UNIVERSITAT DE BARCELONA

Cortical atrophy patterns associated to cognitive impairment in Parkinson's disease

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Cortical atrophy patterns associated to cognitive impairment in Parkinson's disease

Thesis presented by

Carme Uribe Codesal

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Supervised by

Dr Carme Junqué Plaja and Dr Bàrbara Segura Fàbregas

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[…] Tenim a penes
el que tenim i prou: l'espai d'història
concreta que ens pertoca, i un minúscul
territori per viure-la. Posem-nos
dempeus altra vegada i que se senti
la veu de tots solemnement i clara.
Cridem qui som i que tothom ho escolti.
I en acabat, que cadascú es vesteixi
com bonament li plagui, i via fora!,
que tot està per fer i tot és possible.

Miquel Martí i Pol, *Ara mateix*

Als Jordis, la Carme, la Dolors, el
Josep, el Joaquim, el Raül, l'Oriol, la
Meritxell i el Carles. També als que
estan a l'exili, el MHP C. Puigdemont,
la Meritxell, la Clara, el Toni i el Lluis.

Al meu pare, per ser-hi sempre encara
que faci tant que no hi és

Barcelona, 1st March 2019

Dr Carme Junqué Plaja and Dr Bàrbara Segura Fàbregas, professors at the University of Barcelona,

CERTIFY that they have guided and supervised the doctoral thesis entitled 'Cortical atrophy patterns associated to cognitive impairment in Parkinson's disease' presented by Carme Uribe Codesal. They hereby assert that this thesis fulfils the requirements to present her defense to be awarded the title of doctor.

Signatures,

Dr Carme Junqué Plaja

Dr Bàrbara Segura Fàbregas

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Table of Contents

Panels, Tables and Figures

Abbreviations

AD Alzheimer's disease

ADL activities of the daily living

ANOVA analysis of variance

APOE apoliprotein E

ASL arterial spin labeling

BDNF brain derived neurotrophic factor

BNT Boston naming test

COMT catechol-O-methyltransferase

CSF cerebrospinal fluid

CTh cortical thickness

CVLT California verbal learning test

DaTSCAN dopamine transporter imaging

DRS dementia rating scale

DTI diffusion tensor imaging

ESS Epworth's sleepiness scale

FA fractional anisotropy

FAB frontal assessment battery

FDG fluorodeoxyglucose

FWHM full width half maximum

GBA glucocerebrosidase

GBS Gottfries-Brane-Steen scale

GDS geriatric depression scale

GM gray matter

H&Y Hoehn and Yahr

HADS hospital anxiety and depression scale

HC healthy control

HCP-MMP1.0 Human Connectome Project multimodal parcellation version 1.0

HVLT-R Hopkins verbal learning test revised

ICA independent component analysis

IQ intelligence quotient

JLO judgement of line orientation

L-DOPA levodopa, in mg/day

LEDD L-DOPA daily dose, in mg/day

MADRS Montgomery-Asberg depression rating scale

MAO monoamine oxidase

MAPT microtubule associated protein tau

MCI mild cognitive impairment

MD mean diffusivity

MMSE mini-mental status examination

MoCA Montréal Cognitive Assessment

MDS Movement Disorders Society

MRI magnetic resonance imaging

NMS non-motor symptoms scale

PCA principal component analysis

PD Parkinson's disease

PDD Parkinson's disease dementia

PET positron emission tomography

PiB Pittsburgh compound b

PIGD postural instability and gait difficulty

PPMI Parkinson Progression Markers Initiative

PRM pattern recognition memory

QSM quantitative susceptibility mapping

QUIP questionnaire for impulsive-compulsive disorder in Parkinson's disease

RAVLT Rey's auditory verbal learning test

RBDQS REM sleep behavior questionnaire score

RD radial diffusivity

REM rapid eye movement

ROC receiver operating characteristic

ROI region of interest

SCOPA scales for outcomes in Parkinson's disease

SDMT symbol digits modalities test

SNCA α-synuclein gene

SPECT single photon emission computed tomography

STAI state-trait anxiety inventory

TBSS tract-based spatial statistics

TMT trail making test

TOL tower of London

UPDRS Unified Parkinson's disease rating scale

UPSIT University of Pennsylvania smell identification test

VBM voxel-based morphometry

VDF visual form discrimination test

WM white matter

WMS Weschler memory scale

Foreword

This thesis is presented as a compendium of three articles to obtain the degree of Doctor by the University of Barcelona. It is part of the results of five-years work at the Medical Psychology Unit of the Department of Medicine, Faculty of Medicine and Health Sciences. Two of the papers have been published in peer-reviewed journals and the third study is currently under review:

1. Uribe, C.*, Segura, B.*, Baggio, H. C., Abos, A., Marti, M. J., Valldeoriola, F., Compta, Y., Bargallo, N., Junque, C. (2016). Patterns of cortical thinning in nondemented Parkinson's disease patients. *Movement Disorders*, *31*(5), 699–708. https://doi.org/10.1002/mds.26590.

IF(2016): 7.072. Q1 in Clinical Neurology.

2. Uribe, C., Segura, B., Baggio, H. C., Abos, A., Garcia-Diaz, A. I., Campabadal, A., Marti, M.J., Valldeoriola, F., Compta, C., Tolosa, E., Junque, C. (2018). Cortical atrophy patterns in early Parkinson's disease patients using hierarchical cluster analysis. *Parkinsonism and Related Disorders*, *50*, 3–9. https://doi.org/10.1016/j.parkreldis.2018.02.006.

IF(2017): 4.721. Q1 in Clinical Neurology.

3. Uribe, C.*, Segura, B.*, Baggio, H. C., Abos, A., Garcia-Diaz, A.I., Campabadal, A., Marti, M. J., Valldeoriola, F., Compta, Y., Bargallo, N., Junque, C. Progression of Parkinson's disease patients subtypes based on cortical thinning: 4-year follow-up. Under review.

Related Academic Work

List of additional publications of the candidate that are not included in the thesis. These papers are the result of the work in the Parkinson's disease project and other collaborative work during the period of pre-doctoral research position.

Campabadal, A.*, **Uribe, C.***, Segura, B., Baggio, H. C., Abos, A., Garcia-Diaz, A. I., Marti, M.J., Valldeoriola, F., Compta, Y., Bargallo, N., Junque, C. (2017). Brain correlates of progressive olfactory loss in Parkinson's disease. *Park. Relat. Disord.* 41, 44–50. https://doi.org/10.1016/j.parkreldis.2017.05.005.

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Uribe, C.*, Puig-Davi, A.*, Abos, A., Baggio, H. C., Junque, C., Segura, B. (2019). Neuroanatomical and functional correlates of cognitive and affective empathy in young healthy adults. *Frontiers in Behavioral Neuroscience*. https://doi.org/10.3389/fnbeh.2019.00085.

Uribe, C., Junque, C., Gomez-Gil, E., Abos, A., Mueller, S. C., Guillamon, A. (2019). Brain network interactions in transgender persons. Under review.

Garcia-Diaz, A. I., Segura, B., Baggio, H. C., Marti, M. J., Valldeoriola, F., Compta, Y., Bargallo, N., **Uribe, C.,** Campabadal, A., Abos, A., Junque, C. (2017). Structural brain correlations of visuospatial and visuoperceptual tests in Parkinson's disease. *J. Int. Neuropsychol. Soc.* 17, 1–12. https://doi.org/10.1017/S1355617717000583.

Garcia-Diaz, A. I., Segura, B., Baggio, H. C., **Uribe, C.,** Campabadal, A., Abos, A., Marti, M.J., Valldeoriola, F., Compta, Y., Bargallo, N., Junque, C. (2018). Cortical thinning correlates of changes in visuospatial and visuoperceptual performance in Parkinson's disease: A 4-year follow-up. *Parkinsonism and Related Disorders*, *46*, 62–68. https://doi.org/10.1016/j.parkreldis.2017.11.003.

Campabadal, A., Segura, B., Baggio, H. C., Abos, A., **Uribe, C.,** Garcia-Diaz, A. I., Marti, M.J., Valldeoriola, F., Compta, Y., Bargallo, N., Junque, C. (2018). Diagnostic Accuracy, Item Analysis and Age Effects of the UPSIT Spanish Version in Parkinson's Disease. *Arch. Clin. Neuropsychol.* https://doi.org/10.1093/arclin/acy053.

Baggio, H. C.*, Abos, A.*, Segura, B., Campabadal, A., Garcia-Diaz, A., **Uribe, C**., Compta, Y., Marti M.J., Valldeoriola, F., Junque, C. (2018). Statistical inference in brain graphs using threshold-free network-based statistics. *Hum. Brain Mapp.* 39, 2289–2302. https://doi.org/10.1002/hbm.24007.

Baggio, H.C.*, Abos, A.*, Segura, B., Campabadal, A., **Uribe, C.,** Giraldo, D., Perez-Soriano, A., Munoz, E., Compta, Y., Junque, C., Marti, M.J. (2019) Cerebellar resting-state functional connectivity in Parkinson's disease and multiple system atrophy: characterization of abnormalities and potential for differential diagnosis at the single-patient level. *Neuroimage Clinical*. 22, 101720. https://doi.org/10.1016/j.nicl.2019.101720.

Abos, A., Baggio, H.C., Segura, B., Campabadal, A., **Uribe, C.,** Giraldo, D., Perez-Soriano, A., Munoz, E., Compta, Y., Junque, C., Marti, M.J. (2019) Probabilistic tractography for the characterization of white matter abnormalities and discrimination of multiple system atrophy from Parkinson's disease. Under review.

Campabadal, A., Segura, B., Junque, C., Serradell, M., Abos, A., **Uribe, C.,** Baggio, H.C., Gaig, C., Santamaria, J., Compta, Y., Bargallo, N., Iranzo, A. (2019) Cortical gray matter and hippocampal atrophy in idiopathic Rapid Eye Movement sleep behavior disorder. *Frontiers in Neurology*.

https://doi.org/10.3389/fneur.2019.00312.

Campabadal, A., Segura, B., Junque, C., Serradell, M., Abos, A., **Uribe, C.,** Baggio, H.C., Gaig, C., Santamaria, J., Bargallo, N., Iranzo, A. (2019) Comparing the accuracy and neuroanatomical correlates of the UPSIT-40 and the Sniffin' Sticks test in REM sleep behavior disorder. Under review.

Abos, A., Segura, B., Baggio, H.C., Campabadal, A., **Uribe, C.,** Garrido, A., Camara, A., Muñoz, E., Valldeoriola, F., Marti, M.J., Junque, C., Compta, Y. (2019). Disrupted structural connectivity of fronto-deep gray matter pathways in Progressive Supranuclear Palsy. Under review.

Campabadal, A., Junque, C., Dominguez, P., Baggio, H.C., Abos, A., **Uribe, C.,** Marti, M.J., Compta, Y., Valldeoriola, F., Bargallo, N., Segura, B. (2019). Brain atrophy and cognitive dysfunction-related quality of life in Parkinson's disease. Under review.

* These authors contributed equally to the work.

Chapter I

Introduction

It's been 200 years since James Parkinson published "An essay on the shaking palsy" in 1817 and more than 100 years ago Fritz Heinrich Lewy described inclusions located outside the substantia nigra (Goedert et al., 2013). Nowadays, Parkinson's disease (PD) is the second most prevalent neurodegenerative disease and its etiology remains still unknown (Ascherio and Schwarzschild, 2016; Kalia and Lang, 2015). During the past decades, PD diagnosis has been improved thanks to the emergence of neuroimaging techniques. Since 2011, the FDA introduced the dopamine transporter imaging (DaTSCAN) as a diagnostic tool for PD (Seifert and Wiener, 2013). In addition, a bunch of MRI techniques have contributed to the elucidation of the neuroanatomical and neurofunctional bases of clinical manifestations in PD such as cognitive impairment (Politis, 2014; Svenningsson et al., 2012).

Classically, α-synuclein aggregates in neurons of the nigrostriatal dopaminergic system are described as the pathological hallmark of PD. Synaptic dysfunction would be caused by a vicious cycle of accumulating α-synuclein and dopamine dysregulation that finally results in neurodegeneration (Dickson et al., 2009; Goedert, 2015; Kalia and Lang, 2015); albeit this conception has revealed insufficient. PD can no longer be considered a mono-systemic disease (Goedert et al., 2013). As PD definition evolves to conceive the disease as multisystemic (Thenganatt and Jankovic, 2014) with widespread brain degeneration, the study of nonmotor symptoms has raised interest, since they are even present before motor diagnosis (Tolosa et al., 2009, 2007).

Inasmuch as Parkinson's disease cannot be considered a homogeneous single entity, distinct subtypes would compose this neurodegenerative disorder (Kalia and Lang, 2015; Thenganatt and Jankovic, 2014). Indeed, phenotypes characterization are a matter of debate to improve PD clinical management. Nowadays, the highest priority in the international scientific community with respect to PD is articulated in 3 main areas: clinical research, translational and basic research according to the National Institute of Neurological Disorders and Stroke (Sieber et al., 2014). Translational research recommendations include the development of patient stratification tools aiming to define disease signatures and to obtain homogeneous cohorts from such heterogeneous diagnostic entity. The present thesis is conceptualized in this framework.

Fifty years after James Parkinson's essay, JM Charcot in the Salpêtrière Hospital already suggested two different prototypes of the disease based on motor

characteristics: the tremor and the rigid/akinetic form (Goetz et al., 2001). Empirical research on motor subtypes has been very prolific and motor manifestations have been systematically reported as clinical variables in most PD studies. An early study in the 90s followed one of the first large PD cohorts called the DATATOP database where 800 early-untreated PD patients were enrolled and evaluated over 2 years (Parkinson Study Group, 1989). The authors reported two clinical disease progressions based on their motor manifestations, the tremor-dominant subtype and the postural instability and gait difficulty (PIGD) subtype (Jankovic et al. 1990). Another classical PD subdivision is based on the age of disease onset and some authors even proposed that it was "the major determinant" for disease prognosis (Hely et al., 1995). In the DATATOP cohort data, slower disease progression was found in early-onset PD (≤ 40 years) when compared with late-onset PD (≥ 70 years,Jankovic et al., 1990). The same authors later reported similar findings between two groups (≤ 57 and > 57 years) in a sample followed-up approximately over 6 years (Jankovic and Kapadia, 2001).

The interest in dividing PD patients into homogeneous groups also included the characterization of non-motor manifestations as mild cognitive impairment (MCI, Pagonabarraga and Kulisevsky, 2012), presence or absence of anosmia (Doty, 2012), and presence of REM disorders (St Louis et al., 2017) among others (Schapira et al., 2017).

In the next sections, a review on PD patients' clinical subtypes can be found. Firstly, motor subtypes, and early- and late-onset PD characterization will be reviewed. Thirdly, PD subtypes based on non-motor clinical manifestations will be introduced (e.g., PD with visual hallucinations and MCI), and finally, clinical phenotypes identified via cluster analysis techniques. In the present thesis, the study of PD is tackled from a magnetic resonance imaging (MRI) perspective that offers the opportunity to study both structural and functional brain changes.

Distinct motor subtypes or a temporal continuum?

The clinical diagnosis of PD requires the presence of motor cardinal signs: tremor, rigidity, akinesia, bradykinesia or postural imbalance (Hughes et al., 1992). Tremor can be postural, akinetic or it can be present at rest. Tremor at rest is the most common form in PD that helps differentiate from essential tremor (Moustafa et al., 2016). On the other hand, there is the PIGD disorder that can be accompanied by bradykinesia and rigidity, and sometimes it is referred to as the non-tremor phenotype (Nutt, 2016). Tremor-dominant, PIGD-dominant or undetermined motor subtypes (Jankovic et al., 1990; Stebbins et al., 2013) can be identified from the Unified Parkinson's Disease Rating Scale (UPDRS) section III (Fahn and Elton, 1987) and also from its revised version (Movement Disorder Society Task Force on Rating Scales for Parkinson's Disease., 2003) published by the Movement Disorders Society (MDS).

The first study that subtyped 800 unmedicated PD patients from the UPDRS-III scores was performed in the large DATATOP cohort. Jankovic et al. concluded that patients with PIGD subtype had "malignant-PD" with a more rapid rate of disease progression and a late-onset of the disease (Jankovic et al., 1990). PIGD subtype has also been related to the presence of more depression symptoms (Burn et al., 2012) and dementia (Alves et al., 2006). More interestingly, patients with initial tremor-dominant subtype that changed to PIGD over the course of PD were finally diagnosed with PD dementia (PDD, Alves et al., 2006).

On the other hand, tremor-dominant motor subtype has usually been reported as a marker of slower progression (Jankovic and Kapadia 2001) and less frequency of cognitive decline (Jankovic et al., 1990). *Tremoric* patients usually respond better to L-DOPA treatment (Fishman, 2008) probably by potentiating inhibition of the thalamus on the cerebello-thalamic-cerebral network (Dirkx et al., 2017). In fact, Hallet in a short communication pointed out that it is rather important the involvement of basal ganglia and cerebellar circuits in the management of resting tremor than the dopaminergic depletion into resting tremor (Hallett, 2012). In the same line, even when patients with resting tremor showed dopaminergic deficits in the DaTSCAN, the severity of the tremor did not correlate with dopamine depletion (Fishman, 2008).

A subtype called *benign tremulous parkinsonism* has been posteriorly proposed (Josephs et al., 2006). This PD subtype is characterized by tremor predominance and a slow progression of the disease with no other non-motor symptoms. Patients also present less global substantia nigra cell loss than non-benign PD patients (Selikhova et al., 2013). However, there is a high percentage of misdiagnosis and when the PD diagnosis is correct, the course is not benign. Patients eventually end up with PD-related symptomatology such as falls, hallucinations and even dementia (Deuschl, 2013).

MRI techniques allow studying grey matter (GM) and white matter (WM) structural changes, its underlying structural and functional connectivity, and the molecular and metabolic changes of the brain *in vivo* (see **Panels 1.1, 1.2** and **1.3** on pages 28-30 for an explanation of the most common MRI techniques). When comparing both types of tremor and PIGD dominant, regional GM volume reductions were found in the PIGD group in all brain lobes (Rosenberg-Katz et al., 2013). A recent study found that non-tremor patients had significant lower DaTSCAN uptakes values in the less affected side of the caudate nucleus than PD tremor patients (Barbagallo et al., 2017). Also related to the caudate, shape analysis of the left caudate showed atrophy in this structure in PIGD patients compared with controls (Vervoort et al., 2016). Results from a probabilistic tractography methodology, reduced structural connectivity values in nigro-pallidal (globus pallidus-substantia nigra) and fronto-striatal (putamen-precentral cortex, caudate nucleus-supplementary motor area, and thalamus-precentral cortex) pathways were

reported when comparing the two motor subtypes and also the non-tremor group with the controls group (Barbagallo et al., 2017). Vervoort et al., reported decreased fractional anisotropy (FA) in antero-posterior tracts when comparing PIGD patients with a tremor group (Vervoort et al., 2016). Findings in the same direction in the superior longitudinal fasciculus and the corpus callosum were of special relevance. The superior longitudinal tract has projections with all the cortical brain lobes and the crossing fibers of the corpus callosum connect with sensorimotor cortical regions (Vervoort et al., 2016).

PIGD patients also had reduced levels of amyloid-β levels in cerebrospinal fluid (CSF) and increments and decrements in different forms of tau in comparison with the tremor-dominant group (Zuo et al., 2017). Zuo et al., suggested that the PIGD variant would be linked to MCI in PD and that specific phosphorylated tau levels could be a biomarker of motor progression (Zuo et al., 2017). Nevertheless, in a more recent study, measures of amyloid-β and tau levels in a sample of non-demented PD patients did not differ from the controls sample (Winer et al., 2018).

The division of PD according to its motor manifestations is under debate. Primarily, because there is divergent literature on motor subtypes nomenclature and while some describe the tremor-dominant, the PIGD dominant and the mixed or undetermined subtype; others consider two classifications: the *tremoric* and the non-*tremoric* group. Additionally, PIGD subtype has also been referred to as axial motor disability or as the akinetic/rigid subtype in the literature (Kotagal, 2016).

More importantly, the temporal instability of the subtypes is up for debate. Motor phenotypes instability has been found even in the early stages of the disease diagnosis (Simuni et al., 2016). Eisinger et al., reported that motor symptoms remained stable in half of the sample whereas the other half suffered different motor manifestations over a 4 years follow-up (Eisinger et al., 2017). Contradictorily, Rajput et al., found that motor subtypes are good predictors of motor prognosis (Rajput et al., 2017). Recently, a multidimensional continuum (Kotagal, 2016) has been proposed where motor manifestations would be a temporal evolution of the disease (Fereshtehnejad and Postuma, 2017; Nutt, 2016) and where the PIGD PD-type is actually a measure of motor disturbances affected overall by disease progression and by other age-related conditions and comorbidities (Fereshtehnejad and Postuma, 2017). Notwithstanding the clinical importance of motor manifestations, it seems that age at disease onset would be a more important feature than motor subtypes to stratify groups of PD patients. A review of seven studies based on data-driven methodologies with sample sizes ranging from 44 to 176 PD patients (Van Rooden et al., 2010) found that only 2 studies out of the 7 differentiated two motor profiles (the *tremor-dominant* and the *bradykinesia/rigidity and PIGD dominant*), while 6 studies clearly divided patients based on early and late onset (see **Table 1** on page 31). This review

summarized the first studies based on cluster analysis techniques that appeared in the PD literature. Further review of these techniques will be introduced in posterior sections of the thesis.

Panel 1.1 MRI techniques

Structural anatomy GM and WM

Voxel-based morphometry (VBM): VBM estimates the amount of GM in a voxel through its signal intensity (Good et al., 2001; Whitwell, 2009). This technique also allows to estimate subcortical GM structures that represent the volume. Both GM volumes and GM density can be quantified through VBM. For group analyses, images need to be transformed into a standard space, using linear and non-linear registration. VBM techniques are dependent on a good registration of each individual and sometimes ambiguities can arise between what is actual GM atrophy or changes in the folding of gyrification (Bookstein, 2001).

Cortical thickness (CTh): CTh is calculated as the distance between the WM/GM boundary (white surface) and the pial surface (created by expanding the WM surface so that it closely follows the GM-CSF intensity gradient) at each vertex of the reconstructed cortical mantle. FreeSurfer is the most common software suite used to estimate CTh measures (Dale et al., 1999; Fischl and Dale, 2000). Vertex-wise CTh analyses are more informative of cortical topographical differences than VBM.

Diffusion tensor imaging (DTI) measures: diffusion-weighted MRI are sensitive to the microdiffusion of water molecules. Water diffusion in and out the cells is impeded by cell membranes, fibers and macromolecules (Le Bihan, 2003). The principle is that water molecules are always in random motion and bumping into structures and into each other. Diffusion is significantly altered by the presence of bundles of elongated axons, as the water cannot pass easily through the cell membranes. Consequently, the water molecules diffuse (i.e., move) along the direction in which the axons are oriented, in the extracellular and intracellular spaces.

DTI is typically used to investigate tissue microstructure or to examine the wiring of the brain (that is anatomical connectivity, commented below in the tractography section). Different metrics can be obtained from DTI (see **Figure 1** in **Panel 1.2**):

Fractional anisotropy (FA): FA is the degree of anisotropy in a scale ranging from 0 (isotropic) to 1 (anisotropic). It is related to myelin integrity, being the more anisotropic, the more myelinated (Le Bihan, 2003).

Mean diffusivity (MD): it is the overall diffusion inside a voxel, and it is given by the mean of three eigenvalues (λ1, λ2, λ3) which are the magnitude of water diffusion along the longest (principal direction of the diffusion), middle and shortest orthogonal (secondary directions of the water molecules) axes.

Other less frequently used DTI measures: axial diffusivity that corresponds to λ1 eigenvalue, that is the direction of the long axis (secondary direction); and radial diffusivity (RD) which is the mean of λ2 and λ3, that is, the amount of diffusion perpendicular to the long axis.

The most common methodology to assess FA, MD or other diffusion measures within each brain voxels is the FSL tract-based spatial statistics (TBSS) tool (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/TBSS).

All structural MRI techniques can be whole-brain (voxel-wise or vertex-wise) or measures can be extracted from a priori regions of interest (ROI).

Continuation Panel 1.2 MRI techniques

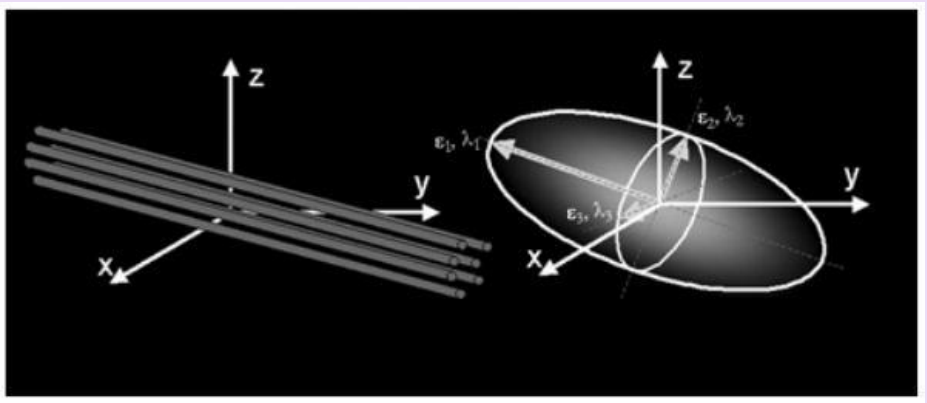

Figure 1 Extracted from Alexander et al., 2007 Neurotherapeutics. Vol 4(3). https://doi.org/10.1016/j.nurt.2007.05.011

Structural connectivity

Tractography: directional information obtained from DTI measures in each voxel is used to generate virtual, three-dimensional white matter maps. Once the white matter tracts are defined, the structural connectivity in the brain can be investigated. Tractography can be deterministic or probabilistic.

Probabilistic tractography is a more recent technique that tries to overcome the deterministic methodology pitfalls that include uncertainty into estimating at every voxel the most likely fiber orientation (see https://www.humanconnectome.org/study/hcp-young-adult/project-protocol/diffusion-tractography for a more detailed explanation of DTI measurements).

Functional connectivity

Functional connectivity is defined as the temporal dependency of neuronal activation patterns of anatomically separated brain regions (van den Heuvel and Hulshoff Pol, 2010). The most common techniques are:

Independent component analysis (ICA) as a data-driven approach to obtain spatial maps from temporal connectivity measures (Beckmann and Smith, 2004; Smith et al., 2014).

Seed-based analysis: correlations seed-to-whole brain or seed-to-seed.

Graph theory analysis: to obtain global and local measurements of large-scale networks (Bullmore and Sporns, 2009).

Perfusion MRI

It is a variant of functional imaging that provides direct information on the delivery of blood to the brain tissue. It offers quantitative measurements that are, for every voxel, a measure of perfusion (i.e., ml of blood delivered per 100 g of tissue per minute).

Arterial spin labeling (ASL) is the most common noninvasive technique to obtain perfusion measures.

The book from Jenkinson and Chappell (2018) Introduction to Neuroimaging Analysis. Oxford editor offers a good overview of all neuroimaging techniques.

Continuation Panel 1.3 MRI techniques

Molecular and metabolic brain activity

Positron emission tomography (PET): uses radiotracers (radioactive material) to evaluate organ and tissue functions. The most well-known radiotracer is the Pittsburgh compound B (PiB) which quantifies amyloid-β in the brain and it is suitable for the diagnosis of AD (Zhang et al., 2014) and PDD (Gomperts et al., 2016).

The tracer fluorine 18-labeled AV-1451 ([^{18}F]AV-1451) captures deposits of tau protein.

Another radiotracer used to study cognition and brain activity in PD is the fluorodeoxyglucose (FDG)-PET (Gratwicke et al., 2015).

Single-photon emission computed tomography (SPECT): SPECT requires gamma-rays' radioisotopes to be injected into the blood. For the diagnosis of PD, the most well-known neuropharmaceutical drug is the ioflupane (^{123}I) which binds with presynaptic dopamine transporters and for that reason, it is usually known as DaTSCAN.

Iron deposition: iron brain deposits can be measured from T2* gradient echo MRI. The most recently improved technique is Quantitative Susceptibility Mapping (QSM) which quantifies brain tissue's magnetic susceptibility from gradient echo signal phase and provides excellent contrast of iron-rich deep nuclei from surrounding tissues. It takes advantage of the paramagnetic property of the brain tissues (Kee et al., 2017).

Table 1 Cluster analysis early studies

		Reijnders 2009	Post 2008	Schrag 2006	Lewis 2005	Dujardin 2004*	Gasparoli 2002	Graham 1999
Motor profiles	Tremor dominant	47%			17%			
	Non-tremor dominant *Bradykinesia/rigidity and PIGD*	17%			26%			
Motor + cognition	Severe motor impairment and MCI							32%
	Mild motor severity and MCI					36%		
	Motor dysfunction only					59%		47%
Age disease onset	Old age and rapid progression	7%	40%	64%	17%		39%	21%
	Young age and slow progression	29%	33%	36%	40%		61%	
	Mid-late age onset		27%					
Sample characteristics		n = 346	n = 131 *de novo*	n = 124	n = 120	n = 44 early PD < 3 years	n = 103 early PD < 5 years	n = 176
Mean age, years		70	67	72	64	66	NS	63
Disease duration, years		8	2	6	8	4	NS	8

NS, not specified. All cluster analyses were based on *k-means*. *Percentages reported do not result in 100% due to the presence of outliers that were not grouped in any disease subtype. Extracted from Van Rooden et al. 2010 Mov Disord Vol 25. https://doi.org/10.1002/mds.23116

Age of disease onset

Age is considered one of the main risk factors for idiopathic PD (Lees et al., 2009) and diagnosis is usually made after the age of 60 although it is also possible before 50 years (de Lau and Breteler, 2006). PD debutants younger than 21 years old are considered juvenile cases (Schrag and Schott, 2006); juvenile PD forms will not be reviewed in this thesis. From the age of the disease onset, PD patients can be divided into early/young-onset and late/old-onset subtypes.

Early-onset PD is frequently linked to genetic factors (Lees et al., 2009; Schrag and Schott, 2006), especially in juvenile cases (Schrag and Schott, 2006). **Panel 2** explains the most common genetic mutations linked to PD**.** Young-onset PD patients tend to have a slower progression of the disease (Ferguson et al., 2015; Foltynie et al., 2002), milder cognitive decline (Tang et al., 2016) and fewer sleep disturbances (Mahale et al., 2015) even when patients had longer disease duration than the late-onset group. The early-onset subtype has a good response to L-DOPA therapy (Jankovic et al., 2000) while dyskinesia (Aquino and Fox, 2015; Mehanna et al., 2014), dystonia (Mehanna et al., 2014) and motor fluctuations can be frequent (Thenganatt and Jankovic, 2014). However, early onset (<50 years) PD have more depressive symptoms (Fereshtehnejad et al., 2014; Mehanna et al., 2014).

Panel 2 Autosomal dominant and recessive genetic mutations in PD

Mutations in LRRK2 are the most common causes of dominant inherited PD and age of onset tends to be similar to sporadic PD. Other autosomal dominant genes are SNCA, VPS35, EIF4G1, DNAJC13 and CHCHD2.

Mutations in Parkin gene such as PARK2 are the most prevalent autosomal recessive gene related to PD and patients frequently debut before 40 years. They are also responsible for the juvenile parkinsonism forms (Giasson and Lee, 2001). Other recessive genes related to PD are PINK1 and DJ-1/PARK7 also linked to an early onset of the disease (Kalia and Lang, 2015).

A lower methylation of SNCA and PARK2 promoter regions would be related to an early-onset of the disease. PD patients with these genetic characteristics also tend to have positive family history of PD (Eryilmaz et al., 2017).

On the other hand, older age of onset (>60 years) is usually associated with a more severe motor and nonmotor PD phenotype, greater impairment of dopaminergic dysfunction in putamen and caudate as measured by DaTSCAN, and reduced levels of α-synuclein and tau in CSF compared with controls (Pagano et al., 2016). Hoehn and Yahr (H&Y) staging, bradykinesia, resting tremor and postural instability scores as measured by UPDRS-III were significantly increased in older-aged onset groups when comparing patients with similar disease durations (Pagano et al., 2016). Late-onset PD (≥70 years) also tend to have a greater proportion of falls (Mehanna et al., 2014). Motor manifestations at

disease onset for the old-onset group are usually tremor at rest while for the early-onset patients, a great proportion tend to debut with akinetic/rigid symptoms (Wickremaratchi et al., 2011).

One of the drawbacks of investigating different ages of disease onset is the arbitrary cut-off (Butterfield et al., 1993; Schrag et al., 1998; Wickremaratchi et al., 2011). Early-onset is usually considered between 20 to 40 years-old and late-onset from 60 years (Schrag and Schott, 2006). Although some studies included in the early-onset subgroup, patients diagnosed up to 50 years (Butterfield et al., 1993) and the late-onset from 50 years (Shih et al., 2007). Others report the majority of clinical differences between early and late-onset in patients older than 70 years (Pagano et al., 2016).

Metabolic brain differences accounting for aging effects at disease onset have been investigated using Positron Emission Tomography (PET) and Single-Photon Emission Computed Tomography (SPECT). There is controversy on the findings and some studies reported similar nigrostriatal dopaminergic loss in the putamen (Liu et al., 2015; Panzacchi et al., 2008) and caudate (Panzacchi et al., 2008) nuclei quantified with DaTSCAN-PET in both early-onset (<45 years for Panzacchi et al., 2008 and <50 years for Liu et al., 2015) and late-onset (>50 years). In contrast, others reported that early-onset PD patients (<50 years) have a greater dopamine neuron loss in the striatum than late-onset PD patients (Shih et al., 2007). More precisely, the putamen would have a greater loss of neurons although early-onset PD patients have a slower disease progression and therefore, it seems that early-onset PD patients have more efficient compensatory mechanisms to cope the disease (De La Fuente-Fernández et al., 2011). The caudate nucleus in proportion to the putamen loss would be preserved in the early-onset group (Liu et al., 2015). On the other hand, mid-late onset PD patients (>50 years) have greater content of iron deposition in putamen than that observed in early PD patients (≤50 years) although both groups had increased levels of iron deposition in the substantia nigra comparing them with similar-aged controls (Xuan et al., 2017). Excessive iron content increases the oxidative processes in the cells and therefore leads to neurotoxicity (Gutteridge, 1992). Correlations between iron content and clinical variables of disease severity were reported in mid-late onset patients but not in the early-onset group possibly due to compensatory mechanisms (Xuan et al., 2017). There is scarce literature on structural MRI studies comparing groups of different ages in disease onset and one functional connectivity seed-to-whole brain correlation study found increased connectivity between the basal ganglia and regional neocortical and cerebellar areas in both PD groups compared with two samples of similar-aged controls although they were not compared between each other (Hou et al., 2016).

Visual hallucinations

Patients with visual hallucinations would constitute a subtype at more risk evolving to PDD (Aarsland et al., 2003; Aarsland and Kurz, 2010; Hobson and Meara, 2004). Longitudinal studies reported that 75% of the patients with visual hallucinations end up with dementia over 2.5 years (Ibarretxe-Bilbao et al., 2010).

Hallucinations in PD are mainly visual, they affect one out of four patients with PD (Fenelon, 2000) or even up to 50% of the PD population in the second half of the disease based on autopsy reports (Williams and Lees, 2005). Alterations in visual function in PD have been reported from the retina to higher associative cortical brain regions (Weil et al., 2016). Visual hallucinations can be a side effect of L-DOPA medication (Armstrong, 2008) or it can worsen them (Connolly and Lang, 2014). However, other factors might be implicated since hallucinations can be present at diagnosis in untreated *de novo* patients and thus cannot be attributed to levodopa effects (Fénelon et al., 2006). The presence of visual hallucinations was proposed to be part of the diagnostic criteria of Lewy body parkinsonism such as PD and Lewy-body dementia (Williams and Lees, 2005), and in 2007 diagnostic criteria for psychosis in PD (Ravina et al., 2007) were published (see **Panel 3**).

Panel 3 proposed diagnostic criteria for PD associated psychosis from Ravina et al., 2007

Characteristic symptoms

- Presence of at least one of the following symptoms (specify which of the symptoms fulfill the criteria):
  - Illusions
  - False sense of presence
  - Hallucinations
  - Delusions
- Primary diagnosis
  - UK brain bank criteria for PD
- Chronology of the onset of symptoms of psychosis
  - The symptoms in Criterion A occur after the onset of PD
- Duration
  - The symptom(s) in Criterion A are recurrent or continuous for 1 month
- Exclusion of other causes
  - The symptoms in Criterion A are not better accounted for by another cause of Parkinsonism such as dementia with Lewy bodies, psychiatric disorders such as schizophrenia, schizoaffective disorder, delusional disorder, or mood disorder with psychotic features, or a general medical condition including delirium
- Associated features: (specify if associated)
  - With/without insight
  - With/without dementia
  - With/without treatment for PD (specify drug, surgical, other)

Frequently, hallucinations appear as minor illusions in early stages of the disease, with the feeling that there is a presence in the room, behind the patient or next to but patients cannot see it. These are usually not disturbing for the patients (Fénelon et al., 2011) and they can be present in more than 40% of *de novo*, unmedicated PD patients (Pagonabarraga et al., 2016). Progressively, this minor illusion evolves to more sophisticated hallucinations which involve "a disturbance in the regulation of the gating and filtering of the external perception and internally generated visual images" (Armstrong, 2008).

The neuropsychological profile of patients with visual hallucinations includes deficits over all the main cognitive domains such as impairment in verbal and visual memory, language comprehension, visuospatial and visuoperceptive functions, verbal fluency and executive function (Ibarretxe-Bilbao et al., 2011; Lenka et al., 2017). Instead, minor hallucinations are not related to any specific neuropsychological impairment (Llebaria et al., 2010). The genetic contribution to psychosis in PD has been poorly investigated and there are no associated well-defined genes linked to it (Ffytche et al., 2017).

The advent of visual hallucinations has been linked to densities of Lewy bodies in the parahippocampal and inferior temporal cortices (Harding et al., 2002). MRI studies comparing non-demented PD patients with and without visual hallucinations have reported specific regional atrophy in brain areas related to higher visual processing. GM reductions in the left lingual gyrus and bilateral superior parietal were found in hallucinating patients compared with controls and non-hallucinating PD (Ramírez-Ruiz et al., 2007). Subcortically, the head of the hippocampus has also been related to non-demented PD patients with visual hallucinations (Ibarretxe-Bilbao et al., 2008). A recent study on the hippocampal subregions in psychosis found widening of the bilateral hippocampal fissure in PD psychotic patients compared with PD without psychosis, thus suggesting hippocampal atrophy (Lenka et al., 2018). Other studies have also stressed the importance of posterior brain atrophy including occipital, parietal and medial temporal lobe degeneration linked to visual hallucinations although findings were uncorrected (Goldman et al., 2014). Longitudinally, PD patients with visual hallucinations have greater atrophy across widespread regions. Of special relevance, the limbic and paralimbic areas in the temporal lobe but also widespread atrophy in the frontal lobe over 2.5 years (Ibarretxe-Bilbao et al., 2010).

Functionally, early studies investigating brain pattern activations of visual associative areas in hallucinating patients have reported: reduced functional connectivity in the right prefrontal (inferior, superior and middle) cortex and in the anterior cingulate gyrus when comparing them with patients without visual hallucinations. Contrarily, when presenting simple visual stimuli (not-related to associative processing), the hallucinating group had hyperactivations in the right

inferior frontal region (Ramírez-Ruiz et al., 2008). Another study reported reduced activation in the lateral occipital cortex and the extrastriate temporal visual cortices in the hallucinating PD group suggesting bottom-up visual processing impairment (Meppelink et al., 2009). When investigating the functional connectivity of the brain at rest, default mode network reduced connectivity was found in PD patients compared with controls, and concretely, PD patients with visual hallucinations had increased connectivity in frontal and parietal regions of this network than non-hallucinating patients (Yao et al., 2014). These abnormalities in the default mode network, together with disrupted connectivity in the visual and attentional networks would define the neural mechanisms of visual hallucinations in PD (Shine et al., 2014).

More recently, once structural and functional studies described the brain changes associated with hallucinations in PD, the focus changed to study minor hallucination phenomena as a possible prodromal stage to reduce, prevent or delay the onset of major (complex) hallucinations and finally, overt dementia. A recent review on MRI findings of hallucinations in PD (Lenka et al., 2015), stresses the importance of the progressive superior parietal atrophy as a marker of evolution from minor hallucinations to complex ones, since this region has also been reported in patients with minor hallucinations (Pagonabarraga et al., 2014). However, methodology discrepancies and different PD disease stages prevent its elucidation. In this early study investigating the neural correlates of minor hallucinations, modest increments and decrements are reported in a very homogeneous sample of PD patients and healthy controls. Compared with controls, PD patients with presence of minor hallucinations had left superior parietal, superior occipital, right cuneus and midbrain volume reductions as well as increments in hippocampal and cerebellar regions. Compared with patients without this phenomenon, decrements were placed in the right precuneus, increments in the left orbitofrontal gyrus and finally, both increments and decrements in specific regions of the cerebellum (Pagonabarraga et al., 2014). A more recent study have found left middle occipital, left parietal and right parahippocampal GM reductions in PD with minor hallucinations compared with non-hallucinating patients (Bejr-Kasem et al., 2018). Functionally, similar results in the default mode network have been reported in patients with minor visual hallucinations from a seed-based approach placed in the posterior cingulate cortex (Bejr-Kasem et al., 2018). Specifically, increased connectivity with bilateral superior parietal, middle temporal and right precentral regions of the default mode network were reported.

Together these findings confirm the involvement of temporal limbic and paralimbic regions as well as posterior cortical brain areas into visuoperceptual and visuospatial functions in visual hallucinations in PD.

Cognition in PD

In 1997, Dubois and Pillon described that the cognitive deficits observed in PD "they mainly include defective use of memory stores and a dysexecutive syndrome. These disorders result from dysfunction of processes that are commonly considered to be controlled by the pre-frontal cortex. […] These deficits may be related to the subcortical pathology of the disease, because they are noticed even at an early stage" (Dubois and Pillon, 1997). Nowadays, the hypothesis that PD only involves fronto-striatal dysfunction has been rejected (Goedert et al., 2013). Both MRI and neuropsychological studies have contributed to the idea that brain atrophy underlying PD-MCI is extensive (Kehagia et al., 2010; Robbins and Cools, 2014). Atrophy can be found through neocortical and subcortical structures even at early stages of the disease (Lee et al., 2014; Pereira et al., 2014) where cognitive decline can already be present (Aarsland et al., 2009).

Cognitive deficits related to PD

Following the classical idea of the fronto-striatal deficits, cognitive dysfunctions were attributed to the frontal lobe: that is, executive function that requires cognitive flexibility and internally guided behavior to answer to external cues (Dubois and Pillon, 1997). This idea was supported by the impairment observed in frontal lobe-related tests such as the Wisconsin Card Sorting Test, Trail Making Test (TMT), Odd Man Out Test, letter fluency, Stroop test and the tower of London test (Dubois and Pillon, 1997). Impairment in flexibility, response inhibition, and working memory were reported to be restored thank to dopamine receptors agonists, monoamine oxidase (MAO) type B inhibitors and catechol-O-methyltransferase (COMT) inhibitors (Kehagia et al., 2010). For example, rasagiline treatment (MAO-B inhibitor) has beneficial effects on the digit span backward test as a measure of attention and on verbal fluency total scores as a measure of executive function in non-demented PD patients (Hanagasi et al., 2011).

However, L-DOPA may also worsen other cognitive abilities (Svenningsson et al., 2012). There is a functional differentiation between the dorsal and the ventral striatum and medication seems to improve dorsal striatum functions such as flexibility while impairing ventral striatal function that would cause impulsivity and impairment in other cognitive functions such as reversal learning and decision making (Cools, 2006; Cools et al., 2003). These deficits would be caused by a "dopaminergic overdose" in less depleted striatal regions (Kehagia et al., 2012, 2010), because dopaminergic denervation follows a dorsal to ventral gradient within the basal ganglia (Grace, 2008; Kish et al., 2010).

Executive function is a complex cognitive domain and working memory, rule-switching and response inhibition include an attentional component that, apart

from being mediated by dopaminergic fronto-striatal circuits, they interact with other neurotransmitter networks in the brain. Indeed, beyond the dopaminergic depletion in PD mainly causing motor dysfunction, the noradrenergic, serotoninergic and cholinergic systems are also involved in PD non-motor symptoms (e.g., cognition) by degeneration of the locus coeruleus, dorsal raphe and the nucleus of Meynert (Jellinger, 2012).

Different cholinergic networks have been related to visuoperceptual deficits such as visuospatial function via the superior parietal and the occipital gyrus; visual hallucinations via the inferior parietal, the cuneus and the lingual gyrus; and visuoperceptual deficits via the middle occipital, the parahippocampal and fusiform gyri. Memory deficits are also related to cholinergic dysfunction in the medial temporal lobe of the hippocampal and parahippocampal formation causing recognition memory deficits and semantic memory impairment (Gratwicke et al., 2015). Cholinergic dysfunction has been proposed as a biomarker of PDD by means of PET imaging (Delgado-Alvarado et al., 2016). Indeed, the most effective treatment for the management of cognitive disturbances in PDD patients is the rivastigmine which is a cholinesterase inhibitor (Seppi et al., 2011).

Overall the great heterogeneity of PD-MCI even in newly diagnosed patients (Aarsland et al., 2009; Muslimovic et al., 2005) and the existence of different neural networks underlying cognitive dysfunction (Cools, 2006; Kehagia et al., 2010), a dual syndrome hypothesis was proposed (Kehagia et al., 2012). In 2004, this research group from Cambridge divided PD-MCI patients according to the presence of frontostriatal deficits as evaluated with the Tower of London, temporal lobe deficits as evaluated by a pattern recognition memory task or global PD-MCI patients with both frontal and temporal deficits (Foltynie et al., 2004). This study was of high importance since the cohort was representative from the Cambridgeshire region in the UK therefore, patients were not enrolled from an outpatient clinic with the subsequent possible bias. From this first work, the cohort was followed-up to three (Williams-Gray et al., 2007), five (Williams-Gray et al., 2009a) and ten (Williams-Gray et al., 2013) years with the aim to establish dementia incidence, cognitive profiles in PD and baseline variables predicting cognitive evolution (Williams-Gray et al., 2007). In addition, different genetic expressions were investigated (Williams-Gray et al., 2009b, 2009a). See **Panel 4** for a brief summary of the genes associated with cognition in PD.

The dual syndrome hypothesis differentiates two cognitive profiles (**Figure 2**): (1) a neuropsychological profile with mainly executive dysfunction linked to dopaminergic amelioration; (2) a subgroup with early deficits in visuospatial function and semantic fluency, dependent on cholinergic dysfunction and linked to posterior cortical and temporal lobe atrophy, with rapid cognitive decline and more probability to end up in PDD (Kehagia et al., 2012). Indeed, PD patients with semantic fluency performance <20 words in 90 seconds, not being able to copy

the pentagons' figure of the Mini-Mental State Examination (MMSE) (Williams-Gray et al., 2007) and aging > 71 years would be at more risk to dementia (Williams-Gray et al., 2009a).

Panel 4 Genes associated to cognition in PD

- H1 haplotype of the microtubule associated protein tau (MAPT) gene has been associated to dementia (Williams-Gray et al., 2009a; Seto-Salvia et al., 2011).
- The glucocerebrosidase (GBA) influence progression to dementia and the heterozygote GBA mutation is more overrepresented in PD than in controls (Seto-Salvia et al., 2012).
- The α-synuclein gene (SNCA) duplications but not polymorphisms is also implicated in PD disease progression to dementia (Kurz et al., 2006; Halliday, 2014).
- The brain derived neurotrophic factor (BDNF) Met/Met allele correlates with MCI and disease duration (Guerini et al., 2009).
- Polimorphisms of DYRK1A have been related to PDD and dementia with Lewy bodies (Jones et al., 2012).
- The gene coding for catechol-O-methyltransferase (COMT) has no effect on dementia in any of the allele forms (Val/Met), which are more related to frontal deficits (Williams-Gray et al., 2009a).
- Appoliprotein E (APOE) ε4 alleles effect on PD are inconsistent contrary to that found in Alzheimer's disease (AD), while some studies found an association of ε4 carriers with PD (Kurz et al. 2009) other did not (Williams-Gray et al., 2009b) and no studies have related conversion to dementia with any form of APOE. However, verbal memory and semantic fluency performance are predicted by the presence of the APOE ε4 allele (Mata et al., 2014).

Reviews on the genetic contribution to cognition in PD can be found in Svenningsson et al., 2012 and Collins and Williams-Gray, 2016.

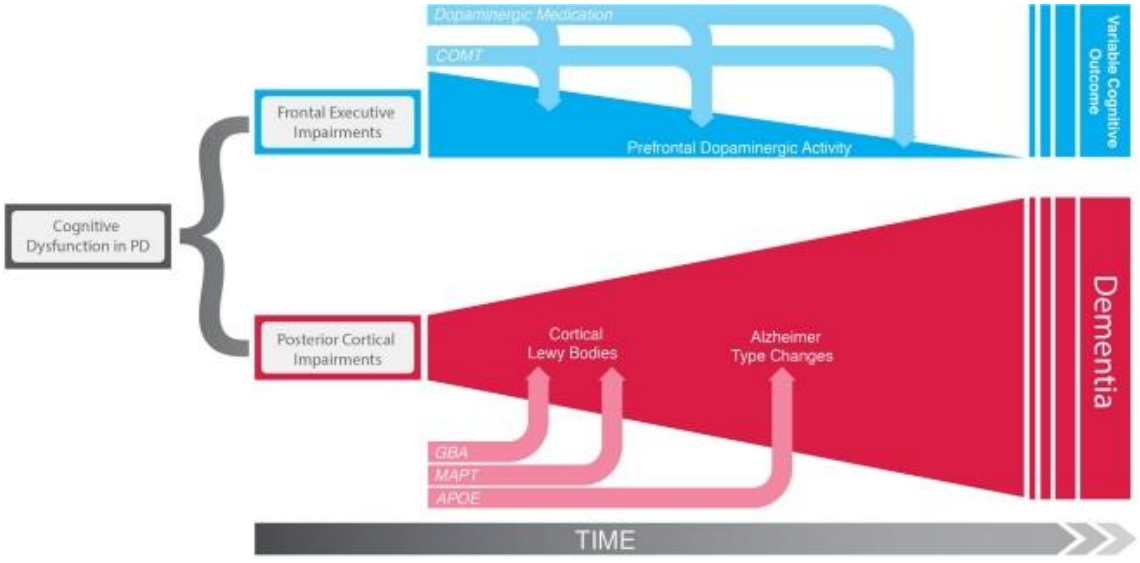

Figure 2 Genes associated to cognition in PD. Extracted from Collins and Williams-Gray 2016 Frontiers in Psychiatry. https://doi.org/10.3389/fpsyt.2016.00089

Progression of cognitive decline

Initial longitudinal prospective studies in PD samples that assessed neuropsychological performance reported miscellaneous results. In part, this is due to different scan intervals and heterogeneous small PD samples of non-demented patients. Back in 2007, a first meta-analysis evaluated 25 longitudinal studies that pooled 901 non-demented PD patients with scan intervals ranging from 2.4 months to 8 years (Muslimović et al., 2007). Overall, subtle cognitive decline was found across all cognitive domains assessed (global cognitive ability, memory, verbal fluency, verbal ability, mental flexibility and reasoning, attention and speed processing, and visuoperceptual and visuoconstructive skills). From this moderate cognitive evolution, the memory domain, visuoconstructive skills, and global cognitive ability were the most impaired. Posterior to this meta-analysis, better well-controlled prospective works have reported a greater decline in processing speed (Broeders et al., 2013b; Gasca-Salas et al., 2014; Muslimović et al., 2009). Modest memory decline was also reported (Broeders et al., 2013b; Muslimović et al., 2009) as well as visuospatial skills and executive function (Muslimović et al., 2009). Indeed, the transition from PD normal cognition to PD-MCI was characterized by the presence of attention, executive and memory impairments whereas patients who converted from PD-MCI to PDD suffered visuospatial deficits over a 2.5-year period (Gasca-Salas et al., 2014). Attention decline over time is less clear in PD patients (Broeders et al., 2013b). See **Table 2** for effect sizes information of longitudinal PD cognitive studies. In the table, we can observe that the greater the scan interval, the larger the effect sizes. However, there is no consensus in the cognitive domains and neuropsychological tests included across studies. Visuospatial function, verbal and visual memory, language and tests that require processing speed and working memory suffered the most significant time effects.

Table 2 Prospective longitudinal studies of cognitive progression in PD

EFFECT SIZES	scan interval	global cognition	executive function	attention and working memory	memory	language	visuospatial function
Schrag 2007	1 year	small					
Starkstein 1992	1 year	small					
Stepkina 2010	0.5-2 years	small		small	small	small	small
Azuma 2003	2 years		small. Medium in letter fluency		small	small	small
Schrag 2017	2 years	small					
Pirogovski-Turk 2017	2-3 years		small	small to medium	small. Medium in CVLT learning, delayed recall and visual memory	small	small
Caparros-Lefebvre 1995	3 years	small	medium. Small in semantic fluency		small		
Starkstein 1990	3-4 years	medium					
Aarsland 2004	4 years	small					
Broeders 2013	5 years	small	small. Medium in TMTB	small. Medium in Stroop Word and Stroop Colors test	small. Medium in RAVLT recognition and faces of the WMS-III	medium	medium to large
Wills 2016	6 years			small			
Palazzini 1995	7 years			small	small	medium	medium to large

Adapted from Roheger et al., 2018, Journal of Parkinon's disease, Vol 8. https://doi.org/10.3233/JPD-181306. Effect sizes were Cohen's d and <0.5 was considered small; 0.5-0.8 was considered medium; >0.8 was considered large. Neuropsychological tests were classified according to MDS PD-MCI task force guidelines into the cognitive domains.

PD-MCI diagnosis

Cognition in PD is conceived as a spectrum (Caviness et al., 2007). As in Alzheimer's disease (AD), PD-MCI definition is of high relevance because patients have a higher risk to develop dementia than cognitively intact PD patients (Domellöf et al., 2015; Janvin et al., 2006; Pedersen et al., 2013). Specific cognitive deficits such as impairment in verbal immediate and delayed recall memory tests and in verbal fluency have been pointed out as markers of PDD (Levy et al., 2002). Nonetheless, not all PD-MCI patients eventually evolve to dementia and follow-up studies also reported that PD cognitively intact patients at baseline end up with dementia over a 4 years follow-up (Janvin et al., 2006). This suggests that the continuum does not follow a simple linear progression. The prevalence of PD-MCI ranges from 19% to 38% (Litvan et al., 2012), although it can be up to 50% (Janvin et al., 2006; Picillo et al., 2014). In newly diagnosed untreated PD patients, the prevalence of MCI is already nearly 20% (Aarsland et al., 2009; Nguyen et al., 2007). This great variability is even more remarkable concerning PD-MCI subtypes (Aarsland et al., 2009; Caviness et al., 2007; Janvin et al., 2006) maybe due to different cut-off criteria and the use of different number of tests.

Initially, PD-MCI diagnostic criteria were taken from the definition of MCI as a pre-stage of AD dementia (Petersen et al., 2001). In this early definition of MCI, memory decline was the key characteristic of the diagnosis. This decline was greater than that observed in normal aging but patients could not reach criteria for probable AD (Petersen et al., 2001). A few years later, these criteria were revised and although memory impairment was still a key point for the characterization of MCI, the criteria for the diagnosis were that decline could be in any cognitive domain being self and/or informant report or derived from comprehensive neuropsychological assessment (Winblad et al., 2004). MCI could be amnestic or non-amnestic and single or multidomain (Winblad et al., 2004).

The MDS PD-MCI task force published new criteria to diagnose MCI especially for PD patients in 2012 (Litvan et al., 2012). Two levels were established: level I allows for the "diagnosis of PD-MCI based on an abbreviated cognitive assessment, because comprehensive testing may not always be practical or available. Level I criteria provide less diagnostic certainty than level II". Level II is a comprehensive assessment that includes the possibility of subtyping PD-MCI in cognitive domains, being single or multi-domain (Litvan et al., 2012). The main difference between PDD and PD-MCI is that in MCI no functional impairment affects the patient's performance on the activities of the daily living (see **Panel 5** on page 44).

After the publication of the criteria, some studies have assessed their utility. Level I criteria were tested at different cut-off points (1 SD, 1.5 SD, and 2 SD). Scores

were then compared with age-matched and/or education-matched normative data and secondly, with premorbid measures. The results presented a great variability in the characterization of PD-MCI (Szeto et al., 2015a). A similar study was previously published with level II criteria and the authors finally concluded that the 2 SD cut-off was the most optimal when comparing PD-MCI published criteria with the consensus-based diagnosis performed in their center (Goldman et al., 2013).

Another goal of the PD-MCI task force is to narrow the recommended test battery for the diagnosis. However, a recent work that included more than 3,000 PD subjects and 1,000 controls from the MDS PD-MCI task force concluded that cognitive performance measured based on published norms revealed a great variability across studies while calculating normative data from controls reduced this variability (Hoogland et al., 2018). This makes difficult to confidently choose sensitive tests for PD cognition. The MDS PD-MCI task force has recently published a multicenter study on 467 PD patients from four large cohorts that related level II PD-MCI criteria (<1.5 SD cut-off) to the evolution of PDD after controlling for demographics and clinical characteristics such as PD disease severity and depression (Hoogland et al., 2017). Recently in this year, similar findings were reported for level I PD-MCI diagnosis in the prediction of PDD (Hoogland et al., 2019).

Panel 5 Diagnostic criteria for PD-MCI according to the MDS for PD-MCI task force (Litvan et al. 2012)

I. Inclusion criteria
- Diagnosis of Parkinson's disease as based on the UK PD Brain Bank Criteria
- 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 (detailed in section III)
- Cognitive deficits are not sufficient to interfere significantly with functional independence, although subtle difficulties on complex functional tasks may be present

II. Exclusion criteria
- Diagnosis of PD dementia based on MDS Task Force proposed criteria
- 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 III. Specific guidelines for PD-MCI level I and level II categories

A. Level I (abbreviated assessment)
- 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)

B. Level II (comprehensive assessment)
- 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:
    - o Performance approximately 1 to 2 SDs below appropriate norms or
    - o Significant decline demonstrated on serial cognitive testing or
    - o Significant decline from estimated premorbid levels

IV. 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)

PDD diagnosis

Dementia onset is insidious (Emre et al., 2007), the final stage of PD where quality of live is considerably reduced (Lawson et al., 2016; Leroi et al., 2012) and it is

the phase of the disease with the most burdensome for caregivers also mainly due to the presence of hallucinations (Aarsland et al., 2000). The most reported risk factors for dementia are old age (Aarsland and Kurz, 2010; Domellöf et al., 2015; Williams-Gray et al., 2013), severity of motor symptoms, mainly PIGD manifestations (Aarsland et al., 2003; Aarsland and Kurz, 2010; Burn et al., 2006), MCI (Aarsland and Kurz, 2010; Domellöf et al., 2015) or specific deficits in neuropsychological tests (Williams-Gray et al., 2013), visual hallucinations (Aarsland et al., 2003; Aarsland and Kurz, 2010) and the haplotype H1 in MAPT genotype (Williams-Gray et al., 2013). It seems that the disease duration or age of onset have no further contributions to the development of dementia beyond age itself (Kehagia et al., 2010).

After 10 years from PD diagnosis (Williams-Gray et al., 2013), dementia occurred in 46% of the population while only 23% of the sample (142 PD patients) had a good outcome. Dementia incidence is estimated over 55 per 1,000 person-years in PD, 2.6 times higher than the estimated incidence in the general population. Mortality at 10 years from the diagnosis is up to 55% causes are usually not related to PD (Williams-Gray et al., 2013). Based on prospective, community-based studies reported estimated incidences are diverse. In a 5-years follow-up study (147 PD patients), the percentage of dementia was slightly lower (almost 30%) although the estimated incidence was higher: 63 per 1,000 person-years (Domellöf et al., 2015). Over 4.2 years (130 patients), estimated dementia incidence was estimated up to 95 per 1,000 person-years (33%). When following a cohort up to 8 years, the prevalence of PD patients evolving to dementia was 80% (Aarsland et al., 2003). Incidence and prevalence can vary between studies because while some explored the probability of developing dementia in PD populations, others explored the prevalence of dementia in PD patients as part of large, prospective population-based cohorts.

Previous to PD-MCI criteria, the MDS task force dedicated to PDD published diagnostic criteria (**Panel 6**) of probable and possible PDD according to the level of uncertainty (Emre et al., 2007). Also in 2007, parallel to the diagnostic criteria publication (Emre 2007) and similar to what would posteriorly be published for PD-MCI, two levels of diagnosis for PDD were established (Dubois et al., 2007). Level I is a “simple short algorithm based on tools that can be used in an office or in the bedside”. It is mainly conceived for clinicians with no expertise in neuropsychological methods and for example, proposes a cut-off <26 in MMSE scores. Level II implies a comprehensive neuropsychological assessment to specify PDD severity or its patterns. It includes four domains: global cognitive efficiency, subcortico-frontal features, instrumental functions and neuropsychiatric features (Dubois et al., 2007).

Panel 6 Diagnostic criteria for PDD from Emre et al., 2007

Features of dementia associated with PD

I. Core features

1. Diagnosis of Parkinson's disease according to Queen Square Brain Bank criteria
2. 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

II. Associated clinical features

1. Cognitive features:
• Attention: Impaired.
• Executive functions: Impaired.
• Visuo-spatial functions: Impaired.
• Memory: Impaired.
• Language: Core functions largely preserved. Word finding difficulties and impaired comprehension of complex sentences may be present
2. 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

III. Features which do not exclude PD-D, 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
• Time interval between the development of motor and cognitive symptoms not known

IV. Features suggesting other conditions or diseases as cause of mental impairment, which, when present make it impossible to reliably diagnose PD-D

• Cognitive and behavioral symptoms appearing solely in the context of other conditions such as:
Acute confusion due to
a. Systemic diseases or abnormalities
b. 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)

Diagnostic criteria for PDD

Probable PD-D

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 visuo-spatial 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 PD-D, lack of behavioral symptoms, however, does not
exclude the diagnosis
C. None of the group III features present
D. None of the group IV features present

Possible PD

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

Neuropathology of cognition in PD

A Lewy-pathology (i.e., α-synuclein inclusions) staging was proposed for PD (Braak et al., 2006b, 2003; Braak and Del Tredici, 2008); which correlates with cognitive status (Braak et al., 2006a). α-synuclein aggregates would follow a caudal to rostral pattern starting in the autonomic neurons of the peripheral nervous system, the olfactory system, and the medulla oblongata and final stages (V and VI) include widespread neocortical regions from the prefrontal cortex and associative sensory areas, extending to premotor and finally primary sensory areas. The motor onset symptomatology and in many cases, PD diagnosis does not take place until stage III, which explains the premotor symptomatology: olfactory dysfunction, constipation or cognitive disturbances at stages I and II (see **Panel 7** and **Figure 3**).

Panel 7 Braak stages

Stage I

Lewy pathology would start in the enteric nervous system in the vagal dorsal motor nucleus of the medulla oblongata and the anterior olfactory nucleus.

α-synuclein aggregates have been found in the gastric mucosa (Sanchez-Ferro et al., 2015).

Stage II

Pathology extends to the locus coeruleus, caudal raphe nuclei and gigantocellular reticular nucleus.

Stage III

Pathology extends to the midbrain, especially the pars compacta of the substantia nigra. Motor diagnosis is usually made at this stage, when nigral cells are already severely depleted.

Stage IV

Most nigral dopaminergic cells are depleted and Lewy-pathology extends to the temporal lobe: the entorhinal cortex, allocortex (CA2-plexus) and transentorhinal areas. Neocortical regions still unaffected.

Stage V and VI

Neocortical regions affected. Prefrontal involvement as well as the anterior cingulate and the insula are the first neocortical regions affected by PD pathology. Also, degeneration from high order sensory associative areas to primary both sensory and motor areas.

(Braak et al., 2003a; 2003b; 2006; Del Tredici 2013; Dickson and Braak, 2009)

Braak staging pathology has revealed useful to describe neuropathological evolution of PD (Jellinger, 2004) although is insufficient in advanced stages (V and VI) of the disease (Jellinger, 2009), especially in dementia (Jellinger, 2008) and in patients with rapid disease progression (Halliday et al., 2008). Therefore, the unifying theory of Lewy-body pathology for PD would be useful only for the typical case of PD but not for older PD onset with a more aggressive type (Halliday et al., 2008).

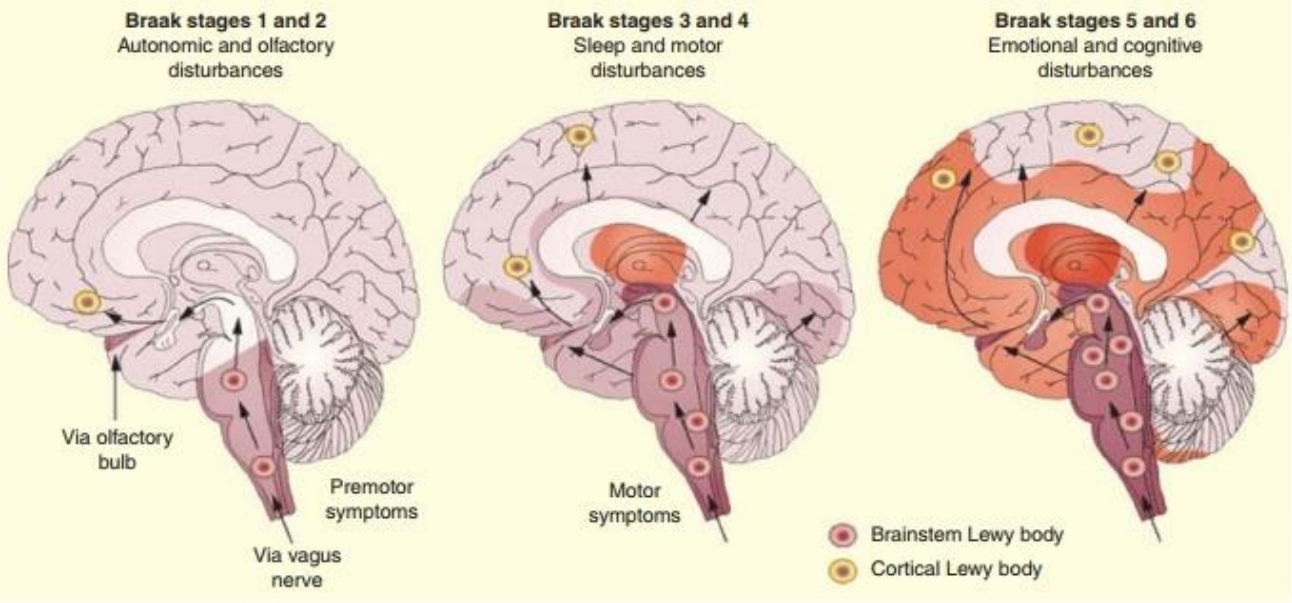

Figure 3 Extracted from Jellinger, 2014 Expert Review of Neurotherapeutics. Vol 14(2). https://doi.org/10.1586/14737175.2014.877842

The pathological mechanisms contributing to PDD are heterogeneous including Lewy body pathology (Del Tredici and Braak, 2013; Irwin et al., 2012), neurofibrillary tangles and senile plaques from AD (Del Tredici and Braak, 2013; Halliday et al., 2014). Lewy body densities seem to be the most important biological marker for PDD and cognition (Aarsland et al., 2005). Densities in the temporal lobe differentiated PDD patients from non-demented patients (Halliday et al., 2014; Harding and Halliday, 2001) and more importantly, independent from the presence of neuritic plaques related to AD pathology, Lewy body presence in the frontal gyrus was a predictor of MCI in PD (Mattila et al., 2000). Indeed, higher Lewy pathology findings in occipital regions of PD patients indicated a more rapid progression to dementia (Toledo et al., 2016).

However, another study found that a combination of both PD-related and AD-related pathologies were the best predictors of PDD (Compta et al., 2011; Jellinger, 2010). Although further research is needed, the neuropathological basis of PDD would be formed by a synergistic effect of α-synuclein aggregates PD-type with other pathologies specially AD-type such as amyloid-β (Delgado-Alvarado et al., 2016) that drives the cognitive evolution of PD patients to overt dementia (Halliday et al., 2014; Irwin and Hurtig, 2018). Interestingly, one longitudinal study has evaluated the predictive value of several markers that could contribute to PDD (Compta et al., 2013). Lower CSF amyloid-β levels, decline in verbal learning, semantic fluency and visuoperceptual scores, and cortical thinning in superior frontal, anterior cingulate and precentral regions were significant predictors of dementia (Compta et al., 2013). In the next section, structural MRI correlates of cognition in PD will be presented.

Structural MRI correlates

Structural MRI studies have reported differences between PD patients and controls. VBM estimates the amount of GM in a voxel through its signal intensity (Good et al., 2001; Whitwell, 2009). This technique also allows to estimate subcortical GM structures that represent the volume. Both GM volumes and GM density can be quantified through VBM (see **Panel 1.1**, on page 28). GM reductions have been found in non-demented PD patients compared with controls in left superior temporal gyrus (Pereira et al., 2012). Subcortically, PD patients also had hippocampal, amygdala and nucleus accumbens volume reductions (Biundo et al., 2013). However, VBM techniques are dependent on a good registration of each individual and sometimes ambiguities can arise between what is actual GM atrophy or changes in folding of gyrification (Bookstein, 2001). In the same study that assessed VBM GM reductions in PD patients, regional cortical thickness was found to be more correlated with age and more extended cortical thinning regions were reported: the bilateral occipital, bilateral inferior and left superior parietal areas, right superior temporal and regions of the right frontal cortex including the pars opercularis, precentral and postcentral gyri (Pereira et al., 2012).

PD-MCI

Structural MRI findings linked to cognition in PD are inconsistent. Global atrophy measures were reported in PD large cohorts such as ventricular enlargement in PD-MCI patients relative to controls and PD cognitively preserved patients (Apostolova et al., 2012; Segura et al., 2014) as also reported in PDD patients (Apostolova et al., 2010). Total GM volumes and mean cortical thickness measures were also reduced in PD-MCI patients (Segura et al., 2014).

GM density studies have reported density reductions not surviving multiple comparisons adjustment in the right anterior temporal gyrus, left prefrontal, insular, right parietal and occipital areas in PD-MCI compared with controls (Song et al., 2011). When comparing them with PD cognitively preserved patients dissimilar in disease duration to PD-MCI, only GM density reductions were found in the right middle frontal area (Song et al., 2011). GM volume reductions have been reported in the left superior temporal gyrus (Yarnall et al., 2014) in PD-MCI patients at an early stage of the disease (mean ± SD disease duration: 5.5 ± 5.0 years). Others reported no significant GM reductions in 11 subjects with early PD-MCI (Dalaker et al., 2010) or differences in temporal and frontal areas that did not survive multiple comparisons correction (S. W. Noh et al., 2014). With a more advanced time in the disease (7.2 ± 5.0 years), GM differences are more evident when comparing PD-MCI patients with controls in superior and inferior temporal regions, in bilateral precentral and postcentral gyri, in the precuneus, superior

and middle frontal gyri, superior lateral occipital and subcortical regions: bilateral amygdala, hippocampus and right putamen (Melzer et al., 2012).

Differences were found in PD-MCI patients compared with PD cognitively intact patients in left frontal areas (Beyer et al., 2007; Mak et al., 2014; S. W. Noh et al., 2014), left precuneus (S. W. Noh et al., 2014), left posterior cingulate (S. W. Noh et al., 2014), and left (Beyer et al., 2007; Mak et al., 2014) and right (Beyer et al., 2007; S. W. Noh et al., 2014) temporal regions. However, none of these results survived multiple comparison correction and patients' cohorts had different disease durations.

Research from cortical thickness studies have revealed to be more sensitive to subtle changes across the cortical mantle (Pereira et al., 2012). When analyzing cortical parcellations, PD-MCI patients had reduced thickness in the cuneus and the olfactory areas compared with controls (Biundo et al., 2013) and increased mean cortical thickness compared with PD normal cognition patients in left temporal inferior and occipital and right parietal and frontal areas including the orbital (Biundo et al., 2013).

Vertex-wise cortical thickness differences reported that PD-MCI diagnosed patients according to MDS criteria level II differentiate from controls in widespread both lateral and middle posterior areas (Mak et al., 2015; Segura et al., 2014) such as the lateral occipital, the superior and inferior parietal, the supramarginal gyrus and the precuneus. Some authors also reported the involvement of left frontal regions (Segura et al., 2014) and middle temporal areas (Hanganu et al., 2013) including the parahippocampal as well as the lateral posterior and inferior temporal gyrus. In early medicated patients, cortical thinning was observed in frontal bilateral regions including the orbitofrontal (Hanganu et al., 2013; Mak et al., 2015). In newly diagnosed unmedicated PD patients reported atrophy between PD-MCI and controls groups was more focal (Danti et al., 2015; Pereira et al., 2014). Thickness reductions were reported in the superior frontal gyrus (Danti et al., 2015), precentral gyrus (Pereira et al., 2014), precuneus (Danti et al., 2015; Pereira et al., 2014), superior (Pereira et al., 2014) and inferior (Danti et al., 2015) parietal gyri, lateral and medial temporal (Danti et al., 2015; Pereira et al., 2014) and lingual gyrus (Pereira et al., 2014).

PD patients with and without MCI also differentiated from each other in left superior temporal, precentral (Pereira et al., 2014), insula (Danti et al., 2015), bilateral postcentral (Pereira et al., 2014; Segura et al., 2014), right superior frontal, middle temporal (Danti et al., 2015), superior parietal (Pereira et al., 2014) and right supramarginal and precuneus regions (Pereira et al., 2014; Segura et al., 2014). Nonetheless, the comprehensive neuropsychological batteries used to diagnose level II PD-MCI patients (Pereira et al., 2014; Segura et al., 2014) did

not cover the language assessment as recommended (Litvan et al., 2012) or the sample size was very small (Danti et al., 2015).

A recent coordinate-based meta-analysis including 15 studies have reported as coincident regions of GM reductions the right supramarginal gyrus and left posterior insula (14 studies) and the mid-cingulate (13 studies) between PD-MCI patients and PD cognitively normal (Mihaescu et al., 2018). This meta-analysis also investigated differences with PDD patients across 11 studies. GM reductions in the bilateral insula differentiated PDD patients from non-demented PD patients in all 11 studies (Mihaescu et al., 2018).

Prospective longitudinal studies are scarce probably due to attrition rates. In a sample of early treated PD patients with mild cognitive deficits cortical thickness reductions were found in bilateral frontal regions in precentral gyrus and pars opercularis and in bilateral temporal regions when compared to controls over a 3-years follow-up and no baseline differences (Ibarretxe-Bilbao et al., 2012). Cortical thinning progression was probably underestimated in this sample that did not differentiate patients from their cognitive prognosis.

Two prospective studies with approximately 1.5 years follow-up (Hanganu et al., 2014; Mak et al., 2015), reported widespread rates of cortical thinning in PD-MCI compared with controls including left lateral and parts of the prefrontal cortex (Mak et al., 2015), left lateral superior temporal cortex extending to the inferior parietal gyrus (Mak et al., 2015), right anterior and posterior medial parts of the temporal cortex (Hanganu et al., 2014), right superior parietal (Hanganu et al., 2014; Mak et al., 2015) extending to the precentral and postcentral gyri (Mak et al., 2015), and right precuneus (Hanganu et al., 2014). When comparing both PD groups, the PD-MCI group had greater rates of atrophy in the superior lateral temporal gyrus, medial superior parietal (Hanganu et al., 2014; Mak et al., 2015) and superior precentral (Mak et al., 2015) atrophy.

Another study followed prospectively 22 PD *de novo* patients with normal cognition over 3 years with no detectable atrophy at baseline (Tessa et al., 2014). Over time, PD patients had increased progressive atrophy in the superior prefrontal, anterior cingulate cortices, the caudate nucleus and the thalamus in comparison with controls regardless their cognitive status (Tessa et al., 2014).

Given the association of PD pathology with AD, a longitudinal study investigated the relationship between a specific pattern of regional GM atrophy found in AD (temporal lobe areas, precuneus, posterior cingulate and peri-hippocampal white matter) with PD neuropsychological performance (Weintraub et al., 2012). Longitudinally, this study included non-demented PD patients and the atrophy index in the AD-type areas was the most significant predictor of long-term cognitive decline (Weintraub et al., 2012).

Overall, the presence of PD-MCI is related to greater atrophy than that observed in controls and more importantly in PD patients with no cognitive decline. Thus, such atrophy is not only due to disease pathological progression but also underlies cognitive dysfunction. However, studies are inconsistent may be due to different methodologies used to diagnose PD-MCI, the number and the type of the neuropsychological tests employed, the different disease duration between cohorts and that, as proposed by the dual syndrome hypothesis, not all types of PD-MCI evolve to dementia where cortical atrophy is generalized and widespread.

PD dementia

Reports on global brain atrophy rates over a year were significantly increased in a small sample of PDD patients in comparison with PD non-demented patients and controls (Burton et al., 2004). More specifically, cortical degeneration in the medial temporal lobe has been related to PDD although less pronounced than in dementia with Lewy bodies and AD (Tam et al., 2005). Bilateral ventricular enlargement, posterior cortical degeneration and right caudate atrophy have been reported in PDD patients compared with PD non-demented and controls (Apostolova et al., 2010). Ventricular enlargement has been described in other types of dementia such as in AD as cognitive decline predictor (Chou et al., 2010).

GM density reductions have been found in PDD patients across all cortical lobes when comparing them with controls, although results were not corrected for multiple comparisons (Song et al., 2011). These differences were more modest when comparing PDD patients with PD-MCI in bilateral middle temporal, right inferior temporal and left middle and superior prefrontal (Song et al., 2011).

From VBM-GM volumes studies, the right hippocampus, the bilateral anterior cingulate gyrus (Summerfield et al., 2005) and the left inferior and parietal lobes (Burton et al., 2004) were reported to be reduced in PDD patients compared with controls. Other studies have reported uncorrected hippocampal (Beyer et al., 2007), parahippocampal (Nagano-Saito et al., 2005) and cingulate atrophy (Beyer et al., 2007) in the left hemisphere as well as in the right inferior frontal gyrus (Nagano-Saito et al., 2005), occipital gyrus, bilateral temporal and amygdalar atrophy (Beyer et al., 2007) when comparing demented patients with controls. Between PDD patients and the non-demented group, GM reductions were found in left fusiform and bilateral lingual gyri of the occipital lobe (Burton et al., 2004) as well as bilateral frontal, temporal (Beyer et al., 2007; Nagano-Saito et al., 2005) and parietal (Beyer et al., 2007) regions, in the thalamus (Beyer et al., 2007; Nagano-Saito et al., 2005), the caudate and the right hippocampus (Nagano-Saito et al., 2005). More interestingly, PDD patients did not differentiate from dementia of Lewy bodies in GM reductions while AD patients had more pronounced atrophy

in the hippocampus, parahippocampal gyrus and inferior temporal gyrus (Burton et al., 2004).

Longitudinally, PDD patients have more increased rates of global brain atrophy than non-demented PD patients and control subjects (Burton et al., 2005). Indeed, PDD patients followed up to 2 years had more discrete GM progressive reductions than non-demented patients located in the right hemisphere, including occipital and temporal regions whereas PD non-demented had progressive loss in paralimbic regions and associative temporo-occipital atrophy (Ramírez-Ruiz et al., 2005). These findings could reflect the neuropathological Braak staging (Braak et al., 2003), that postulated at stage 4 limbic and paralimbic atrophy preceding stages 5 and 6 that includes neocortical degeneration (Braak et al., 2006b, 2003), see **Panel 7** on page 47.

Cluster analysis techniques for the identification of PD subtypes

The most common PD classifications based on their motor and non-motor clinical manifestations have been introduced. Reviewing the literature, one can establish links between PD subtypes. For example, patients with severe motor impairment including tremor and postural instability motor disturbances in turn are usually older at disease onset or they also have PD-MCI; or PD patients with visual hallucinations or depression symptoms are usually the ones who end up with dementia. Therefore, the existence of one particular trait in PD that determines prognosis is improbable and interaction between PD subtypes is not clear in the literature. The emergence of machine learning techniques has allowed to evolve in the study of neurodegenerative diseases. Machine learning is a discipline in the field of the Artificial Intelligence which creates systems that learn automatically for “understanding data” (James et al., 2013). Thus, confers the power to perform studies free of a priori hypotheses from data-driven approaches. **Figure 4** summarizes the increasing number of works that took advantage of these new techniques in the field of PD research.

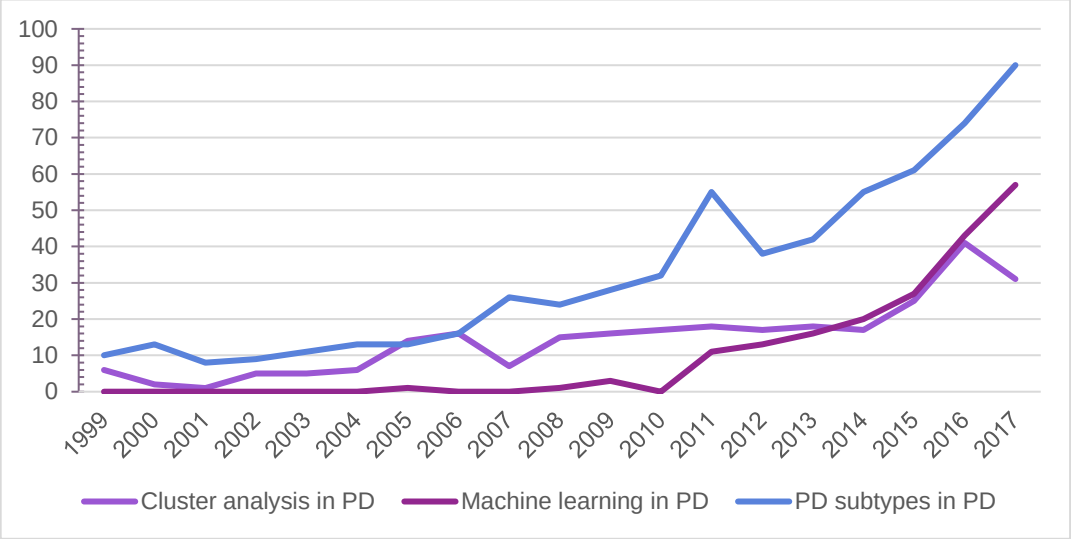

Figure 4 Number of studies per year, from Pubmed in PD samples (http://dan.corlan.net/medline-trend.html).

Machine learning techniques: cluster analysis

Cluster analysis is part of the machine learning techniques that during the past few decades have emerged as one possible future technique for the characterization and prediction of diseases. Though the discipline is fairly new, some of the underlying concepts were introduced back in the XIX century.

The "method of least squares" is the root for linear regression that allows predicting quantitative values; and later on, logistic regression was suited for categorial variables (Hastie et al., 2008; James et al., 2013).

Most of the machine learning techniques can be divided as supervised or unsupervised. Indeed, regression analyses would be one example of supervised prediction (see **Figure 5**). Supervised methodologies are based on algorithms that learn from a training set of labeled examples for generalization to the set of all possible inputs. In other words, for each observation of the predictor measurement there is an associated response measure (James et al., 2013).

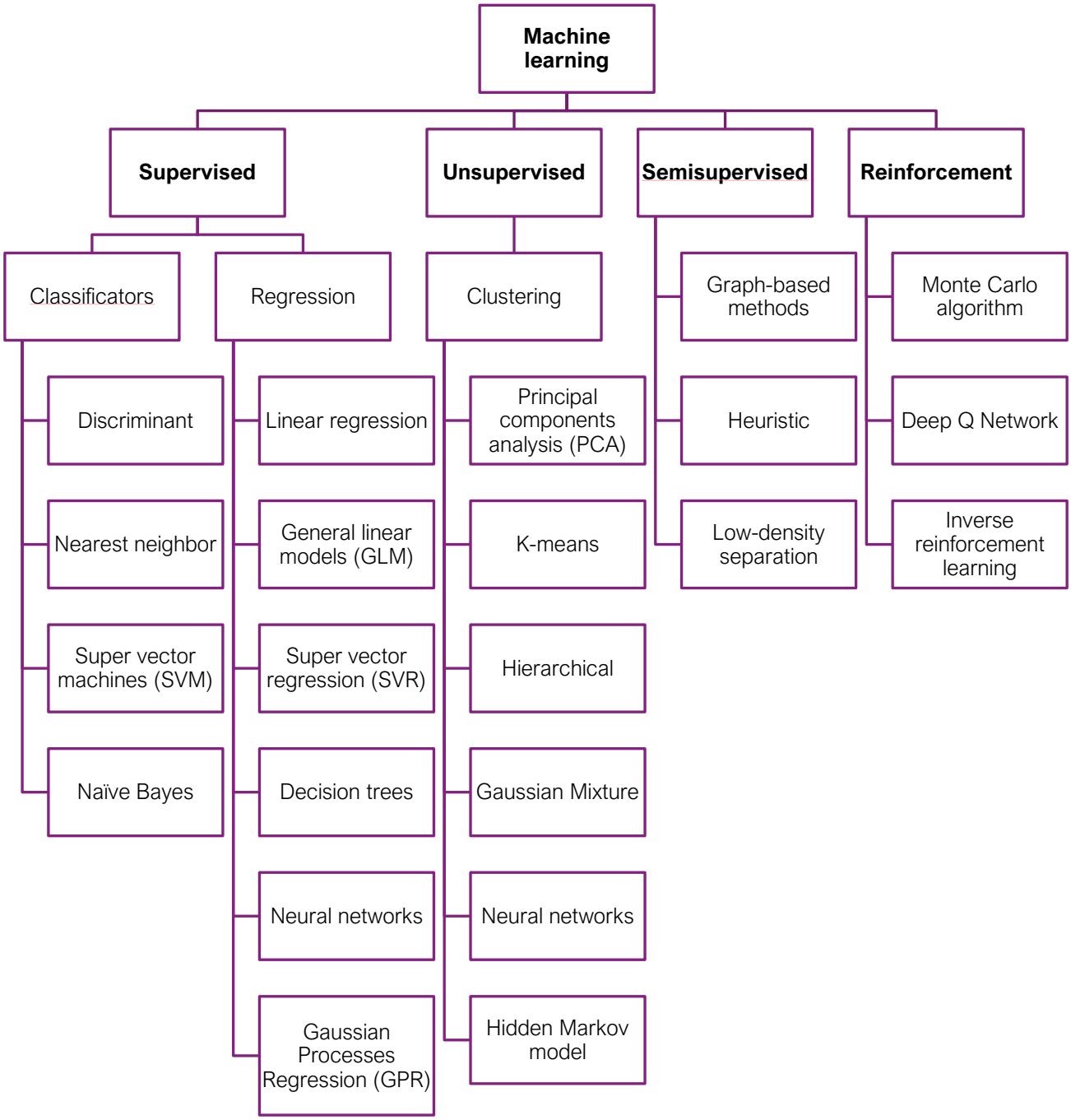

Figure 5 Supervised and unsupervised machine learning techniques

On the other hand, in unsupervised methods there is no outcome measure and the goal is to describe associations and patterns among a set of input measures (Hastie et al., 2008). Cluster analyses are part of the unsupervised methods, where from a bunch of features (variables), algorithm clusters (makes groups) of the observations (e.g., subjects) according to similarity/dissimilarity measures (James et al., 2013). Each cluster analysis technique has its own quantification of similarity between observations, which will determine the way the algorithm split the sample (**Panel 8**).

Panel 8 Cluster analysis techniques: unsupervised techniques

Partitional
- Centroid-based: *k-means*
- Principal component analysis

Hierarchical
- Agglomerative: bottom-up. Includes single linkage, Ward's method…
- Divisive: top-down

Bayesian
- Probabilistic clustering
- Based on hypothesis

Other types of cluster analysis
- 2-step cluster analysis: BIC…
- Model-based cluster analysis, non-gaussian

Partitional clustering methods split data into *k* number of mutually exclusive clusters. Each subject is assigned to a cluster by minimizing the distance from the data point to the mean or median location of its assigned cluster. Usually, a priori hypotheses are needed to determine the number of cluster solutions, although there are several algorithms that can calculate the best optimal cluster solution (James et al., 2013). The belonging into a determined group can change dramatically from one cluster solution to another, since each time the algorithm evaluates the best aggrupation based on the minim dissimilarity between variables. The usual methodology that can be found in early works using these techniques was based on *k-means*.

In hierarchical clustering, the grouped observations conform a multilevel hierarchy where clusters at one level are joined in the next level. Bottom-up clustering initiates from the fact that each observation (subject) constitutes one cluster by itself and, at the final cluster level, all subjects are part of one unique cluster. Divisive clustering is just the opposite, clustering algorithm starts from assuming all subjects are one cluster and splits the sample into as many subjects as there are.

The choice of the distance or dissimilarity measure between two objects is of crucial importance in any cluster analysis technique, being the Euclidean distance

the most commonly used. However, dissimilarity only refers to pairs of observations (or subjects). Specially in hierarchical methods, once the first aggrupation has been made, the distance will be calculated between two clusters where at least one will contain multiple observations (see dendrogram in **Figure 6**). Therefore, the dissimilarity between pairs of clusters made in the previous step will be referred to as linkage measures. The most common types are the complete linkage, the average, single, centroid and Ward's method (see **Table 3** on page 58).

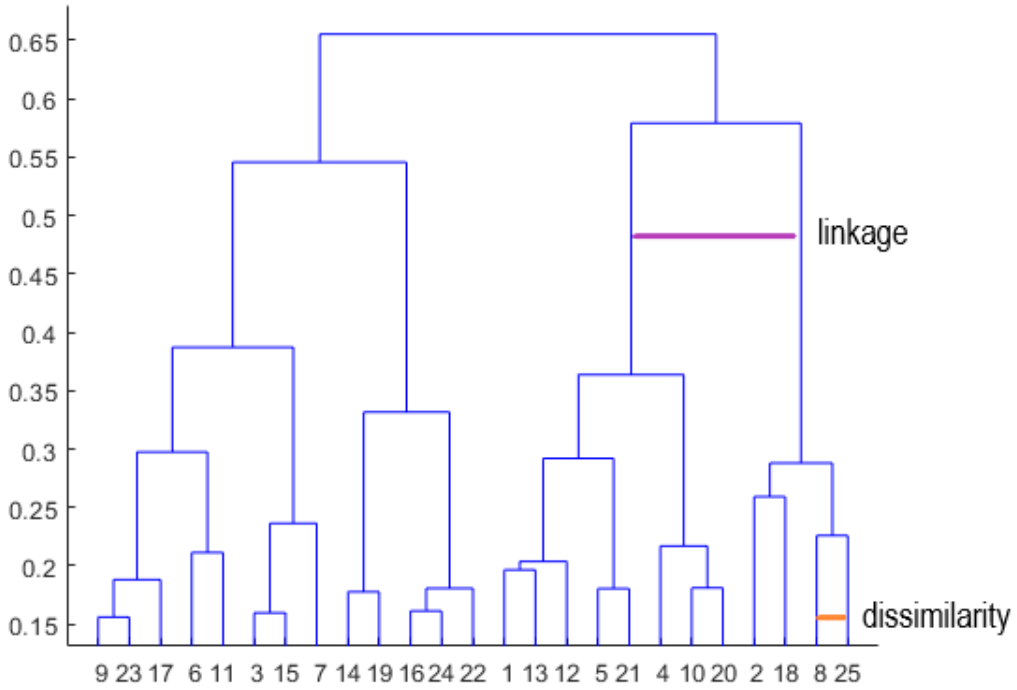

Figure 6 Dendrogram example, modified from the Matlab website help (https://es.mathworks.com/help/stats/dendrogram.html?lang=en). In orange a distance similarity between two observations. In purple linkage distance between two previously formed clusters

Once two observations are clustered, in the next level the aggrupation already considers the former two observations as one that in the same turn will cluster with other single observations or clusters.

There is no standard single criterion that allows to choose the best clustering method. In fact, depending on the type of the data and the aims, multiple clustering techniques will be fitted. For example, a study could aim to explore how the subjects of a sample tend to group. However, there is no clear predefined hypothesis that implies the sample should be divided by an *n* number of clusters. In this case, hierarchical clustering techniques are suitable to explore different levels of aggrupation since they not only give groups but also a structure (James et al., 2013).

Between linkage methods, each can be best fitted depending on the distribution of the data. An early study that compared several types of linkage methods reported that among all, Ward's was the best classifier (Blashfield, 1976). However, the presence of outliers in the features (variables) included in the clustering analysis worsen its performance. Indeed, cluster analysis can be also useful to detect the presence of outliers and after the exclusion, the algorithm can be re-run (Milligan, 1980).

Table 3 Types of linkage methods

Linkage	*Description*
Complete	Maximal intercluster dissimilarity. Compute all pairwise dissimilarities between the observations in cluster A and the observations in cluster B and record the *largest* of these dissimilarities.
Single	Minimal intercluster dissimilarity. Compute all pairwise dissimilarities between the observations in cluster A and the observations in cluster B and record the *smallest* of these dissimilarities. Single linkage can result in extended, trailing clusters in which single observations are fused one-at-a-time.
Average	Mean intercluster dissimilarity. Compute all pairwise dissimilarities between the observations in cluster A and the observations in cluster B and record the *average* of these dissimilarities.
Centroid	A centroid is the vector of the n feature means for the observations in the cluster; in other words, they are the mean of the observations assigned to each cluster. Dissimilarity between the centroid for cluster A (a mean vector of length *p*) and the centroid for cluster B. Centroid linkage can result in undesirable *inversions*.
Ward	Uses the incremental sum of squares; that is, the increase in the total within-group sum of squares as a result of joining groups A and B.

Extracted from James et al., 2013 Statistical Learning. Springer Texts in Statistics.

Multidimensional subtypes in PD based on clinical data

In 1999 a first paper was published with the aim to characterize PD clinical variants from a data-driven approach (Graham and Sagar, 1999). In this study using non-hierarchical cluster analysis, motor function, mood disorders, different aspects of cognition and demographics such as disease duration variables were used to identify three distinct subtypes of PD: the "motor-only", the "motor and cognitive" and the "rapid progression" subtype. These 3 subgroups identified via data-driven methodology were in accordance of previous literature described: the first "motor-only" suggested nigro-putaminal dopamine deficiency, the second subtype could have additional non-dopaminergic implications more related to

PDD processes and the “rapid progression” subtype was related to an older age of disease onset and maybe to multifocal pathology (Graham and Sagar, 1999).

After the first cluster analysis in PD, several other phenotypes have been identified based on this methodological approach using several demographical, clinical and cognitive variables as it has already been introduced above (**Table 1**, in the section of motor subtypes page 31, Van Rooden et al., 2010). In this first review of the literature, authors concluded that most of the studies reported clusters of patients based on their age of disease onset (Gasparoli et al., 2002; Lewis, 2005; Post et al., 2008; Reijnders et al., 2009; Schrag et al., 2006) and less prevalent were the tremor and non-tremor motor phenotypes (Lewis, 2005; Reijnders et al., 2009). Others did classify patients based on motor severity but not on distinct manifestations and the presence of cognitive disturbances (Dujardin et al., 2004; Graham and Sagar, 1999). Posteriorly, a study also using non-hierarchical cluster analysis (*k-means*) identified 4 subgroups: a young disease-onset cluster, a tremor-dominant group, a non-tremor dominant with the highest percentage of PD-MCI and a group with rapid disease progression (Szeto et al., 2015b). Mainly, studies report groups with no-presence or mild motor disturbances, general impairment in all domains or either motor without non-motor symptoms or viceversa (Erro et al., 2016, 2013; Mu et al., 2017; Van Rooden et al., 2011), although each study selected arbitrary clinical variables.

Besides the common motor phenotypes and the presence of cognitive disturbances (Erro et al., 2013; Van Rooden et al., 2011), clinical variables that are usually included in the clustering formation algorithms are: presence of psychotic symptoms, autonomic dysfunction by means of the Scales for outcomes in Parkinson’s disease-autonomic (SCOPA-AUT, Visser et al., 2004), daytime sleepiness and REM sleep behavior disorder (Van Rooden et al., 2011) and depressive symptoms (Erro et al., 2013; Van Rooden et al., 2011). As global measure of non-motor symptoms, one study included the total scores on a dichotomic self-administered questionnaire (Erro et al., 2013). In Van Rooden et al., once the four clustering solution was chosen, the age at onset and the L-DOPA intake doses were the most discriminant variables between clusters (Van Rooden et al., 2011). All studies previously commented used a *k-means* non-hierarchical methodology for the cluster analysis, except for one (Van Rooden et al., 2011) that used a model-based cluster analysis (Banfield and Raftery, 1993) that is not hierarchical nor partitional and follows a non-gaussian distribution.

Three PD subtypes have been recently proposed: the “mainly motor/slow progression”, the “diffuse/malignant” and an “intermediate” group. This prospective study based the clustering classification on orthostatic hypotension, MCI, rapid eye movement sleep behavior disorder, depression, anxiety and UPDRS Part II and III scores from a broad pool of variables (Fereshtehnejad et al., 2015). The authors used a 2-step cluster analysis technique that allows choosing

the best number of clusters and the selected clinical variables were also chose from the Bayesian information criterion. More recently, the same team has published a hierarchical cluster analysis on newly diagnosed drug naïve PD patients using 18 variables as features that included motor and non-motor clinical variables including neuropsychological performance and blood biomarkers (Fereshtehnejad et al., 2017). Unfortunately, structural MRI markers and CSF levels could not be part of the features in cluster analysis. Authors replicated previous results, identifying three clusters of "mild motor-predominant", "intermediate" and "diffuse malignant". Of high relevance was the fact that the diffuse malignant subtype had higher GM cortical atrophy compared with the other two subtypes and healthy controls as well as greater caudate denervation, and lower amyloid-β levels in CSF. Overall suggesting that in *de novo* PD patients with similar disease duration and demographical characteristics, there exists substantial differences in clinical and biomarker measurements (Fereshtehnejad et al., 2017).

Cluster analysis techniques have been used to identify cognitive phenotypes. A study based *on k-means* found five different cognitive groups of patients based on their cognitive performance (Dujardin et al., 2013). The groups composed a gradient from the cognitively intact group to a group of patients with severe impairment in all cognitive domains. In between there was a group of patients with no cognitive impairment but slight mental slowing, mild impairment in cognition except for recognition memory and a fourth patient with all domains impaired (Dujardin et al., 2013). In a recent work, PD *de novo* patients were also classified according to their cognitive profile (LaBelle et al., 2017). In this study, the cluster classification algorithm was like that used for exploratory factor analysis. Six classes were found in a sample of 424 newly diagnosed drug naïve PD patients. There were two opposing groups in the extremes: the weak overall group with mainly impairment in all the neuropsychological tests and the strong overall group with a high standing performance. In between there was a group with average normal-range z-scores in all subtests. The other three classes reported were based on authors assumptions. There was an amnestic group with deficits in learning and recall verbal memory. Another class with marked visuospatial impairment (as measured by the Judgement of Line Orientation Test).The sixth group was the "Strong-Memory" performance that, besides the outstanding performance in the two verbal memory tests, patients showed poor performance in the visuospatial task (LaBelle et al., 2017). These two studies overlapped in the extreme subgroups: the cognitively intact and the one with severe cognitive impairment, while the in between clusters were not that clear, possibly due to the use of different number of tests and variety. Indeed, the last commented study (LaBelle et al., 2017) used a more limited neuropsychological battery. The finding

of an outstanding group (LaBelle et al., 2017) could be also due to the biased sample characteristics.

Table 4 summarizes all cluster analysis studies in PD based on clinical data.

Table 4 Cluster analysis studies in PD

	PD sample	Technique	Features evaluated	Clusters	Description	Clinical characteristics
Graham 1999 (motor and non-motor clinical subtypes)	176 (un)medicated PD Mean disease duration: 7.5 years	k-means	Age of onset and disease duration UPDRS-II, activities of the daily living UPDRS-III, motor section BDI, depression symptoms Premorbid IQ Global cognition, dementia scale Visuospatial function Executive function, working memory and attentional tests.	5	Group 1: good motor control without MCI. Group 2: good motor control with cognitive deficits of the "executive" type. Group 3: older age of onset, poor motor control with motor complications, and global MCI. Group 4: poor motor control without MCI. Group 5: poor motor control with moderately severe global cognitive impairment.	Authors described 3 main PD phenotypes from the 5 clusters: "motor only": Groups 1 and 4 "motor and cognitive": Groups 2 and 5 "rapid progression": Group 3
Gasparoli 2002 (motor and non-motor clinical subtypes)	103 early PD <5 years Prospective 5-years follow-up study	Not specified	UPDRS-III motor section presence of motor fluctuations dyskinesia at 5 years	2	Slow progression: earlier age at onset, lateralization of parkinsonian signs, prevalence of rest tremor Rapid progression: older age, no lateralization of parkinsonian signs, bradykinesia-rigidity and PIGD	

	PD sample	Technique	Features evaluated	Clusters	Description	Clinical characteristics
Dujardin 2004 (motor and non-motor clinical subtypes)	44 PD unmedicated PD patients Prospective 3-years follow-up study	k-means + stepwise discriminant analysis	Age and education UPDRS-III, motor section 7 neuropsychological variables subset from Principal Component Analysis (PCA): Stroop test, semantic and phonetic fluency, verbal memory learning, recall and recognition tests, Mattis DRS scores. Measurements were from time 2. Discriminant analysis was performed on 25 variables: neuropsychological, demographic and 10 ROI from SPECT data. Data were from time 1.	3, reduced to 2	Cluster 1: no MCI and less severe motor disturbances than C2. Cluster 2: reduced overall cognitive efficiency and exacerbated subcorticofrontal syndrome Cluster 3: 2 patients with dementia at follow-up, discarded.	
Lewis 2005 (motor and non-motor clinical subtypes)	120 early stages PD	k-means	age of onset, rate of disease progression, L-DOPA doses UPDRS-III, motor phenotype score BDI, depression symptoms Premorbid IQ MMSE, global cognition PRM, pattern recognition memory TOL, Tower of London	4	C1: younger disease onset Mean age: 60 years and age of onset: 50 C2: tremor dominant C3: non-tremor dominant with significant levels of cognitive impairment and mild depression C4: rapid disease progression but no MCI	*younger onset and tremor subtypes*: slow rate of disease progression, mild motor symptoms, no MCI *non-tremor subtype*: MCI executive impairment type, depression and more rapid disease progression *rapid disease progression*: aggressive course, but no severe motor disturbances or MCI than other groups.

	PD sample	Technique	Features evaluated	Clusters	Description	Clinical characteristics
Schrag 2006 (motor and non-motor clinical subtypes)	124 PD patients	k-means	Age of onset, current age, rate of disease progression fluctuations, dyskinesia dementia	2 and 3	Young onset: higher depression scores, higher L-DOPA doses. Mean age: 60 years and age of onset: 52 Older onset: more rapid disease progression, less motor fluctuations and dyskinesia. Mean age: 70 years	Older group was in turn split into 2 cluster: 1) A group with MCI, more rapid disease progression but less L-DOPA doses than the other older onset group, Mean age of onset: 74 years 2) hallucinations and motor fluctuations. Mean age of onset: 65 years
Post 2008 (motor and non-motor clinical subtypes)	131 *de novo* PD	k-means	age, age of onset, rate of disease progression L-DOPA responsive PD symptoms MMSE, global cognition HADS, affective disturbances	2 and 3 cluster solution	*Young onset*: slower disease progression, less severe motor impairment. Mean age: 58 years *Intermediate:* mainly derived from the young onset group from the 2-cluster solution. Mean age: 66 years *Old onset*: more rapid disease progression and more severe motor impairment than the other groups. Mean age: 74 years	
Reijnders 2009 (motor and non-motor clinical subtypes)	346 PD patients split in 2 equal samples	k-means + classification model	Disease duration, age of onset UPDRS-III motor section UPDRS-IV L-DOPA complications Global cognition, MMSE MADRS, depressive symptoms UPDRS-I apathy UPDRS-I hallucinations	4	*Rapid disease progression*: non-tremor dominant symptoms, low psychopathological scores and low global cognition scores. *Young-onset:* higher L-DOPA complications *Non-tremor dominant*: hypokinetic, rigidity and PIGD type, high psychopathology (hallucinations, apathy and depression) and the lowest global cognition scores *Tremor-dominant*: low psychopathology	

	PD sample	Technique	Features evaluated	Clusters	Description	Clinical characteristics
Van Rooden 2011 (motor and non-motor clinical subtypes)	415 and a second cohort of 387 PD patients	Model-based + second sample validation	SCOPA, motor section, motor phenotypes and motor fluctuations SCOPA-COG, global cognition SCOPA-AUT, autonomic dysfunction Psychotic symptoms REM sleep behavior disorder and daytime sleepiness BDI, depression symptoms HADS; anxiety	4	C1: Mild motor complications and non-dopaminergic domains C2: Severe motor complications C3: mainly non-dopaminergic disturbances C4: all domains severely affected	C1: young age of onset, lower intake of L-DOPA doses and mild clinical disturbances. C2: longer disease duration but the youngest age of onset, severe motor complications, depression and sleep disturbances. High L-DOPA doses C3: old age of onset, mild motor complications and in non-motor clinical variables. C4: old age of onset, long duration L-DOPA intake, severe clinical complications sparing tremor symptoms.

	PD sample	Technique	Features evaluated	Clusters	Description	Clinical characteristics
Dujardin 2013 (cognitive subtypes)	557 PD patients	k-means	13 neuropsychological variables: Global efficiency, Verbal episodic memory, Stroop test, Digits span, TMT, verbal fluencies, visuospatial abilities, speed processing	5	Cluster 1: cognitively intact Cluster 2: cognitively normal, slightly slowed mental speed, working memory, verbal memory and executive function Cluster 3: overall cognitive impairment, recognition memory spared. Cluster 4: all cognitive domains impaired, including memory recognition but with spare of mental flexibility Cluster 5: all cognitive domains severely impaired.	C1: younger and more educated. C3,4 and 5: more severe motor symptoms, longer disease duration, and more axial signs. C4 and 5: hallucinations, depression, apathy and higher blood pressure C5: more presence of dementia
Erro 2013 (motor and non-motor clinical subtypes)	100 *de novo* PD patients Longitudinal 2-years follow-up	k-means	UPDRS-III, motor section NMS; questionnaire non-motor symptoms, divided also by domains MMSE, global cognition FAB, frontal assessment battery HADS, anxiety and depression Cluster analysis was performed on time 1 measures	4	*Benign pure motor*: younger age at onset, mild motor disturbances *Benign mixed motor and non-motor*: mild motor impairment, presence of mild non-motor symptoms such as frontal cognitive impairment, depression and anxiety *Non-motor dominant:* higher memory impairment, digestive and sleep disturbances, depression and anxiety symptoms *Motor dominant*: high motor impairment, rapid progression rate, depression, anxiety, frontal cognitive impairment.	

	PD sample	Technique	Features evaluated	Clusters	Description	Clinical characteristics
Fereshtehnejad 2015 (motor and non-motor clinical subtypes)	113 PD patients Prospective 4.5 years follow-up	2-step cluster analysis	Most informative variables for cluster solutions: UPDRS-III, motor section UPDRS-II, activities of the daily living REM sleep behavior disorder MCI Systolic blood pressure Analysis was performed with variables at time 1	3	*Mainly motor/slow progression*: tremor phenotypes and uncommon falls and freezing. *Diffuse/malignant*: higher presence of falls and gait disturbances, MCI multidomain (frontal and posterior), orthostatic hypotension, REM sleep behavior disorder and hallucinations. *Intermediate:* drop of systolic blood pressure, no MCI, intermediate scores on REM disorder, depression and anxiety	At follow-up, diffuse/malignant had more rapid disease progression, increased the presence of motor and non-motor symptoms and patients more likely developed dementia.
Szeto 2015b (motor and non-motor clinical subtypes)	209 PD patients Mean disease duration: 6 years	k-means	Age of onset, rate of disease progression UPDRS-III, motor phenotype score Premorbid IQ MMSE, global cognition Logical Memory II, TMT B, BDI, depression symptoms L-DOPA dosage	4	*Young age of onset* *Tremor dominant*: low L-DOPA doses and no cognitive impairment *Non-tremor dominant*: high L-DOPA doses, global cognitive impairment and Trail Making Test B impaired scores. *Rapid disease progression*: no severe cognitive impairment or motor disability	

	PD sample	Technique	Features evaluated	Clusters	Description	Clinical characteristics
Erro 2016 (motor and non-motor clinical subtypes)	398 newly diagnosed PD patients	k-means	Gender, age at onset MDS-UPDRS-III MoCA, global cognition GDS, depression symptoms STAI, anxiety UPSIT, hyposmia RBDSQ, sleep disturbances SCOPA-AUT autonomic dysfunction MDS-UPDRS-I for apathy, hallucinations, fatigue	3	G1: lowest motor and non-motor burden G2 and G3 had similar motor dysfunction, greater than G1. G2 had greater non-motor disturbances (apathy, hallucinations and fatigue) than G3.	^{123}[I]-FP-CIT binding SPECT scan: G1 less nigral-striatal denervation
Fereshtehnejad 2017 (motor and non-motor clinical subtypes)	421 *de novo* PD patients Prospective study of at least 1 year	Agglomerative hierarchical, Euclidean distance	age, genetic risk score, orthostatic systolic blood pressure drop, MDS-UPDRS-Part II, MDS-UPDRS Part III, tremor/PIGD scores, ESS, GDS, STAI, QUIP, RBDSQ, SCOPA-AUT, UPSIT, and average z-scores of visuospatial, speed/attention, memory and executive function	3	*Mild-motor:* younger patients, mild motor disturbances and mild non-motor including preserved cognitive decline compared with the other two groups Intermediate: patients with clinical scores in between the two extreme clusters. Diffuse/malignant: severe motor and non-motor impairment except for olfactory dysfunction and hallucinations	GM atrophy from deformation-based morphometry measures: diffuse/malignant > intermediate > mild-motor Diffuse/malignant subtype had the lowest CSF amyloid-β and total tau levels.

	PD sample	Technique	Features evaluated	Clusters	Description	Clinical characteristics
LaBelle 2017 (cognitive subtypes)	424 *de novo* PD patients	Latent class analysis	Neuropsychological variables: Verbal fluency SDMT, speed-processing JLO, visuospatial Working memory, letter sequence Verbal memory, learning and recall	6	*Weak-overall:* worse performance in all test scores Typical overall: average performance in all cognitive domains *Strong-memory:* poor visuospatial function and good performance in learning and recall verbal memory *Weak-visuospatial:* as in the strong memory domain, visuospatial impairment but with no outstanding performance in any other test *Amnestic:* impairment in verbal memory learning and recall and slight impairment in verbal fluency tests *Strong-overall:* outstanding performance in all tests, especially in the verbal memory domain	

Cluster analysis from objective MRI measurements

Frequently, clinical and cognitive features are used to subtype patients. Nevertheless, clinical variables are instrument and examiner-dependent. In other neurodegenerative diseases, machine learning techniques have been used on objective data such as MRI measurements, which have revealed as potential tools for identifying biomarkers.

In AD, unsupervised agglomerative hierarchical cluster analysis revealed three differential patterns of cortical atrophy based on cortical thickness data from the whole cortical mantle (Y. Noh et al., 2014). From the three patterns, one had diffused widespread cortical atrophy while the other two presented parietal dominant atrophy and the third medial temporal cortical thinning.

In frontotemporal dementia, a study also based on hierarchical clustering using GM volumes from 26 regions of interest found 4 subgroups of different cortical GM atrophy compared with controls from a whole-brain voxel-based morphometry approach (Whitwell et al., 2009). Authors reported a pattern of frontal dominant GM atrophy, another frontotemporal, a third temporo-fronto-parietal (widespread) and a final cortical atrophy pattern of temporal-predominant atrophy.

In PD, supervised machine learning techniques have also allowed discriminating PD-MCI patients from cognitively normal patients based on functional connectomics via supervised machine learning techniques (Abós et al., 2017). Motor subtypes have been identified through supervised methods of multimodal MRI information (Cherubini et al., 2014b). Indeed, multimodal MRI measures discriminated PD patients and multiple system atrophy patients (Péran et al., 2018) and also PD from progressive supranuclear palsy (Cherubini et al., 2014a). Nonetheless, no previous studies have attempted to identify different patterns of regional atrophy among PD patients as performed in AD or frontotemporal dementia (Y. Noh et al., 2014; Whitwell et al., 2009).

From the case studies to big data

The most frequent limitation in studies with patients is the small sample size that prevents the generalization of the results. In addition, PD cohorts are usually biased since they are not usually community-based, but from outpatient clinics. These could partially contribute to the great heterogeneity observed in the multidimensionality of PD. Similar to the efforts made with other diseases such as in AD (http://adni.loni.usc.edu/) or in psychiatric disorders (http://enigma.ini.usc.edu/), a multi-site consortium was created for the study of PD. The Parkinson's Progression Markers Initiative (PPMI) has the mission to identify biomarkers of PD progression (https://www.ppmi-info.org/). PPMI has enrolled a great variety and a large number of PD patients over the world from all

participating centers. Indeed, one of the studies presented in this thesis has been performed on MRI and clinical data from the *de novo* PD cohort in PPMI database. Some of the papers from early unmedicated PD groups that have been reviewed in this introduction used PPMI data (Eisinger et al., 2017; Erro et al., 2016; Fereshtehnejad et al., 2017; LaBelle et al., 2017; Pereira et al., 2014; Simuni et al., 2016). The *de novo* cohort enrolled up to 430 eligible PD participants and almost 200 healthy controls that have been followed-up to 8 years. The consortium also has data of three more cohorts: prodromal PD participants (without PD diagnosis) with diagnosis of hyposmia or REM sleep behavior disorder, PD participants without evidence of dopaminergic deficits assessed with DaTSCAN and a genetic cohort with PD and non-PD diagnosis with genetic mutations in LRRK2, GBA or SNCA. PPMI database includes a wide range of meaningful data: demographics, clinical, MRI, PET, SPECT, genome sequencing data, biospecimens such as CSF, DNA, RNA, plasma, serum, urine and blood (Marek et al., 2011).

All the efforts made for identifying PD subtypes finally aim to identify risk factors and gold standard biomarkers to predict PD dementia and therefore, prevent patients losing their independency. A recent review in the *Brain* journal has investigated the power of MRI techniques in predicting this late stage of PD (Lanskey et al., 2018). As final remarks of what could be the future, and actually the present in this field, authors mention multimodal predictors based on machine learning techniques that can predict cognitive decline. However, these algorithms are far from being the key to PD dementia prevention, meanwhile research fails to identify the exact factors that machine learning algorithms need for adequately identifying PD patients' prognosis.

Chapter 2

Objectives and hypotheses

This thesis is contextualized in the identification of PD subtypes based on objective MRI quantitative measures that can serve as markers of PD progression and that would be research center and examiner-independent. The general objective of this thesis is to characterize structural changes in Parkinson's disease over the course of the neurodegenerative process as well as to relate these changes to neuropsychological performance. This aim pursues to identify MRI and neuropsychological markers of higher risk to evolve to dementia.

The general hypothesis is that there are different patterns of cortical atrophy related to cognition in Parkinson's disease already present at the time of the diagnosis and these patterns progress over the course of the disease.

Specific objectives

1. to describe patterns of cortical thickness alterations in PD patients through cluster analysis approach at different stages of the disease.
2. to investigate the clinical and cognitive correlates of the atrophy patterns identified.
3. to explore the cortical brain progression and cognitive decline of the patients identified in each pattern.

Specific hypotheses

1. distinct cortical atrophy patterns in PD would be present in *de novo*, unmedicated patients regardless the presence of MCI.
   1.1. the presence of cortical atrophy would be focal.
2. different patterns of cortical thickness alterations would be present in medicated Parkinson's disease patients.
   2.1. such patterns would present more extensive regional thinning than the *de novo* patients.
   2.2. these brain atrophy patterns would be linked to different cognitive and/or clinical profiles.
   2.3. patients with a frontal pattern of atrophy would have executive function and working memory impairment.
   2.4. patients with a posterior-predominant pattern would have more presence of visual hallucinations and several cognitive deficits such as memory or visuospatial impairment.
3. patterns of cortical thinning identified in the medicated PD sample would follow a different progression over time.

3.1. greater extent of progressive atrophy would be linked to greater motor severity and/or to an older age of disease onset.
3.2. there would be a pattern of patients with higher proportion of dementia and/or PD-MCI converters.

Chapter 3

Methods

Study Samples

The studies presented in this thesis were performed using two samples of healthy controls and PD patients. Medicated PD sample was used in Study 1 and it was followed-up to 4-years for Study 3. Study 2 used a *de novo* PD multicentric sample from the PPMI database (https://www.ppmi-info.org/). In this section, studies are presented in chronological order of execution and publication.

Study 1

Uribe, C.*, Segura, B.*, Baggio, H. C., Abos, A., Marti, M. J., Valldeoriola, F., Compta, Y., Bargallo, N., Junque, C. (2016). Patterns of cortical thinning in nondemented Parkinson's disease patients. *Movement Disorders*, *31*(5), 699–708. https://doi.org/10.1002/mds.26590

Study 2

Uribe, C., Segura, B., Baggio, H. C., Abos, A., Garcia-Diaz, A. I., Campabadal, A., Marti, M. J., Valldeoriola, F., Compta, Y., Tolosa, E., Junque, C. (2018). Cortical atrophy patterns in early Parkinson's disease patients using hierarchical cluster analysis. *Parkinsonism and Related Disorders*, *50*, 3–9. https://doi.org/10.1016/j.parkreldis.2018.02.006

Study 3

3. Uribe, C.*, Segura, B.*, Baggio, H. C., Abos, A., Garcia-Diaz, A.I., Campabadal, A., Marti, M. J., Valldeoriola, F., Compta, Y., Bargallo, N., Junque, C. Progression of Parkinson's disease patients subtypes based on cortical thinning: 4-year follow-up. Under review.

Medicated PD sample

Participants at baseline (Study 1)

The study sample included 121 PD patients recruited from the Parkinson's Disease and Movement Disorders Unit, Hospital Clínic (Barcelona, Catalonia), and 49 healthy subjects from the Aging Institute at the Universitat Autònoma de Barcelona. All subjects underwent comprehensive neuropsychological and MRI evaluation at the Hospital Clínic of Barcelona. 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).

Inclusion criteria for patients were: (i) fulfilling the UK PD Society Brain Bank diagnostic criteria for PD (Hughes et al., 1992); (ii) no surgical treatment with deep-brain stimulation.

Exclusion criteria for PD patients and healthy controls (HC) were: (i) dementia according to the MDS criteria (Emre et al., 2007), (ii) H&Y scale (Hoehn and Yahr, 1967) score > 3, (iii) young-onset PD, (iv) age below 50 years, (v) presence of severe psychiatric or neurological comorbidity, (vi) low global intellectual quotient (IQ) estimated by the Vocabulary subtest of the Wechsler Adult Intelligence Scale, 3rd edition (scalar score ≤ 7), (vii) MMSE (Folstein et al., 1975) score below 25, (viii) presence of claustrophobia, (ix) pathological MRI findings other than mild white-matter hyperintensities in the FLAIR sequence or any others that might be related to PD, and (x) MRI artifacts.

Eighty-eight PD patients and 31 HC were finally selected. Twelve patients and 8 HC were excluded because they fulfilled criteria for dementia or other neurological disease; 6 patients for psychiatric comorbidity; 1 patient with H&Y score > 3; 1 patient who had young-onset PD; 3 patients and 1 HC with low global IQ score; 2 patients for claustrophobia; 3 HC who did not complete the neuropsychological assessment, and 2 patients and 2 HC due to MRI artifacts. We also excluded 4 patients and 3 HC aged below 50 years, and 2 patients and 1 HC because they were outliers in cluster analyses, constituting a cluster by themselves.

Participants of the longitudinal sample over 4-years (Study 3)

Forty-five PD patients and 22 HC returned for follow-up at 3.8±0.4 years apart (range: 3.1-5.3).

At follow-up, a diagnosis of dementia, H&Y score > 3 and MMSE scores below 25 were not considered as exclusion criteria.

At time 2, two patients underwent deep brain stimulation, five patients and one HC died, twelve PD patients and two controls refused to participate or had moved at follow-up, three PD patients and three controls had developed neurological/psychiatric comorbidities, fifteen PD patients had functional impairment and reduced mobility that prevented going to the hospital for MRI scanning, six patients and three HC had MRI motion artifacts or could not finish the scanning protocol and one patient and was excluded due to problems in longitudinal image preprocessing. See **Figure 7**.

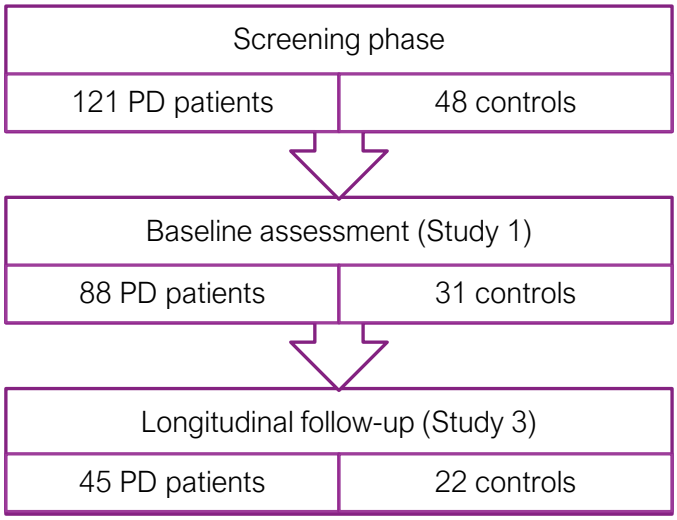

Figure 7 Longitudinal assessment of the medicated sample

Clinical and neuropsychological assessments.

Motor symptoms were assessed by means of the UPDRS-III, motor section (Fahn & Elton, 1987). All PD patients were taking antiparkinsonian drugs, consisting of different combinations of L-DOPA, COMT inhibitors, MAO inhibitors, dopamine agonists and amantadine. In order to standardize doses, the L-DOPA equivalent daily dose (LEDD, Tomlinson et al., 2010) was calculated.

We used a neuropsychological battery following MDS task force recommendations (Litvan et al., 2012), bar language, for which a single measure was used and executive functions for which phonemic and semantic verbal fluency were used as two distinct proxies of executive functions (**Table 5**).

Table 5 Neuropsychological battery of the medicated PD sample (Study 1 and 3)

Mini Mental State Examination (MMSE) (Folstein et al., 1975)	Global cognition
Visual Form Discrimination (VFD, (Benton, AL, Sivan, AB, Hamsher, 1994) Benton's Judgement of Line Orientation (JLO, Benton, Varney, & Hamsher, 1978)	Visuospatial and visuoperceptual functions*
Total learning recall (sum of correct responses from trial I to trial V) delayed recall (total recall after 20 min) from Rey's Auditory Verbal Learning Test (RAVLT, Lezak et al. 2012)	Memory*
Phonemic (words beginning with the letter "p" in 1 minute) fluency Semantic (animals in 1 minute) fluency	Executive functions*
Digit Span Forward and Backward (Wechsler, 1999) Stroop Color-word Test (Stroop, 1935) Symbol Digits Modalities Tests (SDMT, Smith, 1982) Trail Making Test (TMT, in seconds) part A and part B (Lezak et al., 2012)	Attention and working memory*
Short version of the Boston Naming Test (Kaplan et al., 1983)	Language*
Ekman 60 Faces Test (Ekman, 1975)	Facial emotion recognition

* Cognitive domains considered for level II PD-MCI diagnosis.

Neuropsychiatric symptoms were evaluated with the Beck Depression Inventory-II (Beck et al., 1996), Starkstein's Apathy Scale (Starkstein et al., 1992) and Cumming's Neuropsychiatric Inventory (Cummings et al., 1994).

Clinical instruments to assess PD patients' evolution

In addition to the neuropsychological battery described above, two questionnaires were administered after 4 years and a telephonic interview was conducted for those patients who were lost to follow-up.

Functioning in instrumental activies of the daily living (ADL) were assessed with the Lawton and Brody scale (Lawton and Brody, 1969) and the Schwab and England scale (Schwab and England, 1969).

Additionally, the Gottfries-Brane-Steen scale (GBS) (Bråne et al., 2001) was administered to caregivers/family members of PD patients that could not return at time 2 (non-completers) via telephone interview. This scale was administered with the aim to obtain qualitative information from patients lost to follow-up.

MRI acquisition

MRI 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; 1 mm isotropic voxel) and an axial FLAIR sequence (TR=9000 ms, TE=96 ms).

de novo PD sample (Study 2)

Participants

Data used in this study were obtained from the PPMI database (Marek et al., 2011). For up to-date information on the study, visit www.ppmi-info.org. T1-weighted images acquired on 3-tesla Siemens MRI scanners and clinical and neuropsychological data obtained from 119 PD patients and 77 HC assessed between 2010 and 2015 were included. All imaging and non-imaging data corresponded to the same time points and were acquired prior to any L-DOPA intake (**Figure 8**).

Inclusion criteria were: (i) recent diagnosis of PD with asymmetric resting tremor or asymmetric bradykinesia, or two of: bradykinesia, resting tremor, and rigidity; (ii) absence of treatment for PD; (iii) neuroimaging evidence of significant dopamine transporter deficit consistent with the clinical diagnosis of PD and ruling out PD look-alike conditions such as drug-induced and vascular parkinsonism or essential tremor; (iv) available T1-weighted images in a 3T Siemens scanner (for both PD patients and HC) and (v) age > 50 years old (for both PD patients and HC).

Exclusion criteria for all participants were: (i) diagnosis of dementia; (ii) significant neurologic or psychiatric dysfunction; (iii) first-degree family member with PD, and (iv) presence of MRI motion artifacts, field distortions, intensity inhomogeneities, or detectable brain injuries.

A total of 77 *de novo* PD patients and 50 HC were selected. The following participants were excluded from the study: 4 patients and 1 HC due to other neurological disease, 18 PD patients and 20 HC due to MRI motion artifacts at visual inspection performed by an expert radiologist, and 18 PD patients and 5 HC due to cortical thickness preprocessing problems. Finally, we performed an initial cluster analysis for the PD group and another for the control group to detect possible abnormal outliers on MRI data. From these, we discarded 2 PD patients and 1 HC that constituted independent clusters by themselves.

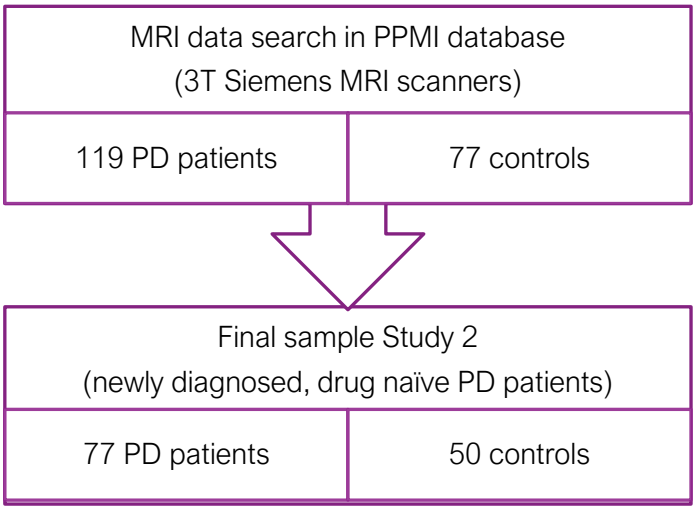

Figure 8 de novo PD sample from PPMI database

Clinical and neuropsychological assessments

Motor symptoms were assessed with the MDS-UPDRS Part III (Goetz et al., 2008) and motor subtypes were established based on the ratio from the means of several items of the MDS-UPDRS Part III (Stebbins et al., 2013).

ADL were evaluated with the Schwab and England Scale (Schwab and England, 1969) for PD patients and MDS-UPDRS Part II for all participants.

Global cognition was assessed with the Montréal Cognitive Assessment (MoCA) test (Nasreddine et al., 2005), and depressive symptoms using the 15-item Geriatric Depression Scale (GDS-15, Sheikh and Yesavage, 1986) with a cutoff score of 5 or more indicating clinically significant symptoms as described in www.ppmi-info.org.

All subjects underwent comprehensive neuropsychological assessment following Movement Disorder Society task force recommendations (Litvan et al., 2012, except for the absence of tests evaluating the language domain). See **Table 6** for detailed information of the neuropsychological tests.

Table 6 Neuropsychological battery of the *de novo* PD sample

Montréal Cognitive Assessment (MoCA) (Nasreddine et al., 2005)	Global cognition
Benton Judgment of Line Orientation short form (15-item version, (Venderploeg et al., 1997)	Visuospatial function*
Phonemic (letter 'f' in 1 minute) fluency Semantic (animals in 1 minute) fluency	Executive function*
Total learning recall Delayed recall Recognition from Hopkins Verbal Learning Test-Revised (HVLT-R, Brandt and Benedict, 2001);	Memory*
Symbol Digit Modalities Test (Smith, 2000) Letter-Number Sequencing (Wechsler, 1999)	Attention and working memory*

* Cognitive domains used for level I PD-MCI diagnosis.

University of Pennsylvania Smell Identification Test (UPSIT) scores were available in a subsample of 55 PD patients and 28 HC due to missing values. The cutoff indicating anosmia was 18 or less (Doty, 1995).

MRI acquisition

All three-dimensional T1-weighted MRI scans were acquired in the sagittal plane on 3T Siemens scanners (Erlangen, Germany) at different centers using an MPRAGE sequence. The acquisition parameters were as follows: repetition time = 2,300/1,900 ms; echo time = 2.98/ 2.96/2.27/2.48/2.52 ms; inversion time = 900 ms; flip angle: 9o; matrix = 240 x 256/256 x 256; voxel = 1 x 1 x 1 mm3.

MCI definition

Initially, z scores for each test and for each subject were calculated based on the control group's means and standard deviations. 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 healthy control 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 domain, or in at least one test per domain in at least two domains.

The neuropsychological tests used for the PD-MCI diagnoses are described in **Tables 5** and **6** (pages 78 and 81).

For the medicated PD sample

The presence of MCI was defined using PD-MCI diagnostic criteria level II (Litvan et al., 2012): the z score of a given test was at least 1.5 lower than the expected score on any 2 test scores. Impairment in each cognitive domain was also established if at least 1 test in the domain was impaired. Level II constitutes a comprehensive assessment to diagnose PD MCI.

For the *de novo* PD sample

The presence of MCI was defined using PD-MCI diagnostic criteria level I (Litvan et al., 2012): (i) MoCA scores as measure of global cognition below 26 (Dalrymple-Alford, 2010) and/or (ii) the z score of a given test was at least 1.5 lower than the expected score on any 2 test scores. Impairment in each cognitive domain was also established if at least 1 test in the domain was impaired. Level I leads to a diagnostic of Possible MCI.

MRI techniques

Cortical thickness preprocessing

Cortical thickness was estimated using the automated FreeSurfer stream (version 5.1, https://surfer.nmr.mgh.harvard.edu/). The procedures carried out by FreeSurfer software include removal of nonbrain data, intensity normalization (Fischl et al., 2001), tessellation of the gray matter/white matter boundary, automated topology correction (Dale et al., 1999; Ségonne et al., 2007), and accurate surface deformation to identify tissue borders (Dale and Sereno, 1993; Fischl et al., 2002; Fischl and Dale, 2000). Cortical thickness is then calculated as the distance between the white matter and GM surfaces at each vertex of the reconstructed cortical mantle (Fischl et al., 2002). In our study, results for each subject were 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.

After Freesurfer preprocessing, results for each subject were visually inspected to ensure accuracy of registration, skull stripping, segmentation, and cortical surface reconstruction. Possible errors were fixed by manual intervention following standard procedures (https://surfer.nmr.mgh.harvard.edu/fswiki/FsTutorial/TroubleshootingData#Fixingerrors).

Longitudinal preprocessing of cortical thickness

For Study 3, the FreeSurfer longitudinal stream was used to process the images of both times (Reuter et al., 2012). Specifically, an unbiased within-subject

template space and image is created using robust, inverse consistent registration (Reuter et al., 2010). Several processing steps, such as skull stripping, Talairach transforms, atlas registration as well as spherical surface maps and parcellations are then initialized with common information from the within-subject template, significantly increasing reliability and statistical power (Reuter et al., 2012). Cortical maps were smoothed with a FWHM of 25 mm to increase sensitivity to detect longitudinal differences in a small sample.

Parcellations of the cortical mantle

For Study 2, we extracted the mean thickness for each of the 360 cortical areas defined in the Human Connectome Project Multi-Modal Parcellation version 1.0 (HCP-MMP1.0, Glasser et al., 2016; CJNeuroLab, 2018). The HCP-MMP1.0 (**Figure 9**) is an atlas that contains 180 areas per hemisphere, and it is based on the multimodal MRI from the Human Connectome Project and an objective semi-automated neuroanatomical approach. The areas are bounded by sharp changes in cortical architecture, function, connectivity, and topography in a group of 210 healthy young adults.

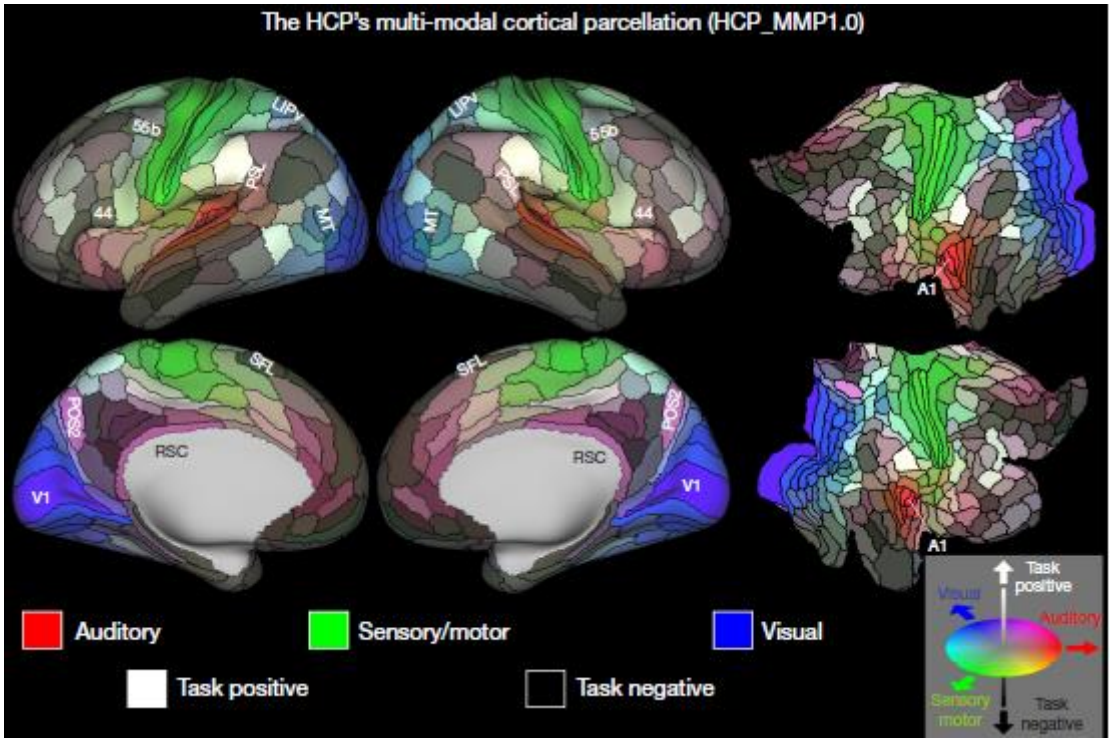

Figure 9 Extracted from Glasser et al. 2016 Nature Vol 536. https://doi.org/10.1038/nature18933

Hierarchical cluster analyses

Ward's linkage method for hierarchical cluster analysis was used for Studies 1 and 2 using MATLAB (release 2014b, The MathWorks, Inc., Natick, Massachussetts).

For Study 1, whole-brain Free-Surfer vertex information (327,684 vertex points) of cortical thickness estimation for each of the 88 PD patients was used. This technique produces hierarchical representations in which the clusters at each level of the hierarchy are created by merging clusters at the next lower level. In hierarchical cluster analysis there is no need to specify the number of clusters a priori because grouping is based on the dissimilarity between groups of observations. To control for variations in global atrophy between patients, we normalized the vertices using the mean cortical thickness of the whole brain (Y. Noh et al., 2014; Whitwell et al., 2009). Ward's clustering linkage method (Ward, 1963) was used to combine pairs of clusters at each step while minimizing the sum of square errors from the cluster mean. Each of the 88 patients was placed in their own cluster and then progressively clustered with others.

For Study 2, mean cortical thickness values for the 360 areas from the HCP-MMP1.0 were used as features for the 77 early PD patients. This feature selection was used to improve the model's performance in calculating similarity/distance measures.

Statistical analysis

Cortical thickness

Intergroup cortical thickness comparisons in Study 1 and 2 were performed using a vertex-by-vertex general linear model with FreeSurfer. The model included cortical thickness as a dependent factor and group as an independent factor. Age and education were considered as nuisance covariates in Study 1 group comparisons when they were significantly different between groups being compared.

All cortical thickness group analyses were corrected for multiple comparisons by using a pre-cached cluster-wise Monte Carlo simulation of 10,000 iterations. Reported cortical regions reached a two-tailed corrected significance level of $p < 0.05$.

Longitudinal cortical thickness

Longitudinal cortical thickness comparisons were performed using the longitudinal two stage model (Reuter et al., 2012) and we computed the symmetrized percent of change of cortical thickness (SPC). SPC is the rate in mm/year ((thickness2-thickness1)/(time2-time1)) with respect to the average thickness (0.5*(thick1+thick2)). In aging or disease, SPC is expected to be negative in most regions (https://surfer.nmr.mgh.harvard.edu/fswiki/LongitudinalTwoStageModel).

Comparisons between groups were assessed using a vertex-by-vertex general linear model. Two statistical models were performed: one sample t-test was performed to test time effect in groups (if the SPC was different from zero); and to test time by group interaction effects, SPC was included as a dependent factor and group as an independent factor. In the second model, age and years of education were considered as nuisance covariates.

As in the cross-sectional analyses, all cortical thickness group analyses were corrected for multiple comparisons by using a pre-cached cluster-wise Monte Carlo simulation of 10,000 iterations. Reported cortical regions reached a two-tailed corrected significance level of $p < 0.05$.

Study I

Demographical and clinical measurements

Demographic, neuropsychological and clinical statistical analyses were conducted using IBM SPSS Statistics 20.0 (2011; Armonk, NY: IBM Corp). We tested for group differences in demographic and clinical variables as well as in neuropsychological performance between HC and PD patient subtypes using an ANOVA with Bonferroni or Tamhane post hoc test when analyzing quantitative variables and Pearson's chi-square test when analyzing categorical variables. For comparisons between the collapsed PD group and HC we used Student's t test.

Cluster evaluation

MATLAB was used to perform principal component analysis (PCA) in order to validate the classification obtained from the cluster analysis. PCA is a multivariate method that can detect correlations in a set of variables (Abdi and Williams, 2010). After discarding vertices with values of zero and vertices that correlated highly with others, PCA was performed with 4,150 vertices (Field, 2009).

Study 2

Demographical and clinical measurements

Demographic, neuropsychological, and clinical statistical analyses were conducted using IBM SPSS Statistics 24.0 (2011; Armonk, NY: IBM Corp). We tested for group differences in demographic and clinical variables as well as in neuropsychological performance between HC and PD patient subtypes using Kruskal-Wallis test followed by Mann-Whitney's pairwise comparisons and Bonferroni correction for non-normally distributed quantitative measures as indicated by the Kolmogorov-Smirnov test; for normally distributed measures, an analysis of variance (ANOVA) followed by Bonferroni post hoc test was used. Pearson's chi squared tests were used for categorical measures.

For comparisons between the collapsed PD sample and HC we used Mann-Whitney's test or Student t test as appropriate.

Cluster evaluation

To determine the optimal number of clusters, we computed the Calinski-Harabasz index with MATLAB. The Calinski-Harabasz criterion is best suited for cluster analysis with squared Euclidean distances. The higher the ratio is, the better the cluster solution. An optimal ratio is determined by a large between-cluster variance and a small within-cluster variance (https://es.mathworks.com/help/stats/clustering.evaluation.calinskiharabaszevaluation-class.html).

Study 3

Cross-sectional analysis of clinical measures

Group differences in demographic variables, disease outcomes and GBS scale scores at time 2 were analyzed with Kruskal-Wallis test followed by Mann-Whitney's pairwise comparisons and Bonferroni correction for quantitative measures. Chi squared test were used where appropriate for categorical measures.

Group differences in demographic and clinical variables between completers and non- completers were analyzed with Mann-Whitney's U test for quantitative measures and Chi squared test for categorical measures at time 1. These analyses were conducted using IBM SPSS Statistics 22.0 (2013; Armonk, NY: IBM Corp).

Repeated measures analyses

Group by time interaction effects in clinical disease-related variables and neuropsychological performance between pattern 2 and 3 patients and HC were assessed through a repeated-measures general linear model and permutation

testing with 10,000 iterations. To control type-I errors, a Bonferroni correction was applied.

The same was applied for the global atrophy measures including total GM volume, subcortical and cortical GM volume, mean lateral ventricular volume and estimated intracranial volume were obtained automatically via whole brain segmentation with the FreeSurfer suite. Global average thickness for both hemispheres was calculated as:

((lh.thickness*lh.surface area)+(rh.thickness*rh.surface area))/(lh.surface area+rh.surface area)

The estimated intracranial volume was considered as a nuisance covariate in the volumetric analyses.

Chapter 4

Results

Study I

Uribe, C., Segura, B., Baggio, H. C., Abos, A., Marti, M. J., Valldeoriola, F., Compta, Y., Bargallo, N., Junque, C. (2016). Patterns of cortical thinning in nondemented Parkinson's disease patients. *Movement Disorders*, *31*(5), 699–708. https://doi.org/10.1002/mds.26590

RESEARCH ARTICLE

Patterns of Cortical Thinning in Nondemented Parkinson's Disease Patients

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ABSTRACT: Background: Clinical variability in the Parkinson's disease phenotype suggests the existence of disease subtypes. We investigated whether distinct anatomical patterns of atrophy can be identified in Parkinson's disease using a hypothesis-free, data-driven approach based on cortical thickness data.
Methods: T1-weighted 3-tesla MRI and a comprehensive neuropsychological assessment were performed in a sample of 88 nondemented Parkinson's disease patients and 31 healthy controls. We performed a hierarchical cluster analysis of imaging data using Ward's linkage method. A general linear model with cortical thickness data was used to compare clustering groups.
Results: We observed 3 patterns of cortical thinning in patients when compared with healthy controls. Pattern 1 (n = 30, 34.09%) consisted of cortical atrophy in bilateral precentral gyrus, inferior and superior parietal lobules, cuneus, posterior cingulate, and parahippocampal gyrus. These patients showed worse cognitive performance when compared with controls and the other 2 patterns. Pattern 2 (n = 29, 32.95%) consisted of cortical atrophy involving occipital and frontal as well as superior parietal areas and included patients with younger age at onset. Finally, in pattern 3 (n = 29, 32.95%), there was no detectable cortical thinning. Patients in the 3 patterns did not differ in disease duration, motor severity, dopaminergic medication doses, or presence of mild cognitive impairment.
Conclusions: Three cortical atrophy subtypes were identified in nondemented Parkinson's disease patients: (1) parieto-temporal pattern of atrophy with worse cognitive performance, (2) occipital and frontal cortical atrophy and younger disease onset, and (3) patients without detectable cortical atrophy. These findings may help identify prognosis markers in Parkinson's disease. © 2016 The Authors. Movement Disorders published by Wiley Periodicals, Inc. on behalf of International Parkinson and Movement Disorder Society

Key Words: Parkinson disease; cluster analysis; neuropsychology; magnetic resonance imaging; cortical atrophy

Parkinson's disease (PD) is associated with progressive cognitive impairment and cortical atrophy.[1] Clinical variability in PD suggests the existence of disease subtypes. A review of cluster analysis studies concluded that there is clear evidence of 2 clinical profiles: one with old-age onset and rapid disease progression and

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another of younger age at onset and slower progression.[2] Recently, Fereshtehnejad and colleagues[3] identified the following 3 subtypes while considering clinical and cognitive variables: motor/slow progression, diffuse/malignant, and intermediate. Patients with diffuse/malignant PD more often had mild cognitive impairment (MCI) and showed faster cognitive deterioration.

Considering the relevance of cognitive status in the risk of dementia, cluster analysis has also been used to describe subtypes according to neuropsychological performance. Dujardin and colleagues[4] described 2 groups. One group was composed of cognitively intact subjects and patients with lower scores on working memory, verbal episodic memory, and executive functions, although within the normal range. The second group included PD patients with varying degrees of impairment in all cognitive domains. The identification of PD subtypes based on objective and replicable measures is critical to define targets for possible future treatments that improve the prognosis of PD. To our knowledge, no previous studies used hypothesis-free, data-driven cluster analysis of objective measures such as structural magnetic resonance imaging (MRI) data to identify subtypes of cortical atrophy in PD patients.

The main objective of this study was to examine cortical thickness in a large sample of nondemented PD patients using cluster analysis to determine whether distinct anatomical patterns can be established and whether different patterns are associated with distinct cognitive profiles.

Methods

Participants

The study sample included 121 PD patients recruited from the Parkinson's Disease and Movement Disorders Unit, Hospital Clínic (Barcelona, Spain), and 49 healthy controls (HC) from the Aging Institute in Barcelona. All participants underwent comprehensive neuropsychological and MRI evaluations. Inclusion criteria for patients were (i) fulfilling UK PD Society Brain Bank diagnostic criteria for PD[5] and (ii) no surgical treatment with deep-brain stimulation. Exclusion criteria for all participants were (i) dementia according to Movement Disorders Society criteria,[6] (ii) Hoehn and Yahr (H&Y) scale[7] score > 3, (iii) young-onset PD, (iv) age < 50 years, (v) severe psychiatric or neurological comorbidity, (vi) low global intelligence quotient estimated by the Vocabulary subtest of the Wechsler Adult Intelligence Scale 3rd edition (scalar score ≤ 7), (vii) Mini Mental State Examination (MMSE)[8] score below 25, (viii) claustrophobia, (ix) pathological MRI findings other than mild white-matter hyperintensities in the FLAIR sequence, and (x) MRI artifacts.

A total of 88 PD patients and 31 HC were selected. The following participants were excluded from the study: 12 patients and 8 HC because of dementia or another neurological disease, 6 patients for psychiatric comorbidity, 1 patient with an H&Y score of > 3, 1 patient with young-onset PD, 3 patients and 1 HC with low IQ scores, 2 patients for claustrophobia, 3 HC who did not complete the neuropsychological assessment, and 2 patients and 2 HC with MRI artifacts. We also excluded 4 patients and 3 HC aged younger than 50 years, and 2 patients and 1 HC because they were outliers in cluster analyses, constituting a cluster by themselves.

Motor symptoms were assessed with the Unified Parkinson's Disease Rating Scale, motor section (UPDRS-III).[9] All PD patients were taking antiparkinsonian drugs that consisted of different combinations of L-dopa, cathecol-O-methyltransferase inhibitors, monoamine oxidase inhibitors, dopamine agonists, and amantadine. To standardize the doses, the L-dopa equivalent daily dose (LEDD)[10] was calculated.

Written informed consent was obtained from all study participants after a full explanation of the procedures. The study was approved by the institutional Ethics Committee for Clinical Research.

Neuropsychological Tests

We used a neuropsychological battery following the Movement Disorders Society task force recommendations[11]; bar language, for which a single measure was used; and executive functions, for which phonemic and semantic verbal fluency were used as 2 distinct proxies. Supplementary Methods 1 describes the tests used in the neuropsychological assessment.

Facial emotion recognition was assessed with the Ekman 60 Faces Test.[12] Emotion recognition has been described to be impaired in PD patients, and the Ekman test has shown sensitivity to the integrity of the orbitofrontal cortex (OFC) in PD.[13] Neuropsychiatric symptoms were evaluated with the Beck Depression Inventory-II,[14] Starkstein's Apathy Scale,[15] and Cumming's Neuropsychiatric Inventory.[16]

Image Analysis

MRI data 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; 1 mm isotropic voxel) and an axial FLAIR sequence (TR = 9000 ms, TE = 96 ms).

Cortical thickness was estimated using the automated FreeSurfer stream (version 5.1, http://surfer.nmr.harvard.edu). Detailed descriptions of FreeSurfer procedures are in Supplementary Methods 2.

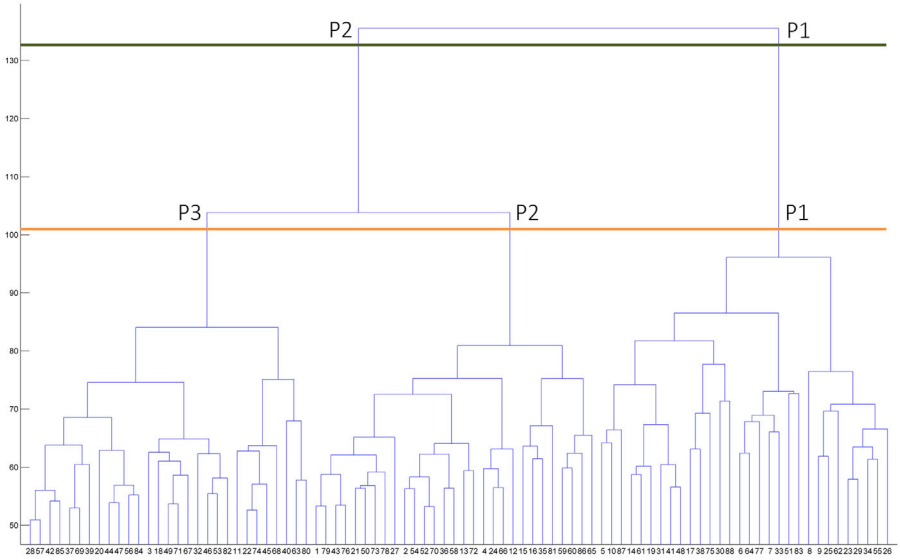

FIG. 1. Dendrogram of PD patients clustered according to vertex-by-vertex information of cortical thickness. **T**he distance along the *y* axis represents the similarity between clusters so that the shorter the distance, the greater the similarity. Numbers on the horizontal axis represent the 88 PD patients included in the cluster analysis. P1, Pattern 1; P2, Pattern 2; P3, Pattern 3. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Cluster Analysis

MATLAB (release 2014b, The MathWorks, Inc., Natick, Massachusetts) was used to perform an agglomerative hierarchical cluster analysis using whole-brain cortical thickness vertex information for each of the 88 PD patients. Each patients' cortical surface data included 327,684 vertices. This technique produces hierarchical representations, and clusters at each hierarchical level are created by merging clusters at the next lower level. In hierarchical cluster analysis, there is no need to specify the number of clusters a priori because grouping is based on the dissimilarity between groups of observations. To control for variations in global atrophy between patients, vertices were normalized using whole-brain mean cortical thickness.[17,18] Ward's clustering linkage method[17-19] was used to combine pairs of clusters at each step while minimizing the sum of square errors from the cluster mean. Each of the 88 patients was placed in their own cluster and then progressively clustered with others. Cluster analysis results are shown as a dendrogram (Fig. 1).

Statistical Analysis

Intergroup cortical thickness comparisons were performed using a vertex-by-vertex general linear model with FreeSurfer. The model included cortical thickness as a dependent factor and group as an independent factor. Age and education were considered as nuisance covariates when they were significantly different between the groups being compared (Table 1). All results were corrected for multiple comparisons using precached clusterwise Monte Carlo simulation with 10,000 iterations. Reported cortical regions reached a 2-tailed corrected significance level of $P < .05$.

Demographic, neuropsychological, and clinical statistical analyses were conducted using IBM SPSS Statistics 20.0 (IBM Corp., Armonk, New York). We tested for group differences in demographic and clinical variables as well as in neuropsychological performance between HC and PD patient subtypes using an analysis of variance with a Bonferroni or Tamhane post hoc test when analyzing quantitative variables and the Pearson chi-square test when analyzing categorical variables. For comparisons between the collapsed PD group and HC we used the Student *t* test. Neuropsychological test scores were calculated as *z* scores and adjusted for age, years of education, and sex as previously described.[20]

MATLAB was used to perform principal component analysis (PCA) to validate the classification obtained from the cluster analysis. PCA is a multivariate method that can detect correlations in a set of variables.[21] After discarding vertices with values of zero and vertices that correlated highly with others, PCA was performed with 4,150 vertices.[22]

Results

Demographic and Clinical Characteristics

Compared with HC, the collapsed PD sample had significantly lower MMSE scores as well as more severe depression, apathy, and global neuropsychiatric symptoms (all $P \leq .001$) (Supplementary Table 1).

TABLE 1. Demographic and clinical characteristics at the 3-cluster level

	PD subtypes				
	Pattern 1 (n = 30)	Pattern 2 (n = 29)	Pattern 3 (n = 29)	HC (n = 31)	Test stats, *P* value
Sex, male, n (%)	15 (50.0)	20 (69.0)	16 (55.2)	16 (51.6)	2.667, .446[a]
Age, y, mean (SD)	70.60 (9.6)	58.03 (8.9)	63.48 (9.5)	64.32 (8.5)	9.401, < .0001[b,f,g]
Education, y, mean (SD)	7.77 (4.8)	13.55 (5.5)	10.55 (4.0)	11.03 (4.2)	7.622, < .0001[b,d,f]
MMSE, mean (SD)	28.57 (1.4)	29.24 (0.9)	29.31 (0.9)	29.68 (0.5)	6.944, < .0001[c,d]
Disease duration, y, mean (SD)	8.77 (6.6)	8.36 (5.7)	6.83 (4.6)	NA	0.949, .391[b]
Age of onset, y, mean (SD)	61.83 (12.7)	49.67 (8.3)	56.66 (10.3)	NA	9.710, < .0001[c,f,h]
Early PD, 5 y n, (%)	12 (40.0)	11 (37.9)	14 (48.3)	NA	0.715, .699[a]
BDI, mean (SD)	13.67 (5.7)	8.88 (6.8)	9.61 (5.7)	6.03 (5.7)	7.888, < .0001[b,d,f]
Apathy, mean (SD)	15.11 (7.9)	11.60 (7.1)	11.29 (6.0)	8.38 (5.1)	4.958, .003[c,d]
NPI, mean (SD)	6.59 (7.8)	4.41 (8.2)	6.21 (6.5)	1.52 (3.2)	3.242, .025[c,d,e]
Visual hallucinations, n (%)	6 (20.0)	6 (22.2)	5 (17.2)	0 (0)	7.900, .245[a]
UPDRS part III, mean (SD)	18.07 (9.1)	15.17 (11.6)	13.07 (8.4)	NA	1.945, .149[b]
Hoehn & Yahr stage, n 1/1.5/2/2.5/3	2/3/16/4/5	9/2/13/3/2	11/0/14/1/3	NA	12.262, .140[a]
LEDD, mg, mean (SD)	764.63 (388.3)	930.52 (576.4)	718.00 (493.9)	NA	1.503, .228[b]
Total MCI, n (%)	20 (66.7)	14 (48.3)	11 (37.9)	NA	5.015, .081[a]
Visuospatial functions, n (%)	10 (33.3)	9 (31.0)	7 (24.1)	NA	0.645, .724[a]
Executive functions, n (%)	16 (53.3)	6 (20.7)	6 (20.7)	NA	9.712, .008[a]
Memory, n (%)	14 (46.7)	11 (37.9)	9 (31.0)	NA	1.529, .466[a]
Attention and WM, n (%)	20 (66.7)	17 (58.6)	14 (48.3)	NA	2.055, .358[a]
Language, n (%)	2 (6.7)	3 (10.3)	2 (6.9)	NA	0.339, .844[a]

Apathy, Starkstein's Apathy Scale; BDI, Beck Depression Inventory-II; HC, healthy controls; LEDD, L-dopa equivalent daily dose; MCI, Mild Cognitive Impairment; MMSE, Mini-Mental State Examination; NA, not applicable; NPI, Cumming's Neuropsychiatric Inventory; PD, Parkinson's disease; UPDRS III, Unified Parkinson's Disease Rating Scale motor section; WM, working memory.
Data are presented as mean (standard deviation) (continuous) or frequencies (categorical).
[a]The Chi-squared test was used.
[b]Analysis of variance followed by Bonferroni post hoc test was used.
[c]Analysis of variance followed by Tamhane (T2) post hoc test was used.
[d]Significant post hoc differences ($P < .05$) between HC and pattern 1.
[e]Significant post hoc differences ($P < .05$) between HC and pattern 3.
[f]Significant post hoc differences ($P < .05$) between pattern 1 and pattern 2.
[g]Significant post hoc differences ($P < .05$) between pattern 1 and pattern 3.
[h]Significant post hoc differences ($P < .05$) between pattern 2 and pattern 3.

PD Subtypes According to Cluster Analysis

Models with 2 and 3 clusters were selected as possible solutions. Detailed information about the 2-cluster and 4-cluster solutions is included as supplementary results (see Supplementary Result 1 and Supplementary Tables 2, 3, and 4).

At the 3-cluster level (Fig. 2a), 3 patterns of cortical thickness were identified. PD patients included in pattern 1 (n = 30, 34.09%) showed reduced cortical thickness when compared with HC in lateral and medial regions bilaterally, including the precentral gyrus, inferior and superior parietal areas, cuneus, posterior cingulate gyrus, and parahippocampal gyrus. Years of education were controlled for when comparing pattern 1 with HC (see Table 1). Pattern 2 included patients (n = 29, 32.95%) with cortical atrophy in bilateral superior parietal and occipital areas and bilateral frontal regions such as the middle frontal, orbitofrontal, and right anterior superior frontal. Patients in the third cluster, pattern 3 (n = 29, 32.95%), showed no significant cortical thinning when compared with HC.

Comparisons between patients in different patterns also showed significant differences (see Fig. 2b). PD patients included in pattern 1 showed cortical thinning in the posterior cingulate/isthmus of the cingulate gyrus and precuneus as well as precentral gyrus in comparison with pattern 2 patients. Pattern 2 patients showed cortical thinning in dorsolateral and orbital frontal regions when compared with pattern 1 patients. Age and years of education were controlled for when comparing these two groups (Table 1).

Pattern 1 patients showed significant cortical thinning in lateral and medial regions bilaterally, including the precentral gyrus, inferior and superior parietal areas, cuneus, posterior cingulate gyrus, and parahippocampal gyrus when compared with pattern 3 patients. On the other hand, when compared with pattern 1 patients, pattern 3 patients showed cortical thinning in the left medial OFC. Age was controlled for when comparing these groups (Table 1).

Finally, pattern 2 patients showed cortical thinning in the superior parietal and occipital areas and in the left dorsolateral frontal cortex in comparison with pattern 3 patients.

Demographic and Clinical Characteristics

There were no significant differences in motor disease severity as measured by the UPDRS-III, H&Y,

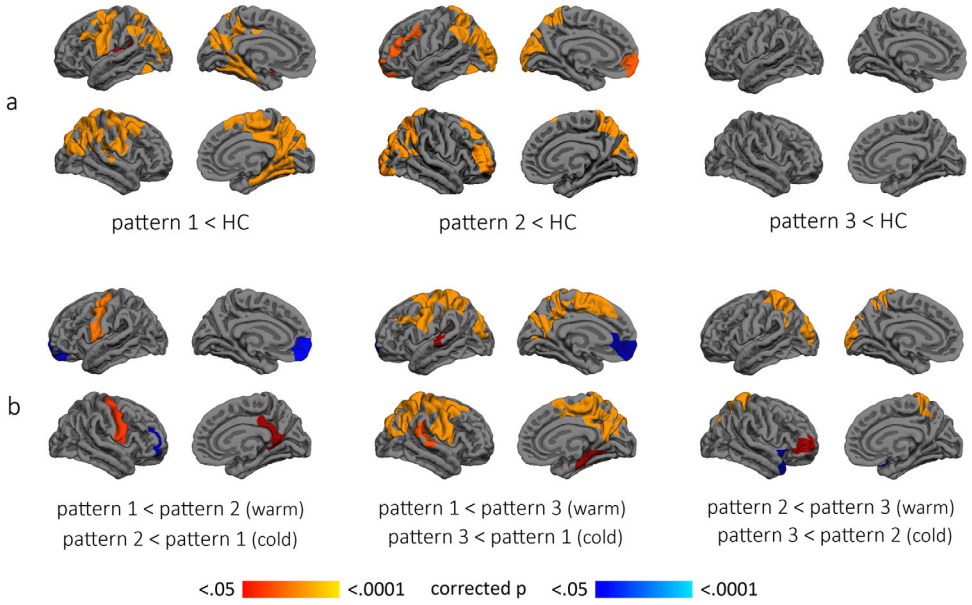

FIG. 2. Cortical atrophy patterns at 3-cluster level. **a**: Color maps indicate significant thinning when compared with healthy controls. **b**: Color maps indicate significant differences in thickness between the 3 patterns. Results were corrected by Monte Carlo simulation. HC, healthy controls. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

and LEDD or disease duration between groups at the 3-cluster level. Patients in pattern 1 had lower MMSE scores than HC and were less educated than both HC and pattern 2 patients. Patients in pattern 2 were younger at PD onset than patients in patterns 1 and 3. Regarding psychiatric symptoms, patients in pattern 1 were more depressed than both HC and pattern 2 patients and more apathetic than HC. Patients in patterns 1 and 3 had more severe global neuropsychiatric symptoms than HC (see Table 1).

Cognitive Profiles of PD Subtypes

Figure 3 summarizes the cognitive profiles of patients in the 3 patterns. When compared with HC, patients in pattern 1 displayed significantly worse performance in Visual Form Discrimination Test, Judgment of Line Orientation Test (JLO), semantic fluency, Rey Auditory Verbal Learning Test total learning and delayed recall, Stroop (Word and Color), Symbol Digits Modalities Test (SDMT), Trail Making Test Part A (TMTA); Trail Making Test Part B (TMTB), and Trail Making Test A minus B (TMTA minus B). Performance in the semantic fluency test was significantly worse in pattern 1 patients than in the 3 other groups (HC and patients in patterns 2 and 3). Pattern 2 patients differed from HC in the JLO, Stroop Word test, SDMT, and TMTB and TMTA minus TMTB tests. Patients in pattern 3 scored significantly lower than HC in the Stroop Word test. The means (SD) of the z scores are shown in Supplementary Table 5. There were no significant differences in the proportion of patients with MCI between groups (Table 1).

Emotion Recognition

There were no significant intergroup differences in overall facial emotion recognition. Analyzing individual emotion recognition, post hoc testing showed that the accuracy in identifying sadness in pattern 2 patients was significantly lower than in the HC group (Bonferroni corrected $P = .044$) (Table 2).

PCA Validation

The patterns identified through PCA were similar to those obtained with cluster analysis. Details and representation of the PCA results are shown in Supplementary Results 2 and Supplementary Figure 1.

Discussion

The main finding of this study is that data-driven analysis can classify PD according to patterns of cortical degeneration. We identified a 3-cluster solution including (1) mainly parietal-temporal atrophy, (2) frontal and occipital atrophy, and (3) nonatrophic PD subtypes. To our knowledge, this is the first study to obtain cortical thinning patterns through cluster analysis in nondemented PD, showing different PD subtypes.

Previous neuroimaging studies assessed cortical atrophy at different clinical stages of PD and showed inconsistent results. Cortical thinning has been identified in de novo,[23] nondemented,[24] MCI,[25-28] and

FIG. 3. Neuropsychological profile at the 3-cluster level. Neuropsychological profiles for healthy controls in green, pattern 1 in blue, pattern 2 in red, and pattern 3 in purple. Data are presented as *z* scores. Lower *z* scores indicate worse performance. BNT, Boston Naming Test; JLO, Judgment of Line Orientation Test; RAVLT total, Rey Auditory Verbal Learning Test total; RAVLT recall, Rey Auditory Verbal Learning Test recall after 30 minutes; SDMT, Symbol Digits Modalities Test; TMTA, Trail Making Test Part A; TMTB, Trail Making Test Part B; TMTA minus B, Trail Making Test A minus B; VFD, Visual Form Discrimination Test. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

demented PD patients.[29] However, the heterogeneity of these results prevents the identification of specific cortical patterns of degeneration in PD progression. The existence of different cortical atrophy subtypes in nondemented PD patients, identified using a hypothesis-free approach, should help clarify the inconsistency of previous results and help study different patterns of structural degeneration over time.

Patients grouped in pattern 1 showed cortical atrophy in dorsal and medial cortices bilaterally, mainly involving parieto-temporal regions. This pattern partially overlapped with the cortical atrophy previously described in nondemented PD patients[24] and patients with MCI.[28] In this previous study, however, PD patients with MCI also showed cortical atrophy in prefrontal and lateral temporal regions.[28] Different methodological approaches might explain the discrepant results. The patterns identified in the present study were based on objective anatomical data without prior patient classification according to the presence or absence of MCI.

Interestingly, we identified a second cortical thinning pattern, specifically involving frontal (medial OFC and rostral middle frontal) and occipital (cuneus and lateral occipital) atrophy. Similar to pattern 1, patients in this group displayed inferior and superior parietal atrophy, but medial parietal and temporal regions were preserved. A similar pattern of degeneration has been identified in studies of brain metabolism in PD patients. Occipital and frontal (18)F-fluorodeoxyglucose positron emission tomography (PET) hypometabolism has been reported as a signature of cognitive impairment in PD.[30-32] Cortical hypoperfusion, mainly in frontal, parietal, and occipital regions, has also been identified using arterial spin labeling perfusion MRI in nondemented PD.[33] Furthermore, metabolic single-photon emission computed tomography and PET studies have suggested the existence of widespread brain metabolic changes associated with cognitive impairment involving multiple domains[34-36] and with single-domain nonamnestic deficits.[36]

To date, atrophy in occipital and frontal regions has not been evidenced using other structural MRI techniques such as voxel-based morphometry.[31,33] In line with our results, previous studies seem to indicate that cortical thickness measures are more sensitive to occipital cortical atrophy in PD.[37,38]

The pathological meaning of the differences between patterns identified in our study is unclear. Prior pathological findings in PD, including Lewy neurites and Lewy bodies containing ubiquitin and α-synuclein aggregations, provide a general progression of brain alterations from the medulla and olfactory bulb to the midbrain, diencephalic nuclei, and finally to the neocortex following Braak staging.[39] Braak's classification has been seen to correlate with neurological deficits in patients with early-onset PD and long disease duration.[40] Conversely, it has also been stated that Braak staging is not related to clinical severity and cognitive impairment.[41] Thus, the relationship between the presence of α-synuclein aggregates and cognitive deficits in PD remains controversial. Recent studies have shown an increase in the severity of α-synuclein pathology in the basal forebrain and hippocampus in combination with more widespread degeneration of cortical dopaminergic and cholinergic pathways in demented PD patients.[42] On the other hand, Alzheimer's disease–type pathology has been highlighted as an important

TABLE 2. Results from emotion recognition tests at the 3-cluster level

	PD subtypes				
	Pattern 1, n = 30, mean (SD)	Pattern 2, n = 29, mean (SD)	Pattern 3, n = 29, mean (SD)	HC, n = 31, mean (SD)	Test stats,[a] *P* value
Anger	−0.23 (1.0)	−0.23 (1.1)	0.00 (0.7)	0.07 (1.0)	0.762, .518
Disgust	−0.45 (1.6)	−0.43 (1.1)	−0.50 (1.0)	0.09 (0.9)	1.513, .216
Fear	0.00 (0.8)	0.07 (0.8)	−0.04 (1.0)	−0.07 (1.0)	0.124, .946
Sadness	−0.19 (1.1)	−0.53 (0.9)	−0.27 (0.7)	0.14 (0.7)	2.587, .057[b]
Happiness	−0.18 (1.6)	−0.58 (1.9)	−0.22 (1.1)	−0.11 (1.0)	0.526, .665
Surprise	−0.40 (1.4)	−0.11 (1.1)	0.06 (0.9)	0.04 (0.9)	1.040, .378
Total score	−0.12 (0.7)	−0.03 (0.6)	0.02 (0.5)	0.02 (1.1)	0.209, .890

HC, healthy controls; PD, Parkinson's disease; SD, standard deviation.
Results of the Ekman 60 Faces Test, presented in *z* scores.
[a]Analysis of variance.
[b]Significant differences between HC and pattern 2 in Bonferroni post hoc test ($P < .05$).

cofactor in the progression of cognitive impairment in PD[43,44] as well as other pathological findings such as cerebrovascular disease and hippocampal sclerosis (see Halliday and colleagues[45] for a review). In our opinion, our results might be related to abnormal protein deposition, including α-synucleinopathy and Alzheimer's disease–type pathology, as has been shown in previous neuropathological and Pittsburgh Compound-B (PiB) PET studies.[46] A neuropathological study of a large sample of demented PD patients showed that all patients had abnormal cortical synuclein aggregates, and 60% also had abnormal amyloid-β deposits.[46] In one PET study of cognitively impaired PD patients, abnormal PiB binding was observed in 17% of the patients.[47] We could speculate that pattern 1 in our sample could be reflecting patients with abnormal amyloid-β associated with abnormal cortical α-synuclein deposition because patients in this group showed atrophy in the medial temporal and parietal cortices, regions reported as sensitive to progressive cortical thinning in cognitively preserved PiB + patients.[48] Patterns 1 and 2 in our study differed in the degree of atrophy in the posterior cingulate, isthmus of the cingulate, and precuneus. In this line, it has been reported that in nondemented PD, higher PiB retention in the precuneus seems to contribute to cognitive decline over time.[49]

In addition, we identified a PD subtype without manifest cortical atrophy. This group showed no significant differences in disease duration, motor symptoms, or LEDD when compared with other PD subtypes. As such, patients in this group were not in an earlier disease stage. Interestingly, other studies reported cortical differences in gray matter atrophy between motor subtypes showing a reduction predominantly in postural-instability and gait-difficulty patients in comparison with tremor-dominant patients.[50] Our results showed no significant differences between groups in motor symptoms measured by the UPDRS. However, the specific motor profile of our groups was not evaluated in depth. Previous studies comparing HC with early PD,[23,28,51] or with PD patients with and without MCI,[26,27] have often described differences that did not survive correction for multiple comparisons. In our opinion, these findings suggest the existence of a subtype of PD with slower cortical degeneration. The absence of structural changes between cognitively unimpaired de novo PD patients and HC has been reported even using techniques sensitive to subtle longitudinal changes such as tensor-based morphometry.[52] Longitudinal cortical thickness studies could assess whether this cortical pattern might constitute a biomarker of better cognitive prognosis.

The 3 PD subtypes identified had specific cognitive characteristics. The parietal-temporal and occipital and frontal subtypes (patterns 1 and 2, respectively) performed significantly worse than HC on JLO, TMTB, TMTA minus TMTB, and SDMT tests, although the occipital and frontal subtype showed less pronounced impairment. In addition, the parietal-temporal subtype also performed worse in RAVLT, Stroop Color, and TMTA and showed more severe depression and apathy symptoms than HC. However, contrary to what might have been expected, there were no differences in the proportion of patients with MCI between PD subtypes. A previous model-based cluster analysis study using neuropsychological data[4] also described heterogeneous cognitive impairment in PD from cognitively intact patients to very severely impaired patients with a progressive severity gradient. The authors found a group of patients within the normal range of cognitive performance, but with lower scores on working memory, verbal episodic memory, and executive functions. In addition, they found a second group of PD patients with varying degrees of impairment in all cognitive domains. Patients in the cognitively impaired cluster were older, less educated, and more apathetic than the cognitively unimpaired patients; these characteristics partially overlap with

the parietal-temporal subtype we describe. However, the cognitively impaired group in the study by Dujardin and colleagues[4] included a wider range of cognitive deficits, from MCI to dementia, whereas our study did not include demented patients. Contrary to our results in which there were no significant differences in motor disease severity or disease duration between cluster groups, Dujardin and colleagues[4] found that the cognitively impaired group showed more severe motor symptoms, longer disease duration, and more axial signs in comparison with cognitively unimpaired patients.

It is noteworthy that, among all the cognitive tests used, only semantic fluency specifically differentiated the parietal-temporal pattern from other PD subtypes. We have previously shown a positive correlation between semantic fluency and medial temporal and precuneus cortical thickness.[13] In addition, semantic fluency has been shown in population-based longitudinal studies to be a predictor of dementia in PD.[53,54] Barker and Williams-Gray[55] suggested that there is a posterior cognitive syndrome with impaired semantic fluency, nondopaminergic deficits, and worse prognosis. In a recent review, Sauerbier and colleagues[56] defined this phenotype as "Park cognitive." Together, these results highlight the usefulness of semantic fluency as an easily administered task that should be included in the routine neuropsychological assessment to help identify this subtype of PD patients.

Focusing on the occipital and frontal subtype, patients were younger at PD onset and showed impaired recognition of sadness in facial expressions. In line with these results, voxel-based morphometry studies showed medial OFC atrophy in younger PD patients (<70 years) when compared with HC[57] and related it with specific cognitive deficits.[58] Specifically, medial OFC volume has been associated with overall[58] as well as negative facial emotion recognition in PD.[13]

Cognitive performance in the nonatrophic subtype followed a similar pattern as that in the other groups. However, only Stroop Word scores were significantly different between the nonatrophic group and HC. Similarly, as we previously mentioned, previous cluster analyses using neuropsychological data reported the existence of a PD subtype composed of cognitively intact patients and patients with lower scores (although within the normal range) on different cognitive domains commonly impaired in PD.[4] These results could lead us to speculate the existence of a subgroup of PD patients with limited cortical atrophy with cognitive profiles similar but possibly less severe than those of patients with faster structural degeneration. Beyond the presence of α-synuclein pathology and Alzheimer's disease–type pathology, functional deficits related to neurotransmitter deficiencies (mostly but not only dopaminergic) as well as defects involving diverse metabolic pathways (abnormal oxidative stress, gene regulation, protein degradation, and synaptic degeneration), translate as an early involvement of the cerebral cortex in PD (see Ferrer[59] and Ferrer and colleagues[60] for reviews). These findings might explain cognitive dysfunctions in the absence of evident structural changes. Alternatively, structural changes might be below the detection threshold of cortical thickness methods in such cases. In this vein, future fMRI connectivity studies might help to characterize the functional changes associated with the cortical thickness patterns herein identified.

Finally, none of the PD subtypes showed significant differences on the digits subtest, Stroop Word-Color, phonemic fluency, or the BNT. The sensitivity of these tests to detect cognitive impairment in PD should be assessed in future studies using different cohorts to validate their role in recommended neuropsychological batteries. Moreover, in light of our results, it would be interesting to include other tests that could be associated with occipital and frontal atrophy, such as emotion recognition tests, in standard protocols. The early identification of these PD subtypes through cognitive and clinical characteristics could facilitate the study of different patterns of deterioration over time. In the near future, longitudinal assessments might help clarify whether the cortical atrophy patterns reported in our results are associated with clinical PD subtypes identified recently as diffuse/malignant with rapid progression to dementia, mainly motor/slow progression and intermediate.[3]

The main strength of our study is the use of cortical thickness as a main variable because this is an objective measure based on validated methods. Clustering analysis using MRI data may allow future studies using other independent cohorts to validate these patterns.

In conclusion, the cluster analysis of cortical thickness data in nondemented PD patients identified 3 subtypes consisting of (1) parieto-temporal pattern of atrophy with significant cognitive impairment, (2) occipital and frontal cortical atrophy with younger PD onset, and (3) patients without manifest cortical atrophy. This effort to identify different PD phenotypes based on objective data could be valuable for the establishment of prognostic markers in PD. ■

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site

Supplementary material

Supplementary Methods 1. Neuropsychological assessment

Visuospatial and visuoperceptual functions were assessed with Benton Visual Form Discrimination (VFD) and Judgment of Line Orientation (JLO) tests; executive functions were evaluated with phonemic (words beginning with the letter “p” in 1 minute) and semantic (animals in 1 minute) fluencies; 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). Attention and WM were assessed with Digit Span Forward and Backward, the Stroop Color-Word Test, Symbol Digits Modalities Tests (SDMT) and the Trail Making Test (in seconds), part A (TMTA) and part B (TMTB); and language was assessed by the total number of correct responses in the short version of the Boston Naming Test (BNT).

Initially, z scores for each test and for each subject were calculated based on the control group’s means and standard deviations. 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.[1] As in a previous study,[2] 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.

Supplementary Methods 2. Cortical thickness procedures

The procedures carried out by FreeSurfer include removal of nonbrain data, intensity normalization,[3] tessellation of the gray matter/white matter boundary, automated topology correction,[4,5] and accurate surface deformation to identify tissue borders).[6-8] Cortical thickness is then calculated as the distance between the white and gray matter surfaces at each vertex of the reconstructed cortical mantle.[8] In our study, results for each subject were 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 of 15 mm.

Supplementary Results 1. PD patterns according to cluster analysis at 2 and 4-cluster level solutions.

At the 2-cluster level, two patterns of cortical atrophy were identified. PD patients included in *pattern 1* (n=30, 34.09%) showed reduced cortical thickness compared with HC in lateral and medial regions bilaterally, including the precentral gyrus, inferior and superior parietal lobules, cuneus, posterior cingulate gyrus and parahippocampal gyrus. As patients included in *pattern 1* were significantly older and less educated than HC (age mean ± SD for *pattern 1*: 70.60 ± 9.6; for HC: 64.3 ± 8.5, F=11.115, p<0.0001; education mean ± SD for *pattern 1*: 7.77 ± 4.8; for HC: 11.0 ± 4.2, F=8.089; p=0.001), age and years of education were controlled for when comparing these groups. Patients in *pattern 2* (n=58, 65.10%) showed reduced cortical thickness in the left lateral occipital region, and bilaterally in the cuneus and medial orbitofrontal areas in comparison with HC.

Demographical and clinical characteristics of the two patterns are in **supplementary Table 2**, neuropsychological tests results in **supplementary Table 3** and the emotion recognition task in **supplementary Table 4**.
At the 4-cluster level, *pattern 1* was divided into two different clusters. As the number of subjects in one group was too small (n=9), we did not perform additional analyses.

Supplementary Results 2. Principal Component Analysis
Eigenvalues extracted from the analyses had the highest separation between the first four components. We chose the first two components because they had the highest separation and explained 12.84% of variance (7.49% the first component and 5.35% the second). The third and fourth components only accounted for 3.74% and 2.95% of the explained variance based on the loadings of the PCA. The first component (x-axis) captured the variability of cortical thickness differences in *pattern 1.* PD patients that had positive loading for the first component were also classified in *pattern 1* (n=25). PD patients who are represented in the PCA plot as negative loading for the first component were from *pattern 2* at the 2 cluster level (n=47). Half of them also had negative loadings for the second component, whereas others were positive. Patients who are represented in the left inferior side of the plot (negative for both components) were those that at the 3 cluster level had no cortical thickness differences with HC (*pattern 3;* n=21). Patients in *pattern 2* at the 3 cluster level had positive loading for the second component (n=26) (**Figure A1**).

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Supplementary Table 1 Demographic and clinical characteristics of the sample

	PD (n =88)	HC (n = 31)	Stats (p value)
Sex, male, n (%)	51 (58.0)	16 (51.6)	0.375 (0.540)[a]
Age, y	64.1 ± 10.6	64.3 ± 8.5	0.099 (0.921)[b]
Education, y	10.6 ± 5.3	11.0 ± 4.2	0.417(0.677)[b]
MMSE	29 ± 1.1	29.7 ± 0.5	4.36 (<0.0001)[b]
Disease duration, y	8 ± 5.7	NA	NA
Age of onset, y	56.12 ± 11.6	NA	NA
Early PD, 5 y, (%)	37 (42.0)	NA	NA
BDI	10.77 ± 6.3	6.03 ± 5.7	-3.582 (0.001)[b]
Apathy	12.70 ± 7.2	8.38 ± 5.1	-3.497 (0.001)[b]
NPI	5.74 ± 7.5	1.52 ± 3.2	-4.183 (<0.0001)[b]
Visual Hallucinations, n (%)	17 (19.8)	0 (0.0)	NA
UPDRS part III	15.5 ± 9.9	NA	NA
Hoehn & Yahr stage, n 1/1.5/2/2.5/3	22/5/43/8/10	NA	NA
LEDD, mg	803.93 ± 494	NA	NA

Abbreviations: BDI = Beck Depression Inventory; HC = Healthy Controls; LEDD = L-Dopa Equivalent Daily Dose; MMSE = Mini-Mental State Examination; NA = not applicable; NPI = Cumming's Neuropsychiatric Inventory; PD = Parkinson's disease; UPDRS III = Unified Parkinson's Disease Rating Scale III.
Data are presented as mean ± SD.

a. The Chi-test was used.
b. T-student test was used.

Supplementary Table 2 Demographic and clinical characteristics at 2-cluster level

	PD subtypes		HC (n = 31)	Stats (p value)
	Pattern 1 (n=30)	Pattern 2 (n=58)		
Sex, male, n (%)	15 (50.0)	36 (62.1)	16 (51.6)	1.545 (0.462)[a]
Age, y	70.60 ± 9.6	60.76 ± 9.5	64.3 ± 8.5	11.115 (<0.0001)[c,e,g]
Education, y	7.77 ± 4.8	12.05 ± 5.0	11.0 ± 4.2	8.089 (0.001)[c,e,g]
MMSE	28.57 ± 1.4	29.28 ± 0.9	29.7 ± 0.5	10.462 (<0.0001)[d,e,f,g]
Disease duration, y	8.77 ± 6.6	7.60 ± 5.1	NA	0.917 (0.362)[b]
Age of onset, y	61.83 ± 12.7	53.16 ± 9.9	NA	3.252 (0.002)[b]
Early PD, <=5 y, (%)	12 (40.0)	25 (43.1)	NA	0.078 (0.780)[a]
BDI	13.67 ± 5.7	9.27 ± 6.2	6.03 ± 5.7	11.824 (<0.0001)[c,e,g]
Apathy	15.11 ± 7.9	11.43 ± 6.5	8.38 ± 5.1	7.489 (0.001)[d,e]
NPI	6.59 ± 7.8	5.31 ± 7.4	1.52 ± 3.2	4.352 (0.015)[d,f]
Visual Hallucinations, n (%)	6 (20.0)	11 (19.6)	0 (0.0)	7.640 (0.106)[a]
UPDRS part III	18.07 ± 9.1	14.12 ± 10.1	NA	1.798 (0.076)[b]
Hoehn & Yahr stage, n 1/1.5/2/2.5/3	2/3/16/4/5	20/2/27/4/5	NA	9.827 (0.043)[a]
LEDD,mg	764.63 ± 388.28	824.26 ± 542.72	NA	-0.593 (0.555)[b]
Total MCI, n (%)	20 (66.7)	25 (43.1)	NA	4.394 (0.036)[a]
Visuospatial functions, n (%)	10 (33.3)	16 (27.6)	NA	0.314 (0.575)[a]
Executive functions, n (%)	16 (3.3)	12 (20.7)	NA	9.712 (0.002)[a]
Memory, n (%)	14 (46.7)	20 (34.5)	NA	1.238 (0.266)[a]
Attention and WM, n (%)	20 (66.7)	31 (53.4)	NA	1.418 (0.234)[a]

Language, n (%)	2 (6.7)	5 (8.6)	NA	0.103 (0.748)[a]

Abbreviations: Apathy = Starkstein's Apathy Scale; BDI = Beck Depression Inventory-II; HC = Healthy Controls; LEDD = L-DOPA Equivalent Daily Dose; MCI = Mild Cognitive Impairment; MMSE = Mini-Mental State Examination; NA = not applicable; NPI = Cumming's Neuropsychiatric Inventory; PD = Parkinson's disease; UPDRS III = Unified Parkinson's Disease Rating Scale, motor section; WM = Working Memory.
Data are presented as mean ± SD(continuous) or frequencies (categorical).

a. The Chi-test was used.
b. T-student test was used.
c. Analysis of variance (ANOVA) followed by Bonferroni post hoc test was used.
d. Analysis of variance (ANOVA) followed by Tamhane (T2) post hoc test was used.
e. Significant differences ($p<0.05$) between HC and Pattern 1.
f. Significant differences ($p<0.05$) between HC and Pattern 2.
g. Significant differences ($p<0.05$) between both PD patterns.

Supplementary Table 3 Neuropsychological tests results at the 2 cluster level solution

	PD subtypes		HC (n=31)	Stats (p value)
	Pattern 1 (n=30)	Pattern 2 (n=58)		
Visuospatial functions				
VFD	-0.83 ± 1.3	-0.59 ± 1.1	-0.04 ± 0.9	4.012 (0.021)[a,c]
JLO	-0.67 ± 0.9	-0.45 ± 1.1	0.06 ± 0.7	4.659 (0.011)[a,c]
Executive functions				
Phonetic fluency	-0.46 ± 1.0	-0.11 ± 1.1	0.01 ± 0.9	1.834 (0.164)[a]
Semantic fluency	-1.37 ± 1.0	-0.18 ± 1.3	0.07 ± 1.0	14.095 (<0.0001)[a,c,e]
Memory				
RAVLT total	-1.19 ± 1.5	-0.46 ± 1.3	0.05 ± 0.9	7.437 (0.001)[b,c]
RAVLT recall	-0.88 ± 1.1	-0.54 ± 1.3	0.02 ± 0.9	4.415 (0.014)[b,c]
Attention and WM				
Span digits forward	0.11 ± 0.9	-0.26 ± 0.9	0.03 ± 0.8	2.084 (0.129)[a]
Span digits backward	0.11 ± 0.7	-0.08 ± 0.9	0.02 ± 0.9	0.467 (0.628)[a]
Stroop Word Test	-0.89 ± 1.2	-0.93 ± 1.3	0.01 ± 0.9	6.762 (0.002)[a,c,d]
Stroop Color Test	-0.49 ± 0.9	-0.21 ± 0.8	0.08 ± 0.9	3.599 (0.031)[a,c]
Stroop Word-Color Test	-0.34 ± 0.7	-0.08 ± 0.8	0.13 ± 0.7	2.783 (0.066)[a]
SDMT	-1.05 ± 0.9	-0.59 ± 0.9	0.01 ± 0.6	11.078 (<0.0001)[a,c,d]
TMT-A	2.09 ± 3.3	0.97 ± 3.0	-0.06 ± 0.8	4.827 (0.010)[b,c]
TMT-B	1.72 ± 2.8	0.98 ±1.9	-0.09 ± 0.6	6.296 (0.003)[b,c,d]
TMT A minus B	-1.80 ± 3.2	-0.95 ± 1.9	0.14 ± 0.7	6.450 (0.002)[b,c,d]
Language				
BNT	-0.07 ± 1.2	-0.24 ± 0.9	0.16 ± 0.7	1.776 (0.174)[a]

Abbreviations: BNT = Boston Naming Test; HC = Healthy Controls; JLO = Judgement of Line Orientation; PD = Parkinson's disease; RAVLT = Rey's Auditory and Verbal Learning Test; SDMT = Symbol Digits Modalities Test; TMT = Trail Making Test; VFD = Visual Form Discrimination; WM = working memory.

Data are presented as mean ± SD. All scores are z scores.

a. Analysis of variance (ANOVA) followed by Bonferroni post hoc test was used.
b. Analysis of variance (ANOVA) followed by Tamhane (T2) post hoc test was used.
c. Significant differences ($p<0.05$) between HC and Pattern 1.
d. Significant differences ($p<0.05$) between HC and Pattern 2.
e. Significant differences ($p<0.05$) between both PD patterns.

Supplementary Table 4 Results from emotion recognition tests at the 2-cluster level

	PD subtypes		HC (n=31)	Test stats (p value)
	Pattern 1 (n=30)	Pattern 2 (n=58)		
Ekman anger	-0.23 ± 1.0	-0.11 ± 0.9	0.07 ± 1.0	0.735 (0.482)[a]
Ekman disgust	-0.45 ± 1.6	-0.47 ± 1.0	0.09 ± 0.9	2.266 (0.109)[b]
Ekman fear	0.00 ± 0.8	0.01 ± 0.9	-0.07 ± 1.0	0.085 (0.918)[a]
Ekman sadness	-0.19 ± 1.1	-0.39 ± 0.8	0.14 ± 0.7	3.345 (0.039)[a,c]
Ekman happy	-0.18 ± 1.6	-0.39 ± 1.5	-0.11 ± 1.0	0.389 (0.679)[a]
Ekman surprise	-0.40 ± 1.4	-0.02 ± 1.0	0.04 ± 0.9	1.408 (0.249)[a]
Ekman total score	-0.12 ± 0.7	-0.00 ± 0.5	0.02 ± 1.1	0.285 (0.753)[a]

Results of the Ekman 60 Faces Test, presented in z scores.
Abbreviations: HC = healthy controls; PD = Parkinson's Disease.

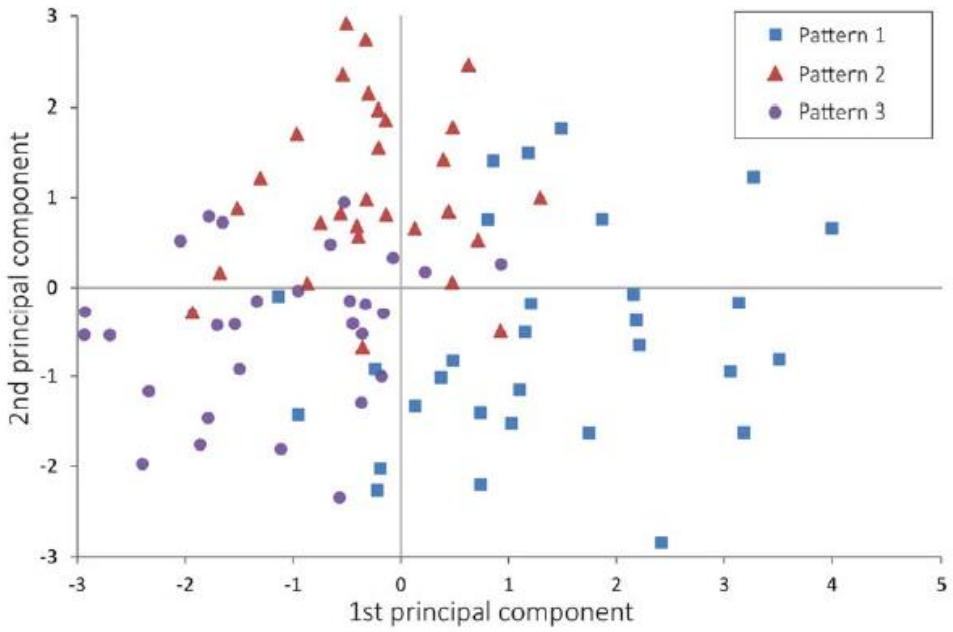
a. Analysis of variance (ANOVA) followed by Bonferroni post hoc test.
b. Analysis of variance (ANOVA) followed by Tamhane (T2) post hoc test.
c. Significant differences ($p<0.05$) between HC and Pattern 2.

Supplementary Table 5 Neuropsychological tests results at the 3 cluster level solution

	PD subtypes			HC (n=31)	Stats (p value)
	Pattern 1 (n=30)	Pattern 2 (n=29)	Pattern 3 (n=29)		
Visuospatial functions					
VFD	-0.83 ± 1.3	-0.55 ± 1.0	-0.62 ± 1.2	-0.04 ± 0.9	2.674 (0.051)[a,c]
JLO	-0.67 ± 0.9	-0.65 ± 1.2	-0.26 ± 1.0	0.06 ± 0.7	3.933 (0.010)[a,c,d]
Executive functions					
Phonetic fluency	-0.46 ± 1.0	-0.05 ± 1.1	-0.17 ± 1.1	0.01 ± 0.9	1.280 (0.285)
Semantic fluency	-1.37 ± 1.0	-0.16 ± 1.1	-0.21 ± 1.5	0.07 ± 1.0	9.325 (<0.0001)[a,c,f,g]
Memory					
RAVLT total	-1.19 ± 1.5	-0.55 ± 1.3	-0.37 ± 1.3	0.05 ± 0.9	5.031 (0.003)[a,c]
RAVLT recall	-0.88 ± 1.1	-0.64 ± 1.4	-0.44 ± 1.3	0.02 ± 0.9	3.061 (0.031)[a,c]
Attention and WM					
Span digits forward	0.11 ± 0.9	-0.55 ± 0.8	0.04 ± 0.9	0.03 ± 0.8	3.687 (0.014)[a,f]
Span digits backward	0.11 ± 0.7	-0.25 ± 0.8	0.10 ± 1.0	0.02 ± 0.9	1.124 (0.342)
Stroop Word Test	-0.89 ± 1.2	-0.99 ± 1.4	-0.88 ± 1.4	0.01 ± 0.9	4.506 (0.005)[a,c,d,e]
Stroop Color Test	-0.49 ± 0.9	-0.38 ± 0.8	-0.05 ± 0.7	0.08 ± 0.9	3.149 (0.028)[a,c]
Stroop Word-Color Test	-0.34 ± 0.7	-0.18 ± 0.9	0.02 ± 0.7	0.13 ± 0.7	2.161 (0.097)
SDMT	-1.05 ± 0.9	-0.70 ± 1.0	-0.48 ± 0.8	0.01 ± 0.6	7.685 (0.000)[a,c,d]
TMT-A	2.09 ± 3.3	1.44 ± 3.8	0.49 ± 1.7	-0.06 ± 0.8	3.848 (0.011)[b,c]
TMT-B	1.72 ± 2.8	1.04 ± 1.6	0.93 ± 2.2	-0.09 ± 0.6	4.178 (0.008)[b,c,d]
TMT A minus B	-1.80 ± 3.2	-0.98 ± 1.6	-0.91 ± 2.1	0.14 ± 0.7	4.267 (0.007)[b,c,d]
Language					
BNT	-0.07 ± 1.2	-0.35 ± 0.9	-0.13 ± 0.9	0.16 ± 0.7	1.448 (0.233)

Abbreviations: BNT = Boston Naming Test; HC = Healthy Controls; JLO = Judgement of Line Orientation; PD = Parkinson's disease; RAVLT = Rey's Auditory and Verbal Learning Test; SDMT = Symbol Digits Modalities Test; TMT = Trail Making Test; VFD = Visual Form Discrimination; WM = working memory. Data are presented as mean ± SD. All scores are z scores.

a. Analysis of variance (ANOVA) followed by Bonferroni post hoc test.
b. Analysis of variance (ANOVA) followed by Tamhane (T2) post hoc test.
c. Significant differences ($p<0.05$) between HC and Pattern 1.
d. Significant differences ($p<0.05$) between HC and Pattern 2.
e. Significant differences ($p<0.05$) between HC and Pattern 3.
f. Significant differences ($p<0.05$) between Pattern 1 and Pattern 2.
g. Significant differences ($p<0.05$) between Pattern 1 and Pattern 3.



Supplementary Figure 1 Principal component analysis results and distribution according to the 3 PD patterns.

Graphics program: Microsoft Excel® and edited with Adobe Photoshop®.

Study 2

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Cortical atrophy patterns in early Parkinson's disease patients using hierarchical cluster analysis

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ABSTRACT

Introduction: Cortical brain atrophy detectable with MRI in non-demented advanced Parkinson's disease (PD) is well characterized, but its presence in early disease stages is still under debate. We aimed to investigate cortical atrophy patterns in a large sample of early untreated PD patients using a hypothesis-free data-driven approach.

Methods: Seventy-seven *de novo* PD patients and 50 controls from the Parkinson's Progression Marker Initiative database with T1-weighted images in a 3-tesla Siemens scanner were included in this study. Mean cortical thickness was extracted from 360 cortical areas defined by the Human Connectome Project Multi-Modal Parcellation version 1.0, and a hierarchical cluster analysis was performed using Ward's linkage method. A general linear model with cortical thickness data was then used to compare clustering groups using FreeSurfer software.

Results: We identified two patterns of cortical atrophy. Compared with controls, patients grouped in pattern 1 (n = 33) were characterized by cortical thinning in bilateral orbitofrontal, anterior cingulate, and lateral and medial anterior temporal gyri. Patients in pattern 2 (n = 44) showed cortical thinning in bilateral occipital gyrus, cuneus, superior parietal gyrus, and left postcentral gyrus, and they showed neuropsychological impairment in memory and other cognitive domains.

Conclusions: Even in the early stages of PD, there is evidence of cortical brain atrophy. Neuroimaging clustering analysis is able to detect two subgroups of cortical thinning, one with mainly anterior atrophy, and the other with posterior predominance and worse cognitive performance.

1. Introduction

Impaired cognition in Parkinson's disease (PD) is often present in untreated patients, over 20% of whom fulfill criteria for mild cognitive impairment (MCI) affecting a wide range of cognitive domains such as executive function, memory, attention, or visuo-spatial function [1]. Advances in magnetic resonance imaging (MRI) acquisition and analysis allowed the identification of cortical implication in early untreated patients. Cortical thinning is present in *de novo* PD patients with MCI involving frontal, temporal [2,3], and parietal [3] regions. However, in newly diagnosed PD patients without MCI, studies failed to find differences between patients and controls [2] or found thinning in small temporal [3] or parietal [4] cortical regions.

The heterogeneity of PD clinical phenotypes has led to increased interest in patient subtyping [5] in an attempt to understand the underlying mechanisms and improve prognostic accuracy. In line

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with these efforts, we have previously identified three subtypes based on hierarchical cluster analysis of cortical thickness. One subtype showed temporal and parietal involvement; another displayed orbitofrontal and occipital atrophy and younger disease onset; and a third group of patients showed no detectable cortical atrophy [6].

The Parkinson's Progression Markers Initiative (PPMI) is a comprehensive observational, international, multicenter study designed to identify PD progression biomarkers such as cerebral imaging in a cohort of recently-diagnosed PD patients [7]. Recent studies have identified Parkinson's subtypes in this cohort based on motor and non-motor data [8,9]. However, there is no evidence regarding subtypes based on objective structural imaging data in early PD.

Using data from the PPMI database, we aimed to examine cortical atrophy patterns in a large sample of newly diagnosed, drug naïve PD patients using a hypothesis-free data-driven approach. In light of previous results, we hypothesized that we would identify different brain cortical atrophy patterns associated with different clinical and neuropsychological characteristics.

2. Methods

2.1. Participants

Data used in this study were obtained from the PPMI database [7]. For up-to-date information on the study, visit www.ppmi-info.org. T1-weighted images acquired on 3-tesla Siemens MRI scanners and clinical and neuropsychological data obtained from 119 PD patients and 77 HC assessed between 2010 and 2015 were included. All imaging and non-imaging data corresponded to the same time points and were acquired prior to any L-DOPA intake. Inclusion criteria were: (i) recent diagnosis of PD with asymmetric resting tremor or asymmetric bradykinesia, or two of: bradykinesia, resting tremor, and rigidity; (ii) absence of treatment for PD; (iii) neuroimaging evidence of significant dopamine transporter deficit consistent with the clinical diagnosis of PD and ruling out PD *look-alike* conditions such as drug-induced and vascular parkinsonism or essential tremor; (iv) available T1-weighted images in a 3T Siemens scanner (for both PD patients and HC) and (v) age > 50 years old (for both PD patients and HC). Exclusion criteria for all participants were: (i) diagnosis of dementia; (ii) significant neurologic or psychiatric dysfunction; (iii) first-degree family member with PD, and (iv) presence of MRI motion artifacts, field distortions, intensity inhomogeneities, or detectable brain injuries. A total of 77 *de novo* PD patients and 50 HC were selected. The following participants were excluded from the study: 4 patients and 1 HC due to other neurological disease, 18 PD patients and 20 HC due to MRI motion artifacts at visual inspection performed by an expert radiologist (HCB), and 18 PD patients and 5 HC due to cortical thickness preprocessing problems (see MRI images section). Finally, we performed an initial cluster analysis for the PD group and another for the control group to detect possible abnormal outliers on MRI data. From these, we discarded 2 PD patients and 1 HC that constituted independent clusters by themselves.

Each participating PPMI site received approval from an ethical standards committee on human experimentation before study initiation and obtained written informed consent for research from all individuals participating in the study.

2.2. Clinical and neuropsychological assessments

Motor symptoms were assessed with the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III and motor subtypes were established based on the ratio from the means of several items of the MDS-UPDRS Part III. Activities of daily living (ADL) were evaluated with the Schwab and England Scale for PD patients and MDS-UPDRS Part II for all participants. Global cognition was assessed with the MoCA, and depressive symptoms using the 15-item Geriatric Depression Scale (GDS-15) with a cutoff score of 5 or more indicating clinically significant symptoms as described in www.ppmi-info.org [7].

All subjects underwent comprehensive neuropsychological assessment following Movement Disorder Society task force recommendations [10] (except for the absence of tests evaluating the language domain). Memory was assessed with the Hopkins Verbal Learning Test-Revised (HVLT-R); visuospatial function was evaluated with the Benton Judgment of Line Orientation short form (15-item version); attention and working memory through the Symbol Digit Modalities Test and Letter-Number Sequencing; and executive function with phonemic (letter 'f') and semantic (animal) verbal fluency [11].

Initially, z scores for each test and for each subject were calculated based on the control group's means and standard deviations. 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 [1]. The presence of MCI was defined using PD-MCI diagnostic criteria level I [10]: (i) MoCA scores as measure of global cognition below 26 [12] and/or (ii) the z score of a given test was at least 1.5 lower than the expected score on any 2 test scores. Impairment in each cognitive domain was also established if at least 1 test in the domain was impaired.

University of Pennsylvania Smell Identification Test (UPSIT) scores were available in a subsample of 55 PD patients and 28 HC due to missing values. The cutoff indicating anosmia was 18 or less [13].

2.3. MRI images

All three-dimensional T1-weighted MRI scans were acquired in the sagittal plane on 3T Siemens scanners (Erlangen, Germany) at different centers using an MPRAGE sequence. The acquisition parameters were as follows: repetition time = 2300/1900 ms; echo time = 2.98/2.96/2.27/2.48/2.52 ms; inversion time = 900 ms; flip angle: 9°; matrix = 240 × 256/256 × 256; voxel = 1 × 1 × 1 mm^3. Cortical thickness was estimated using the automated FreeSurfer stream (version 5.1, http://surfer.nmr.harvard.edu). Detailed information about the processing FreeSurfer stream is described in Segura et al. [14]. After Freesurfer preprocessing, results for each subject were visually inspected to ensure accuracy of registration, skull stripping, segmentation, and cortical surface reconstruction. Possible errors were fixed by manual intervention following standard procedures (https://surfer.nmr.mgh.harvard.edu/fswiki/FsTutorial/TroubleshootingData#Fixingerrors). In addition, we extracted the mean thickness for each of the 360 cortical areas defined in the Human Connectome Project Multi-Modal Parcellation version 1.0 (HCP-MMP1.0) [15,16].

2.4. Cluster analysis

MATLAB (release 2014b, The MathWorks, Inc., Natick, Massachusetts) was used to perform an agglomerative hierarchical cluster analysis using cortical thickness data from the 77 untreated PD patients. To reduce dimensionality and improve the model's performance calculating similarity/distance measures, mean cortical thickness values for the 360 areas from the HCP-MMP1.0 were used as features in the cluster analysis instead of whole-brain vertex information. To control for variations in global atrophy between patients [6], vertices were normalized

using bilateral mean thickness bh.thickness=((lh.-thickness*lh.surfarea) + (rh.thickness*rh.surfarea))/(lh.surfarea + rh.surfarea).

Ward's clustering linkage method [6,17] was used to combine pairs of clusters at each step while minimizing the sum of square errors from the cluster mean. Each of the 77 patients was placed in their own cluster and then progressively clustered with others. Cluster analysis results are shown as a dendrogram (Fig. 1) and a heatmap representing individual values for each cortical region (Supplementary Figure 1 and Supplementary Table 1 for the order of regions as represented in the figure).

2.5. Statistical analysis

Intergroup cortical thickness comparisons were performed using a vertex-by-vertex general linear model with FreeSurfer. The model included cortical thickness as a dependent factor and group as an independent factor. All results were corrected for multiple comparisons using pre-cached cluster-wise Monte Carlo simulation with 10,000 iterations. Reported cortical regions reached a two-tailed corrected significance level of $p < 0.05$.

Demographic, neuropsychological, and clinical statistical analyses were conducted using IBM SPSS Statistics 24.0 (2011; Armonk, NY: IBM Corp). We tested for group differences in demographic and clinical variables as well as in neuropsychological performance between HC and PD patient subtypes using Kruskal-Wallis test followed by Mann-Whitney's pairwise comparisons and Bonferroni correction for non-normally distributed quantitative measures as indicated by the Kolmogorov-Smirnov test; for normally distributed measures, an analysis of variance (ANOVA) followed by Bonferroni post hoc test was used. Pearson's chi squared tests were used for categorical measures.

For comparisons between the collapsed PD sample and HC we used Mann-Whitney's test or Student *t*-test as appropriate.

2.6. Cluster evaluation

To determine the optimal number of clusters, we computed the Calinski-Harabasz index with MATLAB. The Calinski-Harabasz criterion is best suited for cluster analysis with squared Euclidean distances.

The higher the ratio is, the better the cluster solution. An optimal ratio is determined by a large between-cluster variance and a small within-cluster variance.

(https://es.mathworks.com/help/stats/clustering.evaluation.calinskiharabaszevaluation-class.html).

3. Results

3.1. Characteristics of the PD sample

Demographic and clinical (Supplementary Table 2), neuropsychological (Fig. 2a), and cortical thickness (Supplementary Figure 2, Supplementary Table 3) differences between all PD patients and HC are shown in Supplementary Results 1.

3.2. PD cortical thickness subtypes based on cluster analysis

We identified 2 patterns of cortical thinning compared with HC (Fig. 3, Supplementary Table 3). Patients in pattern 1 (n = 33, 42.9%) showed reduced cortical thickness in bilateral orbitofrontal, anterior cingulate, and lateral and medial anterior temporal regions, as well as a small cluster of cortical thickening in the right cuneus,

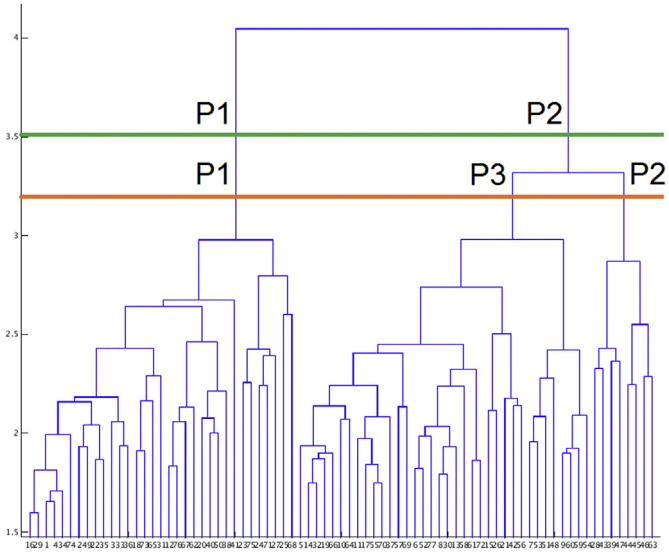

Fig. 1. Dendrogram of PD patients clustered according to mean cortical thickness information.
Abbreviations: P1 = Pattern 1; P2 = Pattern 2; P3 = Pattern 3.

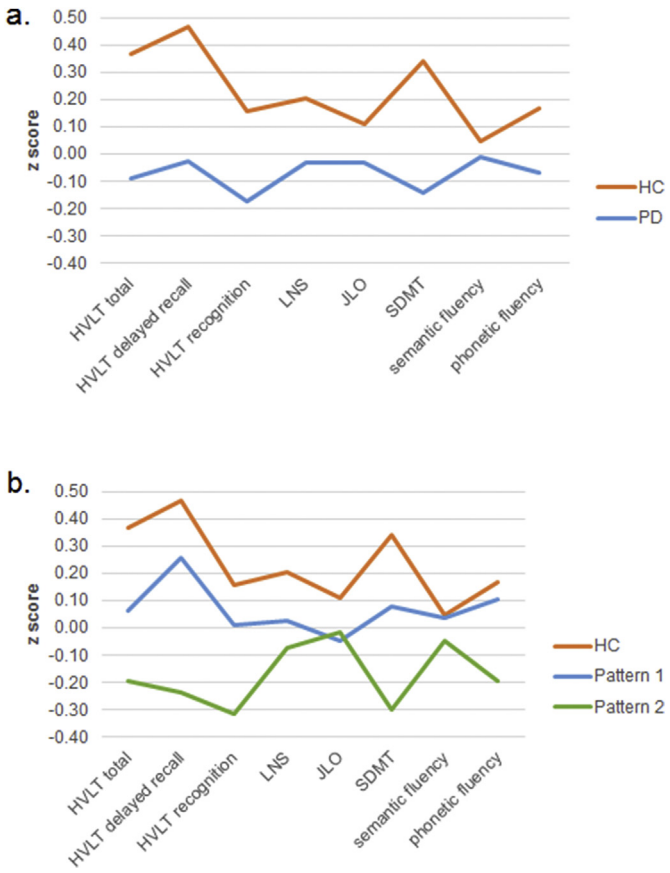

Fig. 2. Neuropsychological performance. (a) Healthy controls in orange and PD collapsed sample in blue. (b) Healthy controls in orange; Pattern 1 patients in blue and Pattern 2 patients in green.
Data are presented as z-scores. Lower z-scores indicate worse performance.
Abbreviations: HC = healthy controls; HVLT total = Hopkins Verbal Learning Test total; HVLT delayed recall = Hopkins Verbal Learning Test recall after 30 min; HVLT recognition = Hopkins Verbal Learning Test recognition after 30 min; JLO = Judgment of Line Orientation Test; LNS = Letter-Number Sequencing; PD = Parkinson's disease; SDMT = Symbol Digits Modalities Test. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

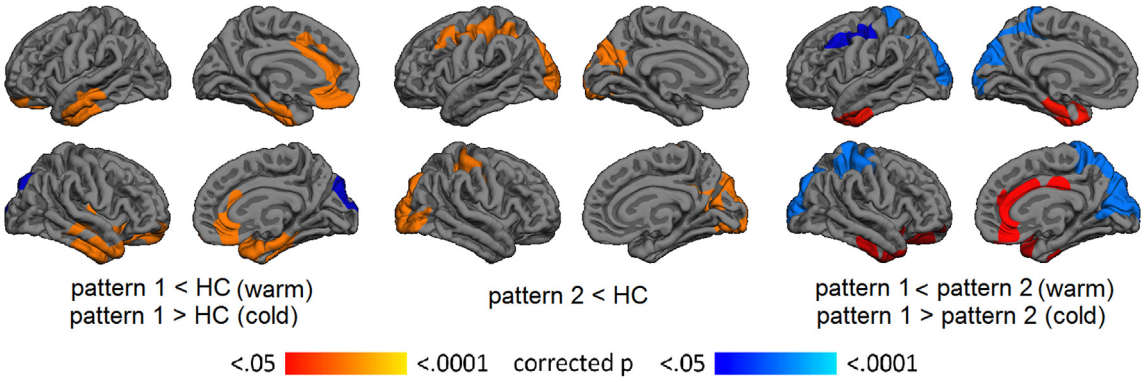

Fig. 3. Cortical thickness differences between groups at 2-cluster level.
Color maps indicate significant differences (corrected $p < 0.05$) between controls and PD subgroups.
Abbreviations: HC = healthy controls. Results were corrected by Monte Carlo simulation. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

compared with HC. Pattern 2 patients (n = 44; 57.1%) had cortical thinning in left postcentral gyrus and bilateral posterior superior parietal, cuneus, and occipital gyri.

There were also cortical thickness differences between PD patterns (Fig. 3). Patients in pattern 1 showed cortical thinning in right orbitofrontal, right anterior cingulate, and bilateral anterior temporal regions when compared with pattern 2 patients. Pattern 2 patients had cortical thinning in bilateral cuneus, precuneus, and posterior superior parietal regions compared with pattern 1.

The two-cluster solution was selected because it had the highest variance ratio (3.36) of the Calinski-Harabasz values. Three and four-cluster solutions offered small cluster partitions and had variance ratios of 2.85 and 2.55, respectively (Supplementary Figure 3).

3.3. Clinical features of PD subtypes

PD patient subgroups showed no significant differences in demographical variables when compared with HC. Patients in pattern 2 scored significantly lower in the MoCA ($U = 17.997$; $P = 0.046$) and scored higher in GDS-15 scale than HC ($U = 20.340$; $P = 0.015$), and had more severe motor symptoms ($U = 938.5$; $P = 0.029$) than pattern 1 patients as measured by the MDS-UPDRS Part III. Both pattern 1 and 2 patients had more disability in ADL (P1: $U = 63.486$; $P < 0.0001$; P2: $U = 58.921$; $P < 0.0001$) than HC as measured by the MDS-UPDRS Part II. They also scored lower in the UPSIT test (P1: $U = 31.326$; $P < 0.0001$; P2: $U = 33.250$; $P < 0.0001$) and had a greater proportion of anosmic cases (P1: $\chi^2 = 7.638$; $P = 0.006$; P2: $\chi^2 = 7.693$; $P = 0.006$) than the HC group (Table 1).

Both PD patterns had more impairment in global cognition scores as measured with the MoCA < 26 (P1: $\chi^2 = 7.539$; $P = 0.006$; P2: $\chi^2 = 10.438$; $P = 0.001$) than HC (Table 1). Regarding neuropsychological results (Fig. 2b), pattern 2 patients performed significantly worse in HVLT-R total learning ($F = 2.971$; $P = 0.055$; post hoc test: $P = 0.050$), HVLT-R delayed recall ($F = 4.352$; $P = 0.015$; post hoc test: $P = 0.013$), and the Symbol Digits Modalities Test ($F = 6.056$; $P = 0.003$; post hoc test: $P = 0.002$) than HC.

4. Discussion

To the best of our knowledge, this is the first study to distinguish cortical atrophy patterns in early drug-naïve PD patients based on objective brain imaging data. Two patterns were identified: one with orbitofrontal, anterior cingulate and temporal atrophy, and another involving occipital and parietal atrophy.

Orbitofrontal involvement seen in Pattern 1 has not been previously described in *de novo* patients. There are previous studies that reported cortical thinning in *de novo* patients in other regions probably due to the different methodology used. These studies classified patients *a priori* according to their cognitive status [3,18]. In these studies, patients with MCI had widespread atrophy involving anterior and posterior regions. Pereira et al. [3] also found cortical thinning in patients with normal cognition but restricted to the right temporal cortex.

Despite showing cortical thinning in orbital regions, pattern 1 patients had no detectable neuropsychological impairments. This could be explained by the lack of tests sensitive to orbitofrontal functions in the PPMI battery, such as facial emotion recognition tasks, which we previously found to be correlated with gray matter reduction in these structures in PD patients [6,19].

In addition, we identified a region of cortical thickening in right cuneus in Pattern 1 patients compared to controls. No previous studies reported gray matter increases in early unmedicated PD patients; this phenomenon was only identified in certain studies raising a debate about a possible plastic effect of long term L-LDOPA administration [20], and therefore would not correspond to the clinical status of our patient sample. Increased cortical thickness in temporo-parietal regions and in precuneus and posterior cingulate was described in asymptomatic mutation carriers of presenilin 1 gene mutation compared with controls. This finding has been interpreted as initial neuroinflammation [21].

Pattern 2 was characterized by atrophy in occipital and parietal regions. Similar parietal thinning has also been described in PD-MCI *de novo* patients [3]. Our sample was not classified *a priori* according to cognitive status, but 32% of cases had MCI. Moreover, pattern 2 patients had a neuropsychological profile of semantic memory impairment that agrees with the thinning of posterior cortical regions as previously reported [14]. The finding of cortical thinning in the primary occipital cortex at the time of diagnosis is noteworthy. It could underlie the color deficits described in manifest PD and even in prodromal stages [22].

Pattern 2 patients showed impaired performance in HVLT-R total learning, delayed recall, Symbol Digits Modalities Test, and MoCA. Impairment in total learning and delayed recall have been found to be good markers of future cognitive deterioration in PD [23], and the Symbol Digits Modalities Test is a suitable marker of cortical thinning in lateral temporo-parietal regions [24]. Posterior cortical-based neuropsychological deficits have been related to higher risk of evolution to dementia [25]. Pattern 2 patients seem to show a worse cognitive phenotype, with greater proportion of MCI

Table 1
Demographic and clinical characteristics of PD subtypes.

	PD patients		HC (n = 50)	Test stats	P value
	Pattern 1 (n = 33)	Pattern 2 (n = 44)			
Sex, male, n (%)	20 (60.6)	28 (63.6)	30 (60.0)	0.143[a]	0.931
Age, y, mean (SD)	61.7 (7.9)	64.2 (8.2)	62.3 (7.5)	1.084[b]	0.341
Education, y, median, (IQ)	16.0 (4.0)	16.0 (6.0)	16.0 (4.3)	0.677[c]	0.713
MoCA, median (IQ)	28.5 (3.0)	27.0 (3.0)	28.0 (2.0)	6.257[c]	0.044[e]
Disease duration, y, median (IQ)	1.0 (2.0)	1.0 (1.8)	NA	705.5[d]	0.822
Age of onset, y, mean (SD)	60.7 (8.1)	63.3 (8.2)	NA	852.5[d]	0.192
MDS-UPDRS part III, median (IQ)	19.0 (9.5)	24.0 (10.8)	NA	938.5[d]	0.029
Hoehn & Yahr stage, n, 1/2/3	12/21/0	16/27/1	NA	0.766[a]	0.682
Motor subtype, n, tremor/PIGD/undetermined	25/3/5	31/10/3	NA	3.410[a]	0.182
GDS-15, median (IQ)	1.5 (3.0)	2.0 (4.0)	0.0 (1.0)	9.458[c]	0.009[e]
Depression, n (%)	6 (18.8)	3 (7.0)	5 (10.0)	2.678[a]	0.262
Apathy item MDS-UPDRS Part I, n (%)	11 (33.3)	6 (13.6)	2 (4.0)	13.538[a]	0.001
Subjective cognitive decline item MDS-UPDRS Part I, n (%)	11 (33.3)	12 (27.3)	7 (14.0)	4.616[a]	0.099
UPSIT, median (IQ)	22.0 (9.0)	20.0 (12.0)	35.5 (4.0)	33.779[c]	<0.0001[f]
Anosmia, n (%)	9 (39.1)	12 (37.5)	2 (7.1)	8.94[a]	0.011
Schwab and England scale, median (IQ)	90.0 (8.0)	95.0 (10.0)	NA	866.0[d]	0.125
MDS-UPDRS Part II, median (IQ)	7.0 (5.5)	5.0 (5.8)	0.0 (0.0)	86.838[c]	<0.0001[f]
Total MCI, n (%)	7 (21.9)	14 (31.8)	3 (6.0)	10.340[a]	0.006
Global cognition impaired, n (%)	6 (18.8)	10 (22.7)	0 (0.0)	12.322[a]	0.002
Visuospatial functions, n (%)	4 (12.9)	4 (9.5)	4 (8.0)	0.526[a]	0.769
Executive functions, n (%)	3 (9.4)	3 (6.8)	2 (4.1)	0.925[a]	0.630
Memory, n (%)	5 (16.1)	16 (38.1)	7 (14.0)	8.575[a]	0.014
Attention and WM, n (%)	2 (6.5)	6 (14.3)	1 (2.0)	5.126[a]	0.077

Abbreviations: GDS-15 = Geriatric Depression Scale shortened version; HC = Healthy Controls; IQ = interquartile range; MCI = Mild Cognitive Impairment; MMSE = Mini-Mental State Examination; NA = not applicable; PD = Parkinson's disease; PIGD = Postural Instability Gait Difficulty; MDS-UPDRS = Movement Disorders Society Unified Parkinson's Disease Rating Scale; UPSIT = University of Pennsylvania Smell Identification Test; WM = Working Memory.
Global cognition impairment was established from the cut-off < 26 in MoCA test. Visuospatial, executive, memory and attention WM impairment was establish from the number of subjects with at least one test impaired in each domain.
Data are presented as mean (SD) or median (IQ) for continuous variables as appropriate or frequencies for categorical.
[a] The Chi-squared test was used.
[b] Analysis of variance test was used.
[c] Kruskal-Wallis test was used.
[d] Mann-Whitney *U* test was used.
[e] Significant differences were found between HC and pattern 2 using pairwise Mann-Whitney test. P-values are given in the text.
[f] Significant differences were found between HC and both patterns using pairwise Mann-Whitney test. P-values are given in the text.

and higher proportion of memory impairment than controls. This pattern is similar to that identified in our previous study using hierarchical cluster analysis in more advanced and medicated PD patients [6].

Pattern 2 patients also had more severe motor symptoms. The results from previous studies seem to show that PD patients with predominant resting tremor at onset have a more benign disease course and slower progression compared with those with a postural instability and gait difficulty (PIGD) dominant subtype. PIGD variant is commonly associated with a faster rate of cognitive decline, higher prevalence of non-motor symptoms, and faster progression [5]. In light of the aforementioned findings, we would expect that pattern 2 patients, with higher rates of MCI, would be related to a predominantly non-tremoric subtype. However, our results showed that, although Pattern 2 showed more severe motor symptoms, the two patient groups did not differ in the proportion of motor subtypes. The instability of motor-feature diagnosis in the first year of the disease might explain the lack of predominance in motor subtyping in this sample of *de novo* PD patients [26]. On the other hand, previous studies showed an association between cognitive dysfunction and clinical phenotypes, such as anosmia. Fullard et al. [27] related the presence of severe olfactory deficits to worse cognitive impairment in untreated PD patients, using PPMI data. Nevertheless, we did not observe differences either in the proportion of anosmia or the UPSIT score between the patient groups. Longitudinal studies could clarify the evolution of these patterns; clearer clinical phenotypes based on motor subtypes or non-motor symptoms would be expected to be identified in more advanced stages of the disease. Future studies could thus clarify the relationship between the identified patterns of atrophy and other PD symptomatology.

In the present study, we did not find a non-atrophic group as found in other studies with newly-diagnosed drug-naïve PD patients [28,29] or even with medicated patients with more advanced disease [6,30–32]. This could be explained by the high sensitivity of our methodological approach to detect subtle differences between patients and HC. We improved the cluster analysis technique using the HCP-MMP1.0 to perform a feature reduction of the imaging data. In the last few years, there has been an increased interest in the potential of machine learning techniques due to their ability to manage large amounts of data, and because they allow hypotheses to be guided by data itself using unsupervised approaches. Nonetheless, clustering algorithms perform better when data sets avoid multicollinearity and the curse of dimensionality. This method seems to be sensitive for detecting subtle cortical atrophy even at early stages of the disease, although further studies are needed to replicate these results. In addition, unsupervised machine learning techniques allowed us to detect PD subtypes from a hypothesis-free data driven approach using objective imaging data rather than clinical data that is examiner-dependent. The use of objective data is especially relevant in multicenter studies, in which there is increased variability of data collection.

One strength of this study is the use of a multicenter cohort of patients from the PPMI data base with a large sample of HC, well-matched with patients regarding age and education. Another strength is that the sample of PD patients is very homogeneous, as it is composed of *de novo* and untreated subjects. Despite this homogeneity on several variables (such as age, time of evolution, and

clinical severity) we were able to detect subtypes of cortical thinning and neuropsychological profile.

The limitations include the short neuropsychological battery that did not allow using level II criteria to diagnose PD-MCI, and the fact that MRI acquisitions were acquired at different research centers (although all scanners were similar and acquisition protocols were standardized). In addition, the PPMI is a research cohort with highly educated participants that might not be representative of the general population. The PPMI sample have scarce cognitive or psychiatric symptoms at baseline, restricting the use of correlational approaches with neuroimaging findings. We would also like to highlight the complexity of PD diagnosis at early stages of the disease. Patients were selected based on neuroimaging evidence of significant dopamine transporter deficit consistent with the clinical diagnosis of PD and ruling out PD look-alike conditions such as drug-induced and vascular parkinsonism or essential tremor. However, certain diagnoses can only be established by pathological findings.

To sum up, two different cortical atrophy patterns can be identified at the time of diagnosis in unmedicated PD patients. Our results establish a starting point to investigate the evolution of these patterns as possible useful markers of clinical prognosis. Moreover, the MRI findings indicate the necessity to review the neuropsychological tests included in cohort studies trying to cover the functional assessment of all cortical regions that have been found to be impaired in PD.

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Declaration of interest

None.

Authors' roles

Research project conception and acquisition of data are explained in Marek et al., 2011 as cited in the text. CJ contributed in the design of the study. CU, AA, AIGD and AC contributed to the analysis of the data and CU, BS, HCB, AA, AIGD, AC, MJM, FV, YC, ET and CJ contributed to the interpretation of the data. CU, BS contributed to the draft of the article. CU, BS, HCB, AA, AIGD, AC, MJM, FV, YC, ET, CJ revised the manuscript critically for important intellectual content and approved the final version of the manuscript.

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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.2018.02.006.

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Cortical atrophy patterns in early Parkinson's disease patients using hierarchical cluster analysis

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Supplementary material:

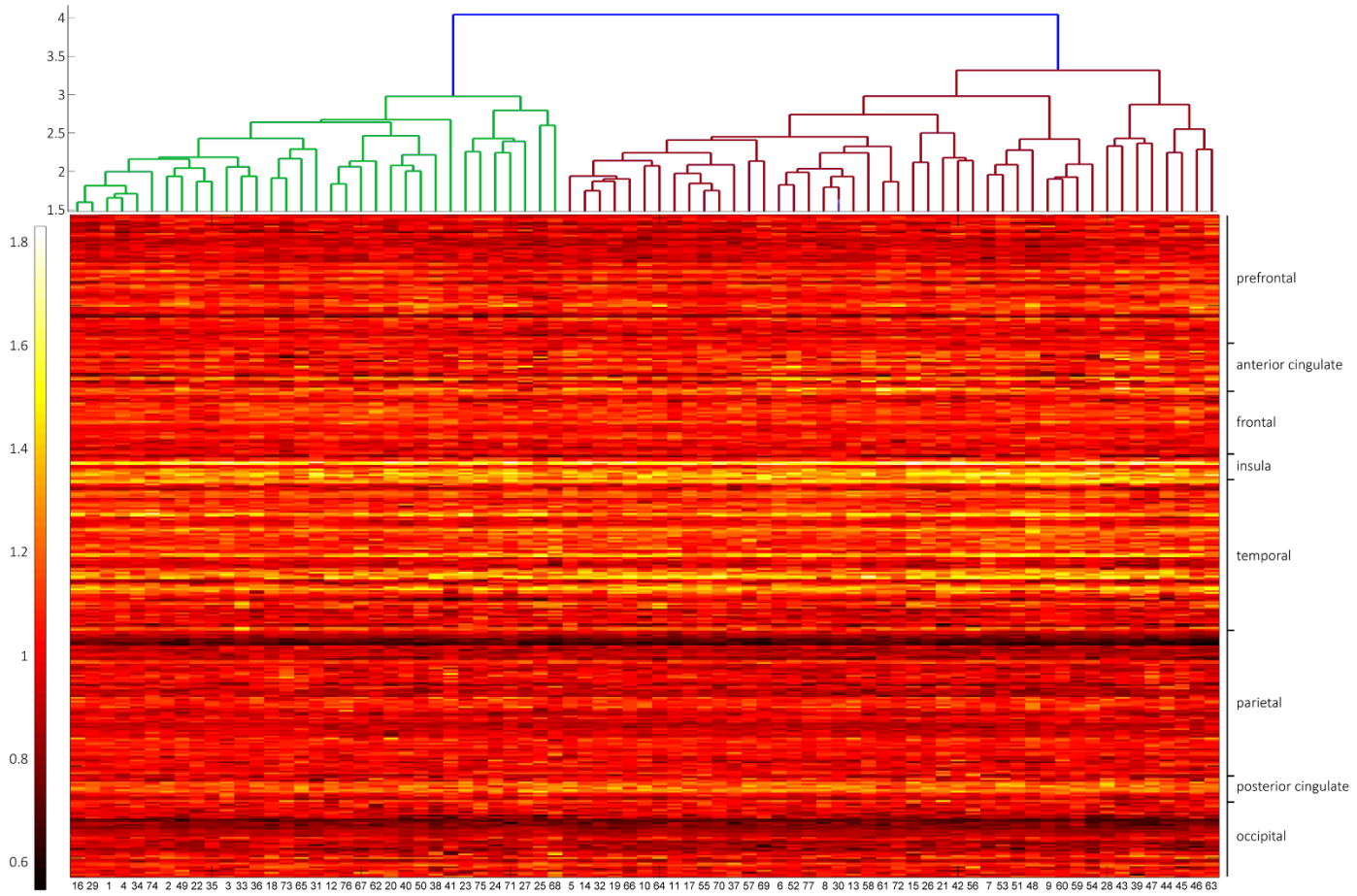
Supplementary Results 1. Characteristics of the collapsed sample.

Compared with HC, the collapsed PD sample had a greater proportion of subjective cognitive decline (chi=4.232; P=0.040) and apathy (chi=7.787; P=0.005) per the MDS-UPDRS Part I items. PD patients also scored significantly higher than HC in GDS-15 scale (U=2,460.0; P=0.002) and MDS-UPDRS Part II (U=3,770.5; P<0.0001) although without clinical relevance (Supplementary Table 2).

Regarding neuropsychological testing, PD patients performed significantly worse than HC in HVLT-R total learning (T=2.233; P=0.027), HVLT-R delayed recall (U=1,401.0; P=0.029), and SDMT (T=2.943; P=0.004) (Figure 2a). PD patients had a greater proportion of PD-MCI level I diagnosis (chi=9.152; P=0.002), more global cognition impairment (chi=12.057; P=0.001), and more olfactory dysfunction (U=168.0; P<.0001) than HC (Supplementary Table 2).

PD patients had cortical thickness reductions in bilateral temporal and occipital regions and in the left lateral superior parietal lobe when compared with HC (Supplementary Figure 2, Supplementary Table 3).

Supplementary Figure 1. Cluster analysis dendrogram and heatmap.



Heatmap displaying mean cortical thickness for each of the 360 regions (rows) and 77 patients (columns) included in the cluster analysis. Subjects are ordered according to the results of the cluster analysis, as shown in the dendrogram in the top part of the figure. Cortical regions are ordered according to brain region/lobe in a roughly anterior-posterior sequence, following the order given in Supplementary Table 1. Cortical thickness values are represented by the colormap shown in the left part of the figure.

Supplementary Table 1. Parcellation order as plotted in the heatmap (Supplementary Figure 1)

1	Area 9 anterior	61	Frontal opercular area 1	121	IntraParietal sulcus area 1
2	Area 10v	62	Frontal opercular area 3	122	Parieto-occipital sulcus area 1
3	Area anterior 10p	63	Frontal opercular area 2	123	Area 5L
4	Polar 10p	64	Area frontal opercular 5	124	Lateral area 7A
5	Area 10r	65	Primary motor cortex	125	Medial area 7A
6	Area 10d	66	Area 52	126	Lateral area 7P
7	Area posterior 10p	67	Anterior ventral insular area	127	Area 7PC
8	Area IFSp	68	Anterior agranular insula complex	128	Area lateral intraParietal ventral
9	Area IFSa	69	Insular granular complex	129	Ventral intraParietal complex
10	Area posterior 9-46v	70	Middle insular area	130	Medial intraParietal area
11	Area 46	71	Posterior insular Area 2	131	Area lateral intraParietal dorsal
12	Area anterior 9-46v	72	Area posterior insular 1	132	Area 43
13	Area 9-46d	73	Area TG dorsal	133	Area OP4/PV
14	Area 8Av	74	Para-insular area	134	Area OP1/SII
15	Area 8Ad	75	Primary auditory cortex	135	Area OP2-3/VS
16	Area 8B lateral	76	Auditory 4 complex	136	RetroInsular cortex
17	Area 9 posterior	77	Auditory 5 complex	137	Area PFcm
18	Superior 6-8 transitional area	78	Area STSv anterior	138	Area PFt
19	Area posterior 47r	79	PeriSylvian language area	139	Anterior intraParietal area
20	Area 8BM	80	Superior temporal visual area	140	Area intraParietal 2
21	Area 9 middle	81	Area TA2	141	Area intraParietal 1
22	Area anterior 47r	82	Area STGa	142	Area intraParietal 0
23	Area 47m	83	Area STSd anterior	143	Area PF opercular
24	Area 47 lateral	84	Area STSd posterior	144	Area PF complex
25	Area 47s	85	Area STSv posterior	145	Area PFm complex
26	Area 11l	86	Area TE1 anterior	146	Area PGi
27	Area 13l	87	Area TE1 posterior	147	Area PGs
28	Orbital frontal complex	88	Area TE2 anterior	148	PreCuneus visual area
29	Posterior OFC complex	89	Area TF	149	Medial area 7P
30	Area 44	90	Area TE2 posterior	150	Area 7m
31	Area 45	91	Area PHT	151	Area 23c
32	Area IFJa	92	Area PH	152	Area temporoParietoOccipital junction 2
33	Area IFJp	93	Area TG ventral	153	Area temporoParietoOccipital junction 3
34	Inferior 6-8 transitional area	94	ParaBelt complex	154	RetroSplenial complex
35	Area 8C	95	Medial belt complex	155	Area 23d
36	Dorsal area 24d	96	Lateral belt complex	156	Area ventral 23 a+b

37	Ventral area 24d	97	Area TE1 middle	157	Area dorsal 23 a+b
38	Area posterior 24 prime	98	Piriform cortex	158	Area 31p ventral
39	Area 33 prime	99	Entorhinal cortex	159	Area 31pd
40	Anterior 24 prime	100	PreSubiculum	160	Area 31a
41	Area p32 prime	101	Hippocampus	161	VentroMedial visual area 1
42	Area a24	102	Perirhinal ectorhinal cortex	162	VentroMedial visual area 3
43	Area dorsal 32	103	ParaHippocampal area 1	163	Area V3CD
44	Area p32	104	ParaHippocampal area 3	164	VentroMedial visual area 2
45	Area 25	105	ParaHippocampal area 2	165	Primary visual cortex
46	Area s32	106	Fusiform face complex	166	Sixth visual area
47	Area anterior 32 prime	107	Posterior inferoTemporal	167	Second visual area
48	Area posterior 24 prime	108	Medial superior temporal area	168	Third visual area
49	Superior frontal language area	109	Area FST	169	Fourth visual area
50	Frontal eye fields	110	Middle temporal area	170	Eighth visual area
51	Premotor eye fields	111	Area temporoParietoOccipital junction 1	171	Area V3A
52	Area 55b	112	ProStriate area	172	Seventh visual area
53	Supplementary and cingulate eye field	113	Ventral visual complex	173	Area V3B
54	Area 6m anterior	114	Area 1	174	Area lateral occipital 1
55	Dorsal area 6	115	Area 2	175	Area lateral occipital 2
56	Area 6mp	116	Area 3a	176	Dorsal transitional visual area
57	Ventral area 6	117	Primary sensory cortex	177	Area PGp
58	Rostral area 6	118	Area 5m	178	VentroMedial visual area 6A
59	Area 6 anterior	119	Area 5m ventral	179	Area V4t
60	Frontal opercular area 4	120	Parieto-occipital sulcus area 2	180	Area lateral occipital 3

For each label, there are two values in the heatmap shown in Supplementary Figure 1: even rows correspond to regions in the left hemisphere and odd rows to those in the right hemisphere, in a total of 360 regions used for the cluster analysis.

Supplementary Table 2 Demographic and clinical characteristics according to group.

	PD (n=77)	HC (n=50)	Test stats	P value
Sex, male, n (%)	48 (62.3)	30 (60.0)	0.070 [a]	0.791
Age, y, mean (SD)	63.1 (8.1)	62.3 (7.5)	0.599[b]	0.550
Education, y, median, (IQ)	16.0 (6.0)	16.0 (4.3)	1,761.0[c]	0.411
MoCA, median (IQ)	27.5 (3.0)	28.0 (2.0)	1,536.5 [c]	0.065
Disease duration, y, mean (SD)	0.9 (1.0)	NA	NA	NA
Age of onset, y, mean (SD)	62.2 (8.2)	NA	NA	NA
MDS-UPDRS part III, mean (SD)	23.1 (0.7)	NA	NA	NA
Hoehn & Yahr stage, n, 1/2/3	28/48/1	NA	NA	NA
Motor subtype, n, tremor/PIGD/undetermined	56/13/8	NA	NA	NA
GDS-15, median (IQ)	2.0 (3.0)	0.0 (1.0)	2,460.0[c]	0.002
Depression, n (%)	9 (12.0)	5 (10.0)	0.121[a]	0.728
Apathy item MDS-UPDRS Part I, n (%)	17 (22.1)	2 (4.0)	7.787[a]	0.005
Subjective cognitive decline item MDS-UPDRS Part I, n (%)	23 (29.9)	7 (14.0)	4.232[a]	0.040
UPSIT, median (IQ)	21.0 (11.0)	35.5 (4.0)	168.0[c]	<0.0001
Anosmia, n (%)	21 (38.2)	2 (7.1)	8.923[a]	0.003
Schwab and England scale, median (IQ)	90.0 (10.0)	NA	NA	NA
MDS-UPDRS Part II, median (IQ)	5.0 (6.0)	0.0 (0.0)	3,770.5[c]	<.0001
Total MCI, n (%)	21 (27.6)	3 (6.0)	9.152[a]	0.002
Global cognition impaired, n (%)	16 (21.1)	0 (0.0)	12.057[a]	0.001
Visuospatial functions, n (%)	8 (11.0)	4 (8.0)	0.295[a]	0.587
Executive functions, n (%)	6 (7.9)	2 (4.1)	0.723[a]	0.395
Memory, n (%)	21 (28.8)	7 (14.0)	3.681[a]	0.055
Attention and WM, n (%)	8 (11.0)	1 (2.0)	3.512[a]	0.061

Abbreviations: GDS-15 = Geriatric Depression Scale shortened version; HC = Healthy Controls; IQ = interquartile range; MCI = Mild Cognitive Impairment; MMSE = Mini-Mental State Examination; NA = not applicable; PD = Parkinson's disease; PIGD = Postural Instability Gait Difficulty; MDS-UPDRS = Movement Disorders Society Unified Parkinson's Disease Rating Scale; UPSIT = University of Pennsylvania Smell Identification Test; WM = Working Memory.
Global cognition impairment was established from the cut-off <26 in MoCA test.
Visuospatial, executive, memory and attention WM impairment was established from the number of subjects with at least one test impaired in each domain.
Data are presented as mean (SD) or median (IQ) for continuous variables as appropriate or frequencies for categorical.

a. The Chi-squared test was used.
b. Student's t test
c. Mann-Whitney U test

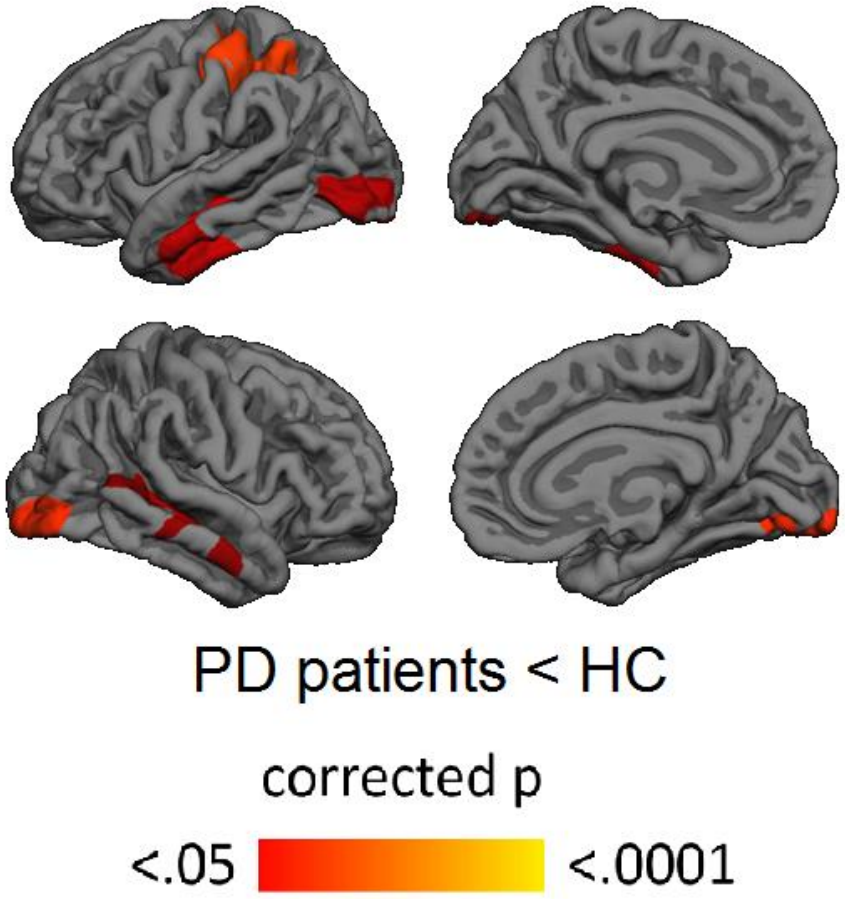
Supplementary Table 3. Cortical thickness information.

Cortical area	Cluster Size (mm^2)	Stats	P-value	MNI coordinates (x,y,z)[1]
healthy controls *vs* PD collapsed sample				
Left inferior temporal	2,064.5	4.515	0.010	-52 -23 -32
Left superior parietal	2,699.7	3.303	0.001	-33 -36 45
Left lateral occipital	1,843.9	2.887	0.020	-36 -88 -5
Right lateral occipital	2,489.1	3.504	0.001	20 -98 -14
Right superior temporal	1,655.1	2.583	0.039	46 -23 -11
healthy controls vs Pattern 1				
Left inferior temporal	3,979.0	5.176	<0.001	-52 -19 -34
Left medial orbitofrontal	3,638.9	3.724	<0.001	-10 33 -14
Right inferior temporal	8,217.9	4.427	<0.001	51 -18 -34
Right lateral occipital	1,865.8	-2.230	0.010	12 -97 13
healthy controls vs Pattern 2				
Left precentral	11,641.6	5.386	<0.001	-32 -20 45
Right lateral occipital	7,863.9	4.889	<0.001	26 -92 17
Right supramarginal	3,108.3	4.313	<0.001	32 -34 41
Pattern 1 vs Pattern 2				
Left postcentral	7,671.7	-6.167	<0.001	-18 -38 67
Left precentral	2,126.2	-3.862	0.007	-33 -17 48
Left entorhinal	2,461.2	3.688	0.002	-20 -15 -27
Right superior parietal	13,384.7	-7.164	<0.001	20 -86 36
Right caudal anterior cingulate	2,217.9	3.193	0.003	6 23 24
Right inferior temporal	1,770.5	3.036	0.015	55 -20 -26
Right lateral orbitofrontal	1,564.4	2.908	0.039	25 10 -16

[1]MNI305 space.

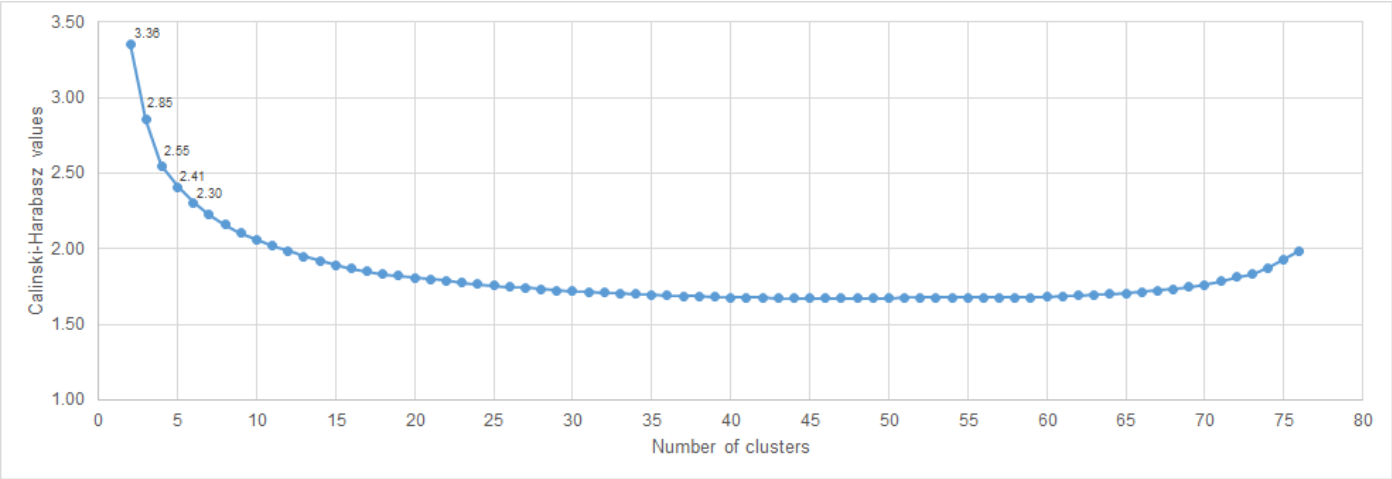
Results were obtained using Monte Carlo simulation with 10.000 iterations applied to cortical thickness maps to provide clusterwise correction for multiple comparisons (1.3). Significant clusters were reported at $p<0.05$. z-Max indicates the maximum -log10(pvalue) in the cluster.

Supplementary Figure 2. Vertex-wise cortical thickness comparison between healthy controls and the collapsed PD sample.



Color maps indicate significant differences. Abbreviations: HC = healthy controls; PD = Parkinson's disease. Results were corrected by Monte Carlo simulation.

Supplementary Figure 3. Calinski-Harabasz index for each possible cluster solution.



Values given are ratios.

Study 3

3. Uribe, C.*, Segura, B.*, Baggio, H. C., Abos, A., Garcia-Diaz, A.I., Campabadal, A., Marti, M. J., Valldeoriola, F., Compta, Y., Bargallo, N., Junque, C. Progression of Parkinson's disease patients subtypes based on cortical thinning: 4-year follow-up. Under review.

Progression of Parkinson's disease patients' subtypes based on cortical thinning: 4-year follow-up

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Keywords: Parkinson disease, cluster analysis, Magnetic Resonance Imaging, cortical atrophy, longitudinal assessment.

Abstract

Background. Three cortical atrophy patterns were previously identified in non-demented Parkinson's disease patients using a data-driven approach based on cortical thickness data: i) parieto-temporal pattern of atrophy with worse cognitive performance (pattern 1), ii) occipital and frontal cortical atrophy with younger disease onset (pattern 2), and iii) non-detectable cortical atrophy (pattern 3). We aimed to investigate the evolution of these three patterns over time. **Methods.** Magnetic resonance imaging and neuropsychological assessment were obtained at baseline and follow-up (3.8±0.4 year apart) in a group of 45 Parkinson's disease patients and 22 healthy controls. FreeSurfer was used for cortical thickness analysis and global atrophy measures. **Results.** Temporo-parietal cortical thinning occurred in all groups and patients showed decline in processing speed and semantic fluency. Pattern 3 patients showed more progressive cortical thinning in the left prefrontal cortex than controls and more right occipital thinning than pattern 2 patients over time. Pattern 1 patients had greater compromise in activities of the daily living and suffered higher attrition rate. **Conclusion.** The three Parkinson's disease phenotypes identified using cluster analysis of cortical thickness data showed different progression over time. The presence of prefrontal thinning and younger disease onset at baseline was associated to less cortical degeneration, whereas initial temporo-parietal pattern of atrophy was associated to worse clinical decline. Non-atrophic patients progressed showing a temporo-parietal cortical thinning.

1. Introduction

Impaired cognitive functions in Parkinson's disease (PD) are present even in untreated patients and around 20% fulfill criteria for mild cognitive impairment (MCI) [1]. The cumulative prevalence of dementia during eight years' evolution is near 80% [2]. A meta-analysis performed in 2007 including 25 heterogeneous longitudinal studies reported that significant cognitive decline was obtained for global cognitive ability, visuoconstructive skills and memory functions [3]. Posteriorly, well-controlled prospective works coincided that the greatest decline was seen in psychomotor speed followed by memory functions but disagreed regarding the progression of attention deficits [4-6]. It has been suggested that the neuropsychological functions sensitive to cognitive decline and progression to dementia are those supported by regions of the posterior cortex [7,8]. Longitudinal magnetic resonance imaging (MRI) studies have contributed to establish the brain substrates for cognitive decline in PD. Voxel-wise and vertex-wise analyses demonstrated that demented and non-demented PD patients had gray matter (GM) reductions over relatively short periods of time [9-11] and these reductions were more remarkable in patients with visual hallucinations [12]. In addition to hallucinations, the presence of MCI is also a predictor of higher rates of cortical thinning [13]. The differences between studies in cortical and subcortical regions that suffer atrophy during the course of the disease could be due to the heterogeneity of the disease. A clinical subtype named diffuse/malignant presenting non-motor features such as MCI, orthostatic hypotension and rapid eye movement sleep behavior disorder, showed a more rapid progression of cognitive decline [14]. Thus, different phenotypes could lead to different patterns of cortical degeneration.

In a previous study using cluster analysis of cortical thickness data in PD patients, we identified three PD subtypes: (i) parieto-temporal pattern of atrophy associated with

significant cognitive impairment, (ii) occipital and frontal cortical atrophy with younger PD onset, and (iii) patients without manifest cortical atrophy [15]. In the current study, we aimed to investigate longitudinally the evolution of these three different cortical atrophy patterns over a 4-year period.

2. Methods

2.1 Participants

Forty-five PD patients from the Parkinson's Disease and Movement Disorders Unit, Hospital Clinic (Barcelona, Spain) and 22 HC from the Aging Institute in Barcelona were assessed twice at 3.8±0.4 years apart (range: 3.1-5.3).

At time 1, 88 PD patients and 31 HC were recruited between October 2010 and March 2012 and classified into three subtypes as previously described [15]. In the present study, only subjects who underwent comprehensive neuropsychological and MRI evaluation at both times were included (see Supplementary Figure 1).

Inclusion criteria for patients at time 1 were: (i) fulfilling the UK PD Society Brain Bank diagnostic criteria for PD; (ii) no surgical treatment with deep-brain stimulation. Exclusion criteria for PD patients and HC were: (i) dementia according to the Movement Disorders Society (MDS) criteria and clinic assessment performed by clinical neurologist (MJM, FV, YC), (ii) Hoehn and Yahr (H&Y) scale score > 3, (iii) young-onset PD, (iv) age below 50 years, (v) presence of severe psychiatric or neurological comorbidity, (vi) low global intellectual quotient estimated by the Vocabulary subtest of the Wechsler Adult Intelligence Scale, (scalar score ≤ 7), (vii) Mini Mental State Examination (MMSE) score below 25, (viii) claustrophobia, (ix) pathological MRI findings other than mild white matter hyperintensities in the FLAIR sequence, and (x) MRI artifacts.

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) [16] was calculated.

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 Neuropsychological and clinical assessment

In line with MDS PD-MCI task force recommendations [17], we assessed five cognitive domains: visuospatial and visuoperceptual functions, executive functions, verbal memory, attention and working memory and language (see Uribe et al., [15] for detailed protocol). As in the baseline study [15], adjusted z-scores were calculated and 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. Furthermore, the presence of dementia was determined if MMSE score was below 26, or if there was cognitive impairment in more than one domain and impaired instrumental activities of daily living (IADL).

Neuropsychiatric symptoms were evaluated with the Beck Depression Inventory-II, Starkstein's Apathy Scale and Cumming's Neuropsychiatric Inventory. Functioning in IADL were assessed with the Lawton and Brody scale and the Schwab and England scale. Additionally, the Gottfries-Brane-Steen scale (GBS) was administered to caregivers/family members of PD patients that could not return at time 2 (non-completers) via telephone interview. This scale was administered with the aim to obtain qualitative information from patients lost to follow-up, specially concerning pattern I patients.

2.3 Preprocessing and analysis of longitudinal imaging data

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

Cross sectional preprocessing of both times was estimated using the automated FreeSurfer stream (version 5.1; available at: http://surfer.nmr.harvard.edu). Detailed description of FreeSurfer procedures is reported in the baseline study [15] and information about the longitudinal cortical thickness preprocessing and the computed symmetrized percent of change (SPC) of cortical thickness are described elsewhere [18]. Cortical thickness maps were smoothed using a circularly symmetric Gaussian kernel across the surface with a full width at half maximum of 25 mm.

2.4 Statistical analysis

Group differences in demographic variables, disease outcomes and GBS scale scores at time 2 were analyzed with Kruskal-Wallis test followed by Mann-Whitney's pairwise comparisons and Bonferroni correction for quantitative measures. Chi squared test were used where appropriate for categorical measures.

Group differences in demographic and clinical variables between completers and non-completers were analyzed with Mann-Whitney's U test for quantitative measures and Chi squared test for categorical measures at time 1. These analyses were conducted using IBM SPSS Statistics 22.0 (2013; Armonk, NY: IBM Corp).

Group by time interaction effects in clinical disease-related variables and neuropsychological performance between pattern 2 and 3 patients and HC were assessed through a repeated-measures general linear model and permutation testing with 10,000 iterations. To control type-I errors, a Bonferroni correction was applied.

Comparisons between groups were assessed using a vertex-by-vertex general linear model. Two statistical models were performed: one sample t-test was performed to test time effect in groups (if the SPC was different from zero); and to test time by group interaction effects, SPC was included as a dependent factor and group as an independent factor. In the second model, age and years of education were considered as nuisance covariates (see Table 1).

All results were corrected for multiple comparisons using pre-cached cluster-wise Monte Carlo simulation with 10,000 iterations. Reported cortical regions reached a two-tailed corrected significance level of $p < 0.05$.

Global atrophy measures including total GM volume, subcortical and cortical GM volume, mean lateral ventricular volume and estimated intracranial volume were obtained automatically via whole brain segmentation with the FreeSurfer suite. Global average thickness for both hemispheres was calculated as:

((lh.thickness*lh.surface area)+(rh.thickness*rh.surface area))/(lh.surface area+rh.surface area).

Group by time interaction effects were assessed by permutation test statistics with 10,000 iterations. Bonferroni was then used to control for multiple comparison. The estimated intracranial volume was considered as a nuisance covariate in the volumetric analyses.

3. Results

There were no significant differences in the assessment interval between groups (H=6.516; *P*=.089).

3.1 Demographic and clinical characteristics

Pattern 2 patients were younger than both HC and pattern 1, younger at disease onset than pattern 1, and had more years of education than patients in pattern 1 and 3 and HC (Table 1).

Regarding functioning in IADLS, patients in pattern 1 had significantly more impairment than HC and pattern 3 patients as measured by the Lawton and Brody scale at time 2. There were also significant differences between HC and pattern 1, pattern 2 and pattern 3 as measured by the Schwab and England scale (Table 1).

Pattern 2 patients and controls had significant time effects in the MMSE scores as measure of global cognition although they were not clinically significant. Regarding L-DOPA intake, a significant interaction was found between the decreased doses of pattern 2 patients compared with an increment in the doses of pattern 3 patients. Regarding psychiatric symptoms over time, patients in pattern 2 had more severe global neuropsychiatric symptoms than HC (Table 2).

Due to the high attrition rate in Pattern 1 patients, this group (n = 7) was not included in the statistical general linear models to investigate cortical thinning progression, clinical evolution and neuropsychological decline.

Table 1 Demographic and clinical characteristics of the sample at both times

	Parkinson's Disease subtypes			Healthy controls (n=22)	Test stats/ *P*-values
	Pattern 1 (n=7)	Pattern 2 (n=16)	Pattern 3 (n=22)		
Age, y, median (IQ range)					
Time 1	76.0 (18.0)	57.5 (13.0)	63.0 (10.0)	66.0 (13.0)	13.740/.003
Time 2	80.0 (18.0)	61.0 (13.0)	67.5 (11.0)	70.0 (13.0)	14.017/.003
Education, y, median (IQ range)	8.0 (6.0)	17.5 (8.0)	10.5 (6.0)	10.0 (8.0)	16.492/.001
Sex, male, n (%)	6 (86.7)	13 (81.3)	12 (54.5)	11 (50.0)	6.081/.108
Disease duration, y, median (IQ range)					
Time 1	4.0 (7.0)	6.0 (8.3)	6.0 (9.0)	NA	1.564/.457
Time 2	7.0 (7.0)	9.0 (7.0)	9.0 (7.0)	NA	0.278/.870
Age of onset, y, median (IQ range)	67.0 (19.0)	47.5 (14.6)	54.5 (12.7)	NA	10.583/.005
Hoehn &Yahr stage, n 1/1.5/2/2.5/3/4					
Time 1	2/0/5/0/0/0	5/1/7/2/1/0	11/0/8/1/2/0	NA	6.466/.595
Time 2	0/0/2/0/4/1	2/0/6/0/8/0	4/0/11/0/7/0	NA	8.629/.196
Instrumental Activities of Daily Living Scales, median (IQ range)					
Lawton and Brody Scale	3.5 (2.0)	7.0 (3.0)	8.0 (2.0)	8.0 (2.0)	17.096/.001
Schwab and England Scale, %	70.0 (20.0)	85.0 (30.0)	90.0 (20.0)	100.0 (0.0)	33.105/<.001
noMCI[1]	2 (28.6)	9 (56.2)	11 (50.0)	21 (95.5)	80.136/<.001 11.734/.019[2]
MCI[1]	3 (42.8)	7 (43.8)	11 (50.0)	1 (4.5)	
Dementia[1]	2 (28.6)	0	0	0	

IQ range, interquartile range; MCI, mild cognitive impairment; NA, not applicable.

P-values are from Kruskal-Wallis test followed by Mann-Whitney pairwise test and Bonferroni correction for continuous variables and chi-squared test for categorical variables.

[1] Proportions of noMCI, MCI and dementia at time 2.

[2] Chi squared test between all groups was 80.136; *P*<.001. Chi squared test between PD groups was 11.734; *P*=.019.

Age showed significant differences between pattern 2 and HC (P=.013 at time 1; P=.015 at time 2) and pattern 1 (P=.009 at time 1; P=.007 at time 2). Years of education showed significant differences between pattern 2 and HC (P=.016), pattern 1 (P =.003) and pattern 3 (P =.011). Age of onset showed significant differences between pattern 1 and pattern 2 (P =.005). At time 2, Lawton and Brody Scale showed significant differences between pattern 1 and HC (P=.001) and pattern 3 (P=.003); Schwab and England Scale showed significant differences between pattern 1 and HC (P<.001) and pattern 2 (P<.001) and pattern 3 (P=.003).

Table 2 Clinical measures of the sample at both times

	Parkinson's Disease subtypes			Healthy controls (n=22)
	Pattern 1 (n=7)	Pattern 2 (n=16)	Pattern 3 (n=22)	
Mini Mental State Examination, mean (SD)				
Time 1	28.3 (2.0)	29.6 (0.6)	29.3 (0.9)	29.8 (0.4)
Time 2	25.7 (4.5)	29.1 (1.0)	29.1 (1.0)	29.3 (0.8)
UPDRS part III, mean (SD)				
Time 1	13.7 (7.0)	13.8 (11.3)	12.5 (9.5)	NA
Time 2	23.9 (15.4)	19.1 (9.5)	14.5 (7.8)	NA
LEDD, mg, mean (SD)				
Time 1	552.9 (386.0)	849.4 (557.9)	603.3 (445.5)	NA
Time 2	924.3 (484.5)	672.8 (326.6)	694.6 (462.1)	NA
Beck Depression Inventory II, mean (SD)				
Time 1	13.9 (5.2)	6.4 (6.1)	8.9 (4.7)	6.6 (5.5)
Time 2	19.7 (9.4)	6.6 (5.3)	8.3 (4.8)	5.1 (4.6)
Starkstein's Apathy Scale, mean (SD)				
Time 1	19.1 (7.5)	11.1 (7.3)	10.7 (5.7)	8.6 (5.8)
Time 2	23.0 (7.0)	10.6 (8.2)	11.3 (5.9)	9.1 (5.5)
Cummings' Neuropsychiatric Inventory, mean (SD)				
Time 1	9.1 (13.7)	5.8 (10.5)	5.4 (6.4)	1.8 (3.5)
Time 2	20.6 (16.4)	9.8 (9.8)	6.2 (6.0)	2.2 (2.5)

LEDD, L-dopa equivalent daily dose; SD, Standard deviation; UPDRS part III, Unified Parkinson's Disease Rating Scale motor section.

Pattern 1 patients were not included into the permutation testing general linear model. All reported significant effects were corrected by Bonferroni.

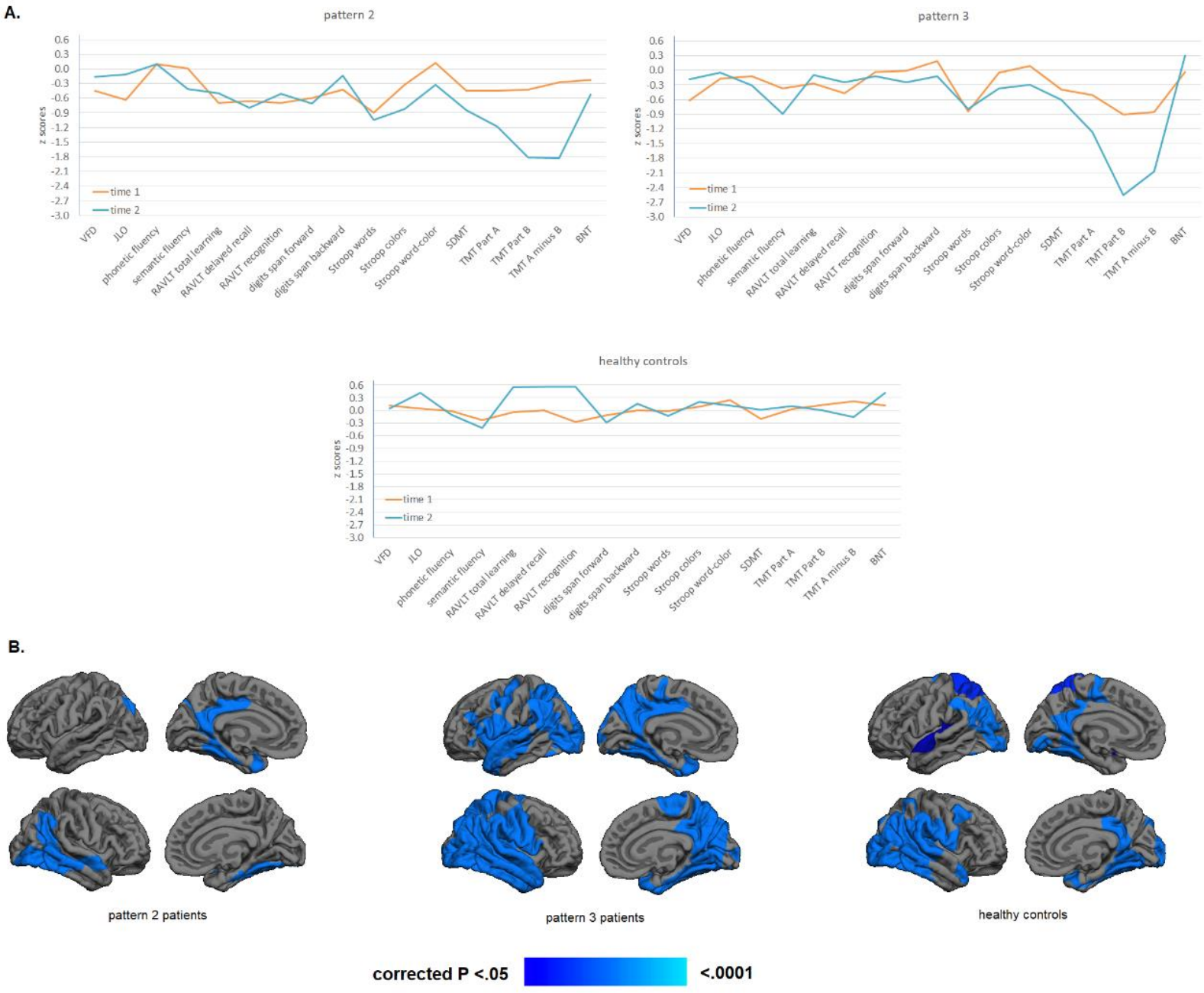
There were significant time effects in MMSE in pattern 2 (t=1.804; =.054) and in controls (t=1.923; P=.035). There was a significant interaction time x group in LEDD medication between pattern 2 and pattern 3 (t=1.825; P=.047). Cummings' Neuropsychiatric Inventory showed significant differences between HC and pattern 2 (t=1.665: P=.036).

3.2 Cognitive decline over time

Both pattern 2 and 3 patients as well as the controls group had worsened their performance over time in the Trail Making Test (TMT) Part A minus B. Specific effect times were found in pattern 2 and 3 patients' groups. Pattern 2 and pattern 3 patients also had decreased performance in semantic fluency, Stroop Word-Color test, Symbol Digits Modalities test (SDMT) and in the TMT Part B over time. Additionally, pattern 2 patients also showed decline in the Stroop Color test. Pattern 3 patients performed worse over time also in the TMT Part A. Patients in pattern 2 declined significantly more than HC in Stroop Color test and SDMT. Pattern 3 patients differed from HC in TMTA, TMTB and SDMT (Figure 1A). In Supplementary Table 1 means and SD of the neuropsychological performance can be found for all groups.

At time 2, 2 (28.6%) patients in pattern 1 converted to dementia and 3 (28.6%) patients had MCI. From the 3 MCI patients, two were converters and the other already had MCI at time 1. In pattern 2 subtype, there were 7 MCI (43.8%), 4 of whom were converters, whereas in pattern 3 there were 11 MCI (50.0%), 6 of whom were converters. In the HC group, 1 (4.5%) control also converted to MCI (Table 1 and Supplementary Table 2).

Figure 1 Neuropsychological and cortical thinning effect times. A) Neuropsychological performance of pattern 2 and 3 PD patients and controls at both times. Time 1 in blue and time 2 in orange. Data are presented as *z-scores*. Lower *z-scores* indicate worse performance. Abbreviations: BNT = Boston Naming Test; JLO = Judgment of Line Orientation Test; RAVLT = Rey's Auditory Verbal Learning Test; SDMT = Symbol Digits Modalities Test; TMT = Trail Making Test; VFD = Visual Form Discrimination Test. B) symmetrized percent of change of cortical thickness. Color maps indicate significant time effect in each group. Results were corrected by Monte Carlo simulation.


A.
pattern 2
pattern 3
healthy controls
z scores
time 1
time 2
VFD
JLO
phonetic fluency
semantic fluency
RAVLT total learning
RAVLT delayed recall
RAVLT recognition
digits span forward
digits span backward
Stroop words
Stroop colors
Stroop word-color
SDMT
TMT Part A
TMT Part B
TMT A minus B
BNT
B.
pattern 2 patients
pattern 3 patients
healthy controls
corrected P <.05
<.0001

3.3 Cortical thickness changes

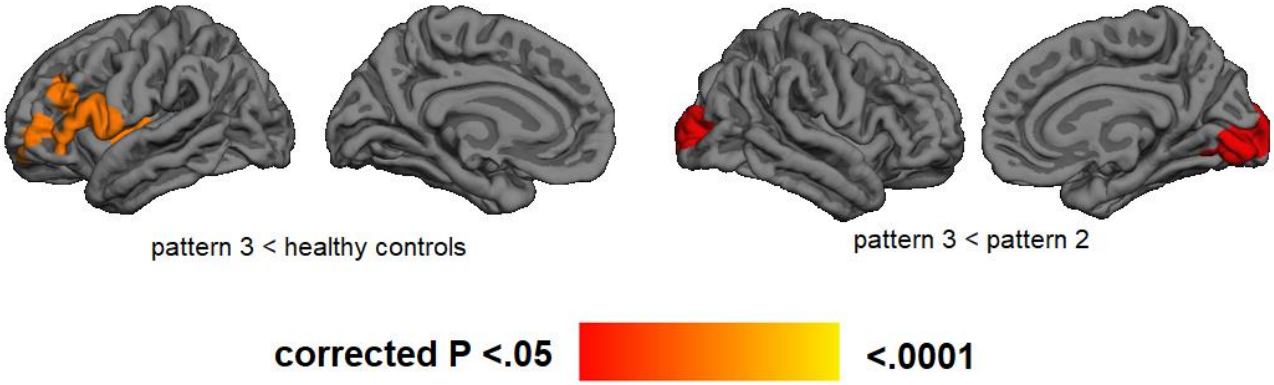
Regarding changes over time, patients in pattern 2 had reductions in left parahippocampal gyrus, left posterior cingulate extending to the midcingulate, left precuneus and right inferior parietal and temporal gyri, fusiform and lateral occipital gyri. Significant cortical thinning in pattern 3 patients was found bilaterally in lateral and medial regions of the temporal and parietal lobes, lateral occipital and extending to frontal regions such as the precentral and postcentral gyri and the left pars opercularis. HC group also showed a significant effect of time, specifically cortical thinning was found in posterior regions, such as right parahippocampal, bilateral fusiform, posterior cingulate, lateral occipital, lingual gyri and both inferior and superior parietal areas extending to the right precentral gyrus (Figure 1B).

Pattern 3 had more cortical thinning in the left pars opercularis gyrus extending to lateral parts of the ventrolateral prefrontal cortex such as the pars triangularis gyrus compared with HC over time (see Figure 2). There were no significant intergroup differences in cortical thickness decline between HC and pattern 2.

Differential changes in cortical thinning were also found between pattern 2 and 3 (Figure 2). Pattern 3 patients had more significant decrements in the right lateral occipital, lingual and pericalcarine gyri compared with pattern 2 patients.

Montreal Neurological Institute coordinates, cluster sizes and significance from longitudinal analyses are summarized in Supplementary Table 3.

Figure 2 Symmetrized percent of change of cortical thickness from the group per time interaction Results were corrected by Monte Carlo simulation.



3.4 Global atrophy changes

Both pattern 2 and pattern 3 patients as well as the controls group suffered significant volume decrements in the total GM volumes. Specifically, pattern 2 patients had significant time effects in subcortical GM volumes whereas pattern 3 patients and healthy controls had significant decrements in the cortical GM volumes over time. From the group x time contrasts, total GM and cortical GM volumes were significantly more decreased in pattern 3 patients than in pattern 2 patients. In addition, pattern 3 patients had more increased lateral ventricle volume over time than pattern 2 patients (Supplementary Table 4).

3.5 Additional results

Demographic and clinical features between PD patients' completers and non-completers in each pattern are in Supplementary Results 1 and Supplementary Table 5. GBS information for PD is also in Supplementary Results 1 and Supplementary Table 6.

4. Discussion

Remarkably, the results from MRI structural analyses showed that cortical thickness has a high sensitivity to time effects. In a period of four years, both patients and controls had

cortical thinning mainly in parieto-temporal regions, as well as global gray matter atrophy. However, PD patients differed in clinical, cognitive and structural degeneration over time according to their initial regional cortical thinning pattern.

Patients from pattern 1 characterized by an extensive parieto-temporal atrophy [15] showed a higher attrition rate and for that reason they were not included in the quantitative MRI analyses. This group showed higher severity of motor symptoms measured by the H&Y scale at baseline, more IADL, and more cognitive impairment assessed by telephone interview at follow-up. Previous longitudinal studies also reported that patients who were lost to follow-up were older, had higher age at disease onset, more axial impairment, scored higher on H&Y and showed higher percentage of PD dementia [5]. Considering the initial sample, we estimated that 15% of PD patients converted to dementia during the follow-up period. This percentage was similar to other population-based studies [5,8,19,20].

The time effect in pattern 2 patients, initially identified as frontal and occipital atrophy pattern [15], showed localized cortical thinning over time mainly in temporal and occipital lobe and posterior cingulate gyrus. These patients were initially younger, with higher education and younger age at onset, probably as indicators of better prognosis. Patients from pattern 2 who dropped out of the study had less years of education, more global cognitive impairment and had more depressive symptoms. Thus, patients from pattern 2 who completed the follow-up assessment probably represent a PD group with better progression of these disease aspects.

On the other hand, pattern 3 and healthy controls that initially were identified as the less atrophic groups, showed an extensive cortical thinning effect in bilateral parietal and temporal regions. This time effect in pattern 3 was similar to cortical atrophy previously

detected in pattern 1 at baseline [15] and it is similar to the cortical degeneration observed in the controls group.

Inter-group comparisons of symmetrized percent of cortical thickness change showed that pattern 3 patients had statistically significant greater cortical compared with healthy controls and pattern 2. Although this group was initially non-atrophic, after a four-year period, they presented significant cortical thinning. These patients differed from normal aging in right frontal lobe and showed higher symmetrized percent of change in the left occipital lobe than pattern 2 PD patients that already showed atrophy in this region. Occipital thinning compared to controls has been observed in cross sectional [21] and longitudinal studies in demented PD patients [9], in PD-MCI [22] and in PD with visual hallucinations [23,24]. However, these studies also reported more widespread atrophy including other lobes.

Global atrophy measures also revealed higher volume decrements in pattern 3 patients than in pattern 2, as well as increased ventricular enlargement. Previous literature has reported an association between global atrophy measures [25,26] with cognitive impairment. However, the proportion of MCI was not significantly different between pattern 2 and 3.

Regarding the neuropsychological assessment, our results identified that semantic fluency, TMT, SDMT and Stroop tests were sensitive to time effect. This result agrees with previous findings in longitudinal studies showing processing speed impairment in PD over time assessed by Digit Symbol Test and TMTA [4,5]. Contrarily to the expected results accounted by aging effects, we did not find statistical memory decline. This could be due to a test-retest effect. In favor of this interpretation we can see that, although non-significant, the healthy control group showed a slight increase in their performance. Other longitudinal studies reported memory loss but the follow up was longer [3,5].

After four years, patients from patterns 2 and 3 showed reduced semantic fluency performance. At baseline, semantic fluency test differentiated the parieto-temporal pattern from other PD subtypes [15]. In light of our new findings, such worsened performance could be related to the progressive posterior parietal and temporal thinning observed in PD. Cognitive differences between healthy controls and pattern 3 patients in executive function and processing speed were coherent with cortical atrophy results in prefrontal regions.

In summary, patients from pattern 1 were mainly lost to follow-up due to functional impairment in IALD and had the highest proportion of dementia. Patients from pattern 2 showed modest progressive temporal and parietal cortical thinning and probably better evolution. Finally, pattern 3 patients were non-atrophic at baseline but progressed showing temporo-parietal cortical thinning. In conclusion, cortical thinning in PD subtypes follows different progression over time.

Disclosures.

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Declaration of interest. None.

Authors' contribution.

CJ and BS contributed to the research project conception and in the design of the study. CU, AA and AC contributed to the acquisition of the data. CU, AA, AIGD and AC contributed to the analysis of the data and CU, BS, HCB, AA, AIGD, AC, MJM, FV, YC, NB and CJ contributed to the interpretation of the data. CU, BS contributed to the draft of the article. CU, BS, HCB, AA, AIGD, AC, MJM, FV, YC, NB, CJ revised the manuscript critically for important intellectual content and approved the final version of the manuscript.

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Supplementary material

Progression of Parkinson's disease patients' subtypes based on cortical thinning: 4-year follow-up

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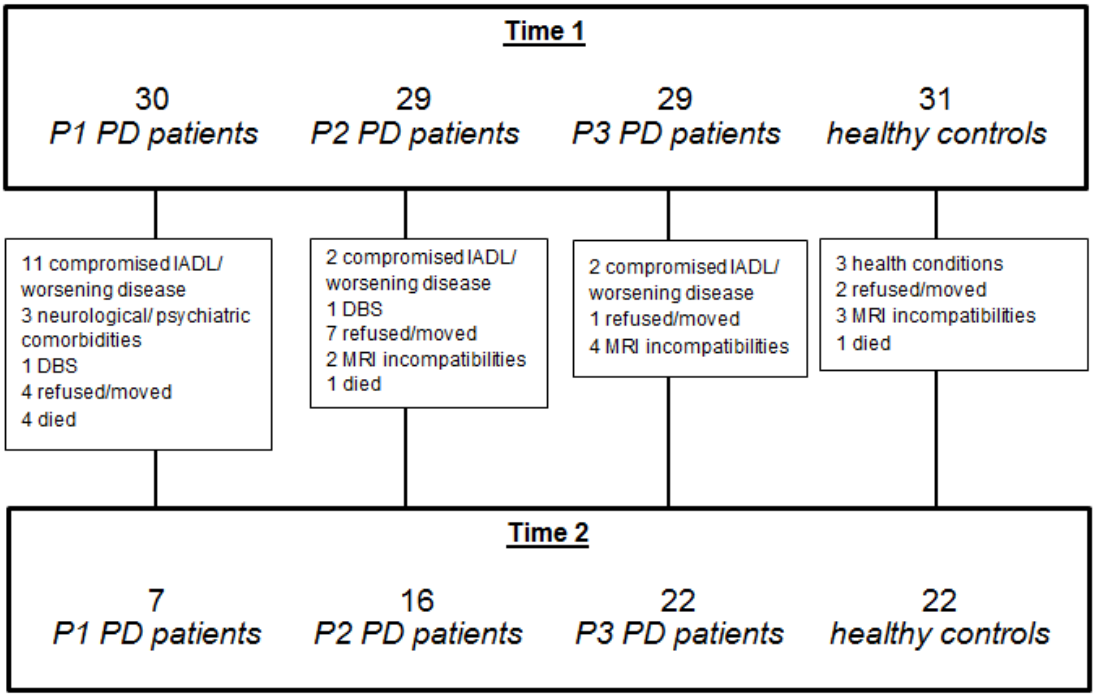
Supplementary Figure 1 Flowchart of participants who participated at both times and those lost to time 2



Abbreviations: DBS = deep brain stimulation; IADL = instrumental activities of daily living; MRI = magnetic resonance imaging; P1 = Pattern 1; P2 = Pattern 2; P3 = Pattern 3; PD = Parkinson's disease.

Supplementary Results 1. Information of completers and non-completers

In pattern 1 patients, the proportion of females (chi=4.658; *P*=.031) and the H&Y stages scores (chi=10.784; *P*=.029) were higher in non-completers than in completers. In the pattern 2 subtype, non-completers had less years of education (U=40.500; *P*=.004), had lower global cognition scores (U=58.500; *P*=.045) and were more depressed (U=108.000; *P*=.026) than completers. Non-completers in the pattern 3 subtype had higher LEDD (U=122.000; *P*=.021), see Supplementary Table 7.

Regarding GBS information, PD non-completers in pattern 1 had more severe intellectual impairment, more impairment in IADL, more symptoms associated to dementia and more GBS global scores than non-completers in both pattern 2 (GBS-I: P=.004; GBS-ADL: P=.007; GBS-S: P=.017; GBS total score: P=.005) and pattern 3 (GBS-I: P=.007; GBS-ADL: P=.004; GBS-S: P=.016; GBS total score: P=.004). Pattern 1 non-completers also had more emotional impairment than pattern 3 non-completers (*P*=.021). See Supplementary Table 8.

Supplementary Table 1 Neuropsychological performance at time 1 and 2 of PD subtypes and healthy controls

	Parkinson's disease subtypes			healthy controls (n=22)
	Pattern 1 (n=7)	Pattern 2 (n=16)	Pattern 3 (n=22)	
Visual Form Discrimination, mean (SD)				
Time 1	-0.9 (1.2)	-0.5 (0.7)	-0.6 (1.3)	0.1 (0.8)
Time 2	-1.2 (1.6)	-0.2 (1.0)	-0.2 (0.9)	0.1 (0.9)
Judgement of Line Orientation, mean (SD)				
Time 1	-0.6 (1.0)	-0.6 (1.3)	-0.2 (1.0)	0.1 (0.7)
Time 2	-0.8 (1.5)	-0.1 (0.7)	-0.0 (0.9)	0.4 (0.6)
Phonetic fluency, mean (SD)				
Time 1	-0.1 (0.9)	0.1 (1.1)	-0.1 (1.2)	-0.0 (1.0)
Time 2	-1.1 (1.0)	0.1 (1.1)	-0.3 (0.8)	-0.1 (1.0)
Semantic fluency, mean (SD)				
Time 1	-1.0 (0.7)	0.0 (1.1)	-0.4 (1.1)	-0.2 (0.6)
Time 2	-1.9 (1.3)	-0.4 (0.7)	-0.9 (1.5)	-0.4 (0.7)
RAVLT total, mean (SD)				
Time 1	-0.5 (1.2)	-0.7 (1.4)	-0.3 (1.3)	-0.0 (0.8)
Time 2	-0.9 (2.2)	-0.5 (1.4)	-0.1 (1.2)	0.6 (0.9)
RAVLT recall, mean (SD)				
Time 1	-0.6 (1.0)	-0.7 (1.4)	-0.5 (1.1)	0.0 (0.9)
Time 2	-1.1 (0.8)	-0.8 (1.5)	-0.2 (1.6)	0.6 (1.0)
RAVLT recognition, mean (SD)				
Time 1	0.5 (1.7)	-0.7 (1.9)	-0.0 (1.3)	-0.3 (0.9)
Time 2	0.3 (1.1)	-0.5 (1.4)	-0.1 (1.3)	0.6 (0.5)
Digits forward, mean (SD)				
Time 1	-0.2 (0.6)	-0.6 (0.9)	-0.0 (1.0)	-0.1 (0.8)
Time 2	-0.3 (0.6)	-0.7 (1.0)	-0.3 (0.9)	-0.3 (0.9)
Digits backward, mean (SD)				
Time 1	0.1 (0.7)	-0.4 (0.7)	0.2 (1.0)	0.0 (0.9)

Time 2	-0.1 (0.6)	-0.1 (1.1)	-0.1 (0.8)	0.2 (0.7)
Stroop Word test, mean (SD)				
Time 1	-1.0 (1.6)	-0.9 (1.5)	-0.8 (1.5)	-0.0 (0.9)
Time 2	-1.8 (1.7)	-1.1 (0.9)	-0.8 (0.9)	-0.1 (0.7)
Stroop Color test, mean (SD)				
Time 1	-0.6 (0.8)	-0.3 (0.9)	-0.0 (0.8)	0.1 (1.0)
Time 2	-1.1 (1.2)	-0.8 (0.9)	-0.4 (0.8)	0.2 (0.7)
Stroop Word-Color test, mean (SD)				
Time 1	-0.3 (0.7)	0.1 (0.9)	0.1 (0.7)	0.2 (0.8)
Time 2	-0.6 (1.1)	-0.3 (0.8)	-0.3 (0.7)	0.1 (0.8)
Symbol Digits Modalities test, mean (SD)				
Time 1	-1.0 (1.3)	-0.4 (1.1)	-0.4 (0.9)	-0.2 (0.6)
Time 2	-1.4 (1.2)	-0.8 (1.1)	-0.6 (0.9)	0.0 (0.7)
Trail Making Test Part A, mean (SD)				
Time 1	-2.0 (4.8)	-0.4 (1.1)	-0.5 (1.8)	-0.0 (0.9)
Time 2	-5.7 (8.0)	-1.2 (2.2)	-1.3 (2.0)	0.1 (0.7)
Trail Making Test Part B, mean (SD)				
Time 1	NA	-0.4 (0.7)	-0.9 (2.4)	0.1 (0.7)
Time 2	NA	-1.8 (3.4)	-2.6 (4.9)	0.0 (1.1)
Trail Making Test A minus B, mean (SD)				
Time 1	NA	-0.3 (0.6)	-0.9 (2.3)	0.2 (0.6)
Time 2	NA	-1.8 (3.1)	-2.1 (4.1)	-0.2 (0.9)
Boston Naming Test, mean (SD)				
Time 1	-0.1 (0.7)	-0.2 (0.8)	0.0 (0.9)	0.1 (0.8)
Time 2	0.1 (1.0)	-0.5 (0.8)	0.3 (0.7)	0.4 (0.6)

NA, not applicable; RAVLT, Rey's Auditory Verbal Learning Test; SD, standard deviation.

Data are z-scores adjusted by age, education and sex.

Permutation tests were calculated with 10,000 iterations. Pattern 1 patients were not included in the permutation testing due to small sample size.

There was a significant time effect in pattern 2 concerning semantic fluency (t=2.041; P=.010), Stroop Color (t=2.284; P=.049), Stroop Word-Color (t=2.985; P=.009), Symbol Digits Modalities (t=2.231; P=.048), Trail Making Test Part B

(t=2.188; P=.029) and Part A minus B (t=2.545; P=0.001). There was a trend between pattern 2 and controls in Stroop Color (t=2.182; P=.058) and there was significant group effect in Symbol Digits Modalities (t=2.639; P=.018).
There was a significant time effect in pattern 3 concerning semantic fluency (t=2.592; P=.029), Stroop Word-Color (t=2.970; P=.001), Symbol Digits Modalities (t=1.728; P=.006), Trail Making Test Part A (t=3.390; P=.004), Part B (t=2.775; P=.005) and A minus B (t=2.192; P=.059). There were significant differences between pattern 3 and HC in Symbol Digits Modalities (t=2.218; P=.008), Trail Making Test Part A (t=2.615; P=.032) and Part B (t=1.826; P=.030).
There was a significant time effect in controls in Trail Making Test A minus B (t=0.709; P=.0.054).

Supplementary Table 2 Proportion of mild cognitive impairment or PD dementia converters within groups

	Parkinson's disease subtypes			healthy controls (n=22)
	Pattern 1 (n=7)	**Pattern 2 (n=16)**	**Pattern 3 (n=22)**	
converters, n (%)	4 (57.1)	4 (25.0)	6 (27.3)	1 (4.5)
no-converters, n (%)	3 (42.9)	12 (75.0)	16 (72.7)	21 (95.5)

Chi squared test between all groups was 9.262; *P*=.026. Chi squared test between PD groups was 2.643; *P*=.267.

Supplementary Table 3 Cortical thickness information of longitudinal analysis

Cortical area	Cluster size (mm^2)	Stats	*P*-value	MNI coordinates (x,y,z)[1]
Time effects				
healthy controls				
Left superior parietal	3,209.2	-3.775	.001	-21 -48 59
Left superior temporal	2,503.1	-3.590	.013	-48 -5 -13
Left lingual	12,810.4	-3.275	<.001	-21 -51 -3
Right supramarginal	30,676.3	-6.147	<.001	61 -41 21
Pattern 2				
Left fusiform	8,134.5	-5.252	<.001	-37 -37 -24
Right lateral occipital	11,814.8	-3.444	<.001	45 -78 -11
Pattern 3				
Left superior temporal	40,118.0	-4.860	<.001	-47 12 -22
Right lingual	46,995.1	-5.891	<.001	20 -51 -4
Group per time effects				
healthy controls vs Pattern 3				
Left pars opercularis	5,642.5	2.288	<.001	-50 10 3
Pattern 3 vs Pattern 2				
Right lateral occipital	3,722.0	-4.408	.001	28 -94 8

[1]MNI305 space.

Results were obtained using Monte Carlo simulation with 10.000 iterations applied to cortical thickness maps to provide clusterwise correction for multiple comparisons (1.3). Significant clusters were reported at $p<0.05$.

Supplementary Table 4 Global atrophy measures

	Parkinson's disease subtypes			healthