinical settings.

In our studies, we have investigated visuospatial and visuoperceptual impairment in Parkinson's disease patients, as well as its evolution over time. We assessed 121 Parkinson's disease patients and 41 healthy matched control subjects, applying well-validated and widely used neuropsychological tests, and followed the sample for an approximate period of four years. We identified the neuroanatomical substrates of these deficits using surface-based cortical thickness measures and tract-based spatial statistics for white matter microstructure integrity parameters.

Parkinson's disease patients exhibit a posterior temporo-parieto-occipital pattern of cortical thinning that is related to the impairment of visual cognition processes; however, these correlates do not appear to follow the classical dissociation described in the current literature of the healthy visual system pathways. In Parkinson's disease patients with mild cognitive impairment, this degeneration is more pronounced and widespread, and follows a posterior-anterior pattern of cortical thinning. Moreover, after a four-year follow-up, Parkinson's disease patients with mild cognitive impairment exhibit a differential pattern from cognitively normal patients, that involves temporo-parieto-occipital regions, and is related to changes over time in visuospatial and visuoperceptual measures. Conversely, white matter microstructure appears altered in the posterior corpus callosum in Parkinson's disease, whereas visuospatial, visuoperceptual and visuoconstructive measures exhibit widespread long- and short-range correlates with white matter degeneration.

Our results give support to the hypothesized relationship between impairment in visuospatial and visuoperceptual functions and the degeneration of predominantly posterior cortices over time, establishing the structural basis of cognitive decline in Parkinson's disease. These findings could have translational implications and contribute to the validation of the use of these tests in clinical as well as research settings. Further research involving multimodal approaches of structural and functional neuroimaging techniques in longitudinal settings could shed light on the characterization of the neuroanatomical substrate of cognitive decline in Parkinson's disease.

RESUM

La malaltia de Parkinson és un trastorn neurodegeneratiu d'elevada incidència que es manifesta amb una gran varietat de símptomes no-motors. Entre els sintomes no-motors, el deteriorament cognitiu és present en una elevada proporció del pacients i produeix un gran impacte en la seva qualitat de vida i el seu pronòstic. La caracterització del deteriorament cognitiu en la malaltia de Parkinson és un important repte de recerca i, tot i que existeix una elevada disparitat entre les troballes actuals, els dèficits visoespacials i visoperceptius es poden considerar com un domini específic que pot mostrar alteracions de forma primerenca i mostrar una relació amb la gravetat de la malaltia i la seva progressió. Els dèficits originats en el còrtex posterior es consideren un marcador pronòstic de l'aparició de demència a la malaltia de Parkinson, fet que posa de relleu la importància de la seva identificació primerenca en el maneig clínic.

En els nostres estudis, hem identificat i catacteritzat el deteriorament visoespacial i visoperceptiu a la malaltia de Parkinson, així com la seva evolució en el temps. Hem recollit dades de 121 pacients i 41 controls sans aparellats segons variables sociodemogràfiques, tot aplicant tests validats i àmpliament utilitzats en l'àmbit clínic. Hem seguit la seva evolució per un període aproximat de quatre anys. Per tal de identificar els substrats neuroanatòmics d'aquests dèficits, hem utilitzat mesures de gruix cortical basades en l'estimació de superfícies, i mesures adreçades a l'avaluació de la integritat de la microestructura de la substància blanca.

Els malalts de Parkinson presenten un patró de deteriorament cortical localitzat en regions posteriors temporo-parieto-occipitals, que està relacionat amb els dèficits observats en les funcions visoespacials i visoperceptives. Tot i així, aquests correlats no segueixen la dissociació descrita a la literatura clàssica sobre les vies del sistema visual en subjectes normals. En pacients amb deteriorament cognitiu lleu, els patrons d'atrofia cerebral són mes pronunciats i generalitzats, tot seguint un patró posterior-anterior de pèrdua del gruix cortical. El seguiment realitzat ens ha permès identificar un patró diferencial de degeneració en els pacients amb deteriorament cognitiu lleu, localitzat principalment en la regió temporo-parieto-occipital i que està relacionat amb la pèrdua de funcions visoespacials i visoperceptives. De forma coherent, l'alteració de la microestructura de la substància blanca es localitza a la part posterior del cos callós. Ara bé, la pèrdua de funcions visoespacials, visoperceptives i visoconstructives es relaciona amb la pèrdua de la integritat de regions cerebrals més extenses, que impliquen fascicles intra- i interhemisfèrics.

Els resultats evidencien la relació entre el deteriorament de les funcions visoespacials i visoperceptives i la degeneració neuroanatòmica predominantment del còrtex posterior. Aquestes troballes contribueixen a establir la base estructural del deteriorament cognitiu en la malaltia de Parkinson i poden tenir implicacions translacionals, ja que contribueixen a la validació de l'ús d'un conjunt de tests en el maneig clínic i

en termes de recerca. En el futur, la combinació d'estudis multimodals estructurals i funcionals de caire longitudinal poden contribuir en la caracterització del substrat neuroanatòmic i neurofuncional del deteriorament cognitiu a la malaltia de Parkinson i determinar-ne el valor pronóstic d'evolució a demència.

ANNEX 1

Supplementary Table 1. JLOT error type analyses by Ska et al. (1990).

QO1	An oblique line is incorrectly identified as another oblique line and is different by only one spacing
QO2	An oblique line is incorrectly identified as another oblique line and is different by two or three spacings
QO3	Both oblique lines are displaced one or two spacings in the same direction, and maintain the initial spacing
QO4	Both oblique lines are displaced without maintaining the initial spacing
V	The vertical line is incorrectly identified as an oblique or horizontal line
H	A horizontal line is incorrectly identified as an oblique or vertical line
VH	The vertical line and one of the horizontal lines are incorrectly identified
IQO	An oblique line is displaced from the original quadrant to the other quadrant
IQOV	An oblique line is displaced from the original quadrant to the other quadrant, and the vertical line is incorrectly identified
IQOH	An oblique line is displaced from the original quadrant to the other quadrant, and a horizontal line is incorrectly identified

ANNEX 2

Visuospatial and visuoperceptual impairment and its relation to global atrophy in Parkinson's disease

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Visuospatial and visuoperceptual impairment in relation to global atrophy in Parkinson's disease*

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Parkinson's disease (PD) patients differed from controls of similar age in visuospatial and visuoperceptual functions at diagnosis moment, and these deficits have been shown to be neuropsychological markers of evolution to dementia. The aim of this study was to relate these dysfunctions with measures of brain. The sample of this study consisted of 92 PD patients and 36 healthy subjects matched by age, sex and education. All subjects were evaluated with Judgment of Line Orientation, Visual Form Discrimination and Facial Recognition Tests *and magnetic resonance imaging at 3 Tesla. We found significant differences between patients and controls in all three tests and in the mean of cortical thickness, gray matter volume and ventricular system. All visuospatial and visuoperceptual tests correlated with the measures of global atrophy suggesting that they are reflecting the brain degeneration associated to PD.*
Keywords: *Parkinson's disease, visuospatial/visuoperceptual, MRI, cortical thickness, brain atrophy.*

Alteraciones visuoespaciales y visuoperceptivas en la enfermedad de Parkinson y su relación con parámetros de atrofia global

Los pacientes con enfermedad de Parkinson (EP) comparados con controles de similar edad muestran alteraciones visuoespaciales y visuoperceptivas desde el momento del diagnóstico, y se ha demostrado que estas alteraciones

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actúan como marcadores neuropsicológicos de la evolución a demencia. El objetivo de este estudio es relacionar estas alteraciones con las medidas globales de atrofia cerebral. La muestra consta de 92 EP y 36 sujetos sanos emparejados por edad, sexo y educación. Todos los sujetos fueron evaluados mediante el Judgment of Line Orientation, Visual Form Discrimination y Facial Recognition Test *y se obtuvieron datos de neuroimagen estructural con un aparato de Resonancia Magnética de 3 tesla. Se observaron diferencias entre los pacientes y los controles en los tres tests usados y en las medidas de grosor cortical total, volumen de sustancia gris y sistema ventricular. Todos los tests visuoespaciales y visuoperceptivos correlacionaron con medidas de atrofia global, lo cual sugiere que son indicadores útiles de la degeneración cerebral asociada a la EP.*

Palabras clave: *Enfermedad de Parkinson, imágenes de resonancia magnética, grosor cortical, alteraciones visuoespaciales y visuoperceptivas, atrofia cerebral.*

Introducción

Parkinson's disease (PD) is considered to be one of the most common neurological diseases associated with aging. The prevalence ranges from 1-3% in the general population (Galvin, Pollack, & Morris, 2006; Riedel *et al.*, 2008). Classically, PD was regarded as a motor disease, but it is now recognized as a systemic neurodegenerative illness. Cognitive dysfunction and impairment as well as mood disorders and apathy have been increasingly viewed as important symptoms that accompany the disease even in preclinical stages. It has been stated that, after 20 years, 80% of PD patients evolve to dementia, whereas only 25% of them are recognized by clinicians in routine daycare (Svenningsson, Westman, Ballard, & Aarsland, 2012). The disease may course with impaired executive function (Williams-Gray, Foltynie, Brayne, Robbins, & Barker, 2007; Williams- Gray *et al.,* 2009; Aarsland *et al.,* 2009), visuospatial and visuoperceptual dysfunctions (Williams-Gray *et al*., 2007-2009; Aarsland, Brønnick, Larsen, Tysnes, & Alves, 2009) and verbal memory impairment (Aarsland *et al.,* 2009) but relatively spared language, except for semantic fluency (Williams-Gray *et al*., 2007; 2009).

Visuospatial and visuoperceptual deficits can be seen early in the disease course, but their main interest is their power to predict subsequent evolution to dementia (Williams-Gray *et al.,* 2009; Svenningsson *et al.,* 2012). Several studies have assessed the differential impairment of these functions in subcortical dementias, and PD has been stated to have a distinct pattern of alteration compared with other types of dementias, such as Alzheimer's disease (Ala, Hughes, Kyrouac, Ghobria, & Elble, 2001; Cormack, Aarsland, Ballard, & Tovée, 2004; Tiraboschi *et al.,* 2006; Saka & Elibol, 2009). For this reason, they have been regarded as screening tools for cognitive impairment and evolution to dementia in clinical settings (Williams-Gray *et al.,* 2009; Helmes, 2013).

Previous neuroimaging research has focused on describing the progress of global atrophy in PD patients using total gray matter and ventricular measures. Gray matter changes have been related to cognitive decline and dementia (Ibarretxe-Bilbao *et al.*, 2012; Zarei *et al.*, 2013; Camicioli *et al.,* 2011) and recent research has demonstrated that gray matter decrease holds a high discriminant power in accurately identifying demented PD patients (Zarei *et al.*, 2013). Nevertheless, progressive gray matter reductions have already been described in early stages of the disease (Ibarretxe-Bilbao *et al.*, 2012). Gray and white matter losses are related to enlargement of the ventricular system in PD patients. Apostolova *et al.* (2010) found that left and right ventricles were significantly larger in PD patients with dementia compared with healthy subjects and their non-demented peers. Also, it has been shown that ventricular volumes are significantly increased in PD patients with MCI and correlate with memory performance (Dalaker *et al.*, 2011).

In sum, visuospatial and visuoperceptual impairment and atrophy measures have been associated with cognitive decline and exhibit a predictive value in the evolution to dementia, but hitherto and to our knowledge, the relationship between these two measures has not been studied. Thus, the aim of this study is to assess the neuropsychological performance in these cognitive functions and its relation with global structural changes in a large sample of non-demented PD patients.

Methods

Subjects

This study included 121 patients, recruited from an outpatient movement disorders clinic (Parkinson's Disease and Movement Disorders Unit, Service of Neurology, Hospital Clínic, Barcelona, Spain), and 49 healthy subjects, recruited from the Institut de l'Envelliment (Barcelona, Spain). Controls were matched for age, sex and years of education to their patient peers. This study was approved by the institutional ethics committee; all subjects agreed to participate voluntarily and written informed consent was obtained after full explanation of the procedures.

Inclusion criteria for patients consisted of meeting the diagnostic criteria for PD established by the UK PD Society Brain Bank (Daniel & Lees, 1993). The following exclusion criteria were considered: [1] presence of dementia according to the Movement Disorders Society criteria (Dubois, Burn, Goetz, & Aarsland; 2007), [2] Hoehn and Yahr scale score ≥3, [3] young-onset PD, [4] presence of psychiatric and/or neurologic comorbidity, [5] low IQ score (scaled score score <8 on the Vocabulary subtest from the WAIS-IV -Wechsler Adults Intelligence Scale), [6] Mini-Mental State Examination (MMSE) score <24, [7] claustrophobia, [8] pathological findings non compatible with PD in MRI and [9] MRI artifacts. (demographic data of patients and healthy controls are summarized in table 1).

TABLE 1. DEMOGRAPHIC AND CLINICAL DATA OF THE SAMPLE.

Demographics	*Patients (n=92)*	*Controls (n=36)*	t^a, χ^b	*p value*
Age	63.98 ± 11.10	63.36 ± 10.53	-0.287[a]	0.775
Sex (male/female)	37/55	19/17	0.521[b]	0.300
Education, years	10.61 ± 5.36	11.36 ± 4.34	0.750[a]	0.454
Age at onset	56.04 ± 12.19			
Evolution, years	8.39 ± 5.91			
Patients with hallucinations	n=19			

Note: Values are mean ± Standard Deviation (*SD*); [a]Student *t* test statistics; [b]Chi squared statistics.

Neuropsychological Assessment

The neuropsychological assessment comprised the evaluation of all cognitive functions, and the assessment of visuospatial and visuoperceptual functioning was obtained through the following neuropsychological tests: [1] Benton's Judgment of Line Orientation (JLO; Benton, Hannay, & Varney; 1975), [2] Benton's Visual Form Discrimination (VFD; Benton, Sivan, & Hamsher; 1994), and [3] Benton's Facial Recognition (FRT; Benton *et al.*,1994) tests.

Global measures of atrophy analysis

FreeSurfer software (version 5.1; available at http://surfer.nmr.harvard.edu) was used to assess global brain atrophy. Along the process, cortical surface 3D model of cortical thickness (CTh) is created using intensity and continuity information, as described in detail by Fischl & Dale (2000). Independent steps are performed in the initial preprocessing of images for each subject: removal of non-brain tissue, automated Talairach transformation, intensity normalization, tessellation of the gray matter / white matter boundary, automated topology correction and surface deformation to optimally place the gray matter / white matter and gray matter / cerebrospinal fluid (CSF) boundaries. The resulting representation of CTh is calculated as the distance between tissue boundaries. All surface models in our study were visually inspected for accuracy and were carefully manually corrected if necessary.

Segmentation of brain volume and cortical thickness parcellations were obtained based on an automatic procedure included in Freesurfer 5.1 (Desikan *et al.*,

2006; Fisch *et al.*, 2002). Variables used in order to calculate global measurement of atrophy were: bilateral mean thickness, total cortex volume, total gray matter volume, and the lateral ventricular system (left and right lateral ventricles).

Statistical Analyses

Statistical analyses of visuospatial and visuoperceptual functions, global atrophy, and neuropsychological and clinical variables were carried out using the statistical package PASW-20 (2011; SPSS, Inc., Chicago, IL). Z scores were obtained in order to assess patients' performance in visuospatial and visuoperceptual tests. Clinical and demographical variables and brain atrophy group differences were analyzed with Student *t* test statistics or ANCOVA in case of volumetric global measures of atrophy. Cohen's *d* was used to measure effect size in clinical and demographical variables (Ellis, 2009). Correlations analyses were performed among visuospatial and visuoperceptual tests and those with global atrophy measures. All the volumetric analyses were controlled for intracranial volume (ICV).

Results

Clinical and demographical analyses

Raw scores significantly differed between PD patients and healthy subjects in MMSE, NPI (Cumming's Neuropsychiatric Inventory) and BDI (Beck Depression Inventory-II), and all effect sizes indicated a large effect (see table 2). Age and education showed correlations with visuospatial and visuoperceptual tests, which were higher in all cases for PD patients than for controls. The highest correlations were seen between age and VFD, and education and FRT.

TABLE 2. CLINICAL DATA FOR PATIENTS AND CONTROL SUBJECTS.

	Patients	*Controls*	*t*	*p value*	*d*[a]
MMSE	29.05 ± 1.11	29.69 ± 0.47	4.581	.0001	.75[b]
NPI	5.67 ± 7.39	1.68 ± 3.13	-4.124	.0001	.70[a]
BDI	10.87 ± 6.15	6.15 ± 5.64	-2.845	.0001	.80[a]
UPDRS-III	17.60 ± 10.92				
H&Y	1.89 ± 0.57				
LEDD	803.70 ± 494.18				

Note: MMSE: Mini-Mental State Examination; NPI: Cummings' Neuropsychiatric Inventory; BDI: Beck Depression Inventory; UPDRS-III: Unified Parkinson's Disease Rating Scale-III; H&Y: Hoehn & Yahr; LEDD: Levodopa Equivalent Daily Dose.
[a] Cohen's *d* statistics (Group 1=Patients/Group 2=Control subjects); [b]Group 1=Control subjects/Group 2=Patients.

Clinical variables showed significant correlations with visuospatial and visuoperceptual tests, except for JLO and VFD with LEDD (Levodopa Equivalent Daily Dose) and healthy subjects with MMSE. However, visuospatial and visuoperceptual performance was still significantly different between patients and controls when controlling the possible effect of these variables (table 3 and table 4).

TABLE 3. PEARSON'S *R* CORRELATIONS AMONG DEMOGRAPHICAL VARIABLES AND VISUOSPATIAL AND VISUOPERCEPTUAL TESTS.

	Age		***Education***	
	HC	*PD*	*HC*	*PD*
JLO	-.471**	-.502**	.467**	.485**
VFD	-.243	-.416**	.329*	.514**
FRT	-.498**	-.432**	.117	.390**

Note: JLO: Judgment of Line Orientation; VFD: Visual Form Discrimination; FRT: Facial Recognition Test; IQ: Intelligence Quotient; HC: Healthy Controls; PD: Parkinson's Disease; **p<0.05.

TABLE 4. PEARSON'S *R* CORRELATIONS AMONG CLINICAL VARIABLES AND VISUOSPATIAL AND VISUOPERCEPTUAL TESTS.

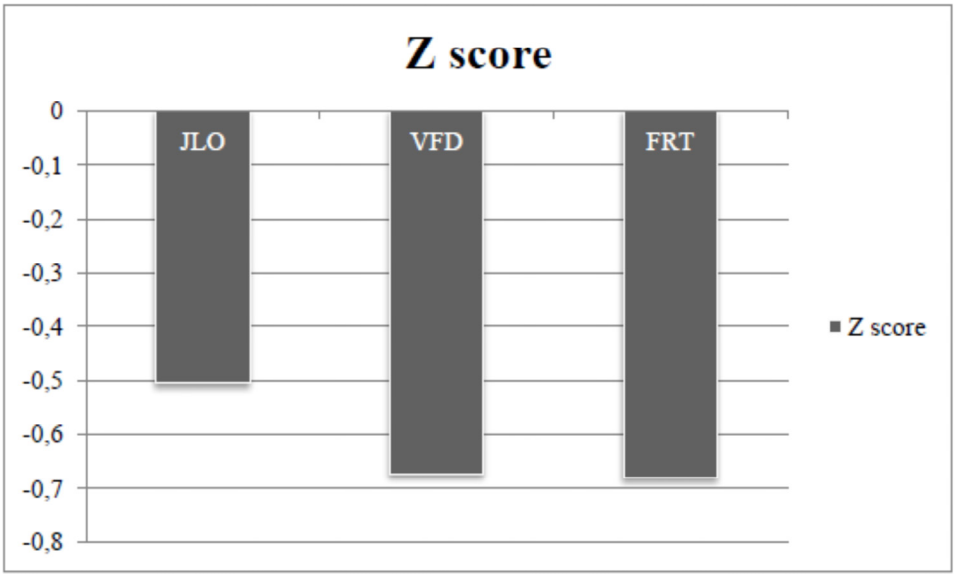
	Age at onset	***H&Y***	***MMSE***		***LEDD***
	PD	*PD*	*HC*	*PD*	*PD*
JLO	-.348**	-.277*	-.132	.405**	-.197
VFD	-.275**	-.238*	.130	.279**	-.061
FRT	-.221*	-.191	.235	.487**	.303**

Note: JLO: Judgment of Line Orientation; VFD: Visual Form Discrimination; FRT: Facial Recognition Test; H&Y: Hoehn & Yahr; MMSE: Mini-Mental State Examination; LEDD: Levodopa Equivalent Daily Dose; HC: Healthy Controls; PD: Parkinson's Disease; *p<0.05; **p<0.01.

Visuospatial and visuoperceptual performace

Visuospatial and visuoperceptual tests showed significant differences between patients and healthy subjects, indicating that patients performed significantly worse than controls. VFD *(z*=-0.671) and FRT *(z*=-0.678) showed the greatest *z* scores, corresponding to a moderate difference between PD patients and controls, followed by JLO *(z*=-0.504; see figure 1). Correlations between visuospatial and visuoperceptual tests (JLO, VFD and FRT) showed that all tests exhibit high correlations between them in PD patients, but not in healthy subjects (see table 5). The highest

correlations were seen between JLO and FRT, followed by JLO and VFD and, lastly, VFD and FRT.



Note: JLO: Judgment of Line Orientation; VFD: Visual Form Discrimination; FRT: Facial Recognition Test.

Figure 1. Graphic representation of visuospatial and visuoperceptual z scores.

TABLE 5. PEARSON'S *R* CORRELATIONS BETWEEN VISUOSPATIAL AND VISUOPERCEPTUAL TESTS.

	JLO		***VFD***		***FRT***	
	HC	*PD*	*HC*	*PD*	*HC*	*PD*
JLO	1	1	.237	.467**	.260	.493**
VFD	.237	.467**	1	1	.143	.423**
FRT	.260	.493**	.143	.423**	1	1

Note: JLO: Judgment of Line Orientation; VFD: Visual Form Discrimination; FRT: Facial Recognition Test; HC: Healthy Controls; PD: Parkinson's Disease; **p<0.01

Global atrophy measures

Mean group differences in global atrophy analysis showed significant decreases in PD patients (see table 6) in the left lateral ventricular system, cortex volume, total gray matter volume and mean cortical thickness.

Global atrophy correlations analyses (see table 7) showed, except for JLO and right inferior lateral ventricle, significant results between JLO, VFD and FRT and mean thickness bilaterally, lateral ventricular system, total gray matter volume and cortex volume.

TABLE 6. MEAN VALUES AND STANDARD DEVIATIONS OF GLOBAL ATROPHY MEASURES FOR PD PATIENTS AND HEALTHY SUBJECTS. MEAN DIFFERENCES BETWEEN GROUPS ASSESSED WITH STUDENT *T* TEST STATISTICS OR F IN ANCOVA.

	Patients		***Controls***		t^c/F
	Mean	*SD*	*Mean*	*SD*	
Mean Thickness[a]	2.44	0.11	2.49	0.09	2.610[c]**
Cortex Volume[b]	428325.38	48131.76	442560,56	292443.84	5.028*
Total Gray Matter Volume[b]	601545.31	64185.97	611615.79	54335.30	2.027
Left Lateral Ventricle[b]	12783.52	7770.29	9886.78	4422.71	4.452*
Left Inferior Lateral Ventricle[b]	512.58	354.91	372	262.28	4.396*
Right Lateral Ventricle[b]	11549.65	6464.13	9388.94	4141.44	3.270
Right Inferior Lateral Ventricle[b]	383.96	264.12	328.25	181.67	1.132
Total Ventricular System[b]	25229.71	14297.25	19975.97	8436.63	4.219*

Note: [a] All values are mm. [b] All values are mm^3. *SD*: Standard Deviation. [c] *t*: Student t test statistics. *F*: ANCOVA (volumetric measures of global atrophy were controlled by total intracranial volume). *p<0.05 **p<0.01

TABLE 7. PEARSON'S *R* CORRELATIONS BETWEEN VISUOSPATIAL AND VISUOPERCEPTUAL TESTS AND GLOBAL MEASURES OF ATROPHY.

	Test		
	JLO	***VFD***	***FRT***
	r	*r*	*r*
Mean Thickness	.294**	.226*	.314**
Cortex Volume	.402**	.304**	.269**
Total Gray Matter Volume	.411**	.282**	.303**
Left Lateral Ventricle	-.224*	-.257**	-.316**
Left Inferior Lateral Ventricle	-.184*	-.253**	-.280**
Right Lateral Ventricle	-.296**	-.305**	-.368**
Right Inferior Lateral Ventricle	-.151	-.190*	-.284**
Total Ventricular volume	-.266**	-.290**	-.354**

Note: JLO: Judgment of Line Orientation; VFD: Visual Form Discrimination; FRT: Facial Recognition Test. *p<0.05; **p<0.01.

Discussion

In this study, we have shown that PD patients had significantly lower performance in Benton's tests than healthy subjects, and they exhibited significant correlations with measures of global atrophy and clinical variables. Thus, these results suggest that visuospatial and visuoperceptual performance reflects the structural deterioration that PD patients show from early stages of the disease.

Previous studies have shown that visuospatial and visuoperceptual dysfunctions are already present in non-demented PD patients (Foltynie, Brayne, Robbins, & Barker, 2004; Muslimovic, Post, Speelman, & Schmand, 2005; Aarsland *et al.,* 2009; Elgh *et al.,* 2009), and they have been related to gray matter volumetric changes using voxel-based-morphometry (VBM), mainly in posterior cortex and bilateral parietal regions (Pereira *et al.*, 2009), but this relationship has not been studied using screening measures of global atrophy.

From a classical point of view, the visual system has been postulated to be divided into two streams (Ungerlieder & Mishkin, 1982; Goodale & Milner, 1992), namely, a dorsal pathway, related to spatial aspects of visual processing, and a ventral stream, which refers to the perceptual features of visual processing. However, a recent review has postulated the implication of widespread regions, suggesting the involvement of functional subdivisions, including parieto-premotor, parieto-temporal and parieto-prefrontal pathways. In addition, the authors of this review have highlighted the relevance of common areas between these pathways, and the possible convergence of this information in posterior temporal cortical regions (Kravitz, Saleem, Bake, & Mishkin; 2011). In agreement with this study, we have found that visuospatial and visuoperceptual tests show high intercorrelations, suggesting that they have similar substrates.

Visuospatial and visuoperceptual performance and global atrophy have increasingly been proposed as predictors of cognitive impairment and progression to dementia in PD patients (Apostolova *et al.*, 2011; Williams-Gray *et al.*, 2007-2013; Zarei *et al.*, 2013). Recently, in a 10-year population-based longitudinal study, it has been shown that the pentagon item from MMSE, as a measure of these functions, has a predictive value in the evolution to dementia (Williams-Gray *et al.*, 2013). In addition, Compta *et al.* (2013) also found that visuospatial and visuoperceptual dysfunction was a significant baseline dementia predictor in an 18-month follow up study. The authors also report the evolution of cortical thinning in PD patients to be a biomarker of dementia-risk and disease progression. Our results suggest that Benton's visuospatial and visuoperceptual tests could be regarded as useful screeners of cognitive decline and global brain atrophy. However, longitudinal studies implying both measures are needed to assess their value in the prediction of dementia.

On the other hand, the correlations between neuropsychological tests and age and education were also significant in PD subjects in all cases, with a moderate to

large size effect, indicating that these results could probably be affected by these covariates. Indeed, age (Fjell *et al.*, 2012; Williams-Gray *et al.*, 2013) and education (Cohen *et al.*, 2007) have been reported to have a differential role and an effect themselves on the progression of the disease. Whereas early onset PD patients show more rapid cognitive decline and poorer prognosis (Reid, Hely, Morris, Loy, & Holiday; 2011), advanced age and late PD onset has been associated with higher dementia risk (Dubois, Pillon, Sternic, Lhermitte, & Agid; 1990). Also, higher levels of education have been stated to modulate the cognitive performance in PD (Cohen *et al*., 2007); thus, this set of evidence suggests these two variables could exert a confounding effect in neuropsychological performance and that further research is needed to assess it.

In conclusion, our results indicate that global atrophy is related to visuospatial and visuoperceptual deficits detected by routine clinical practice in the assessment of cognitive performance in non-demented PD patients.

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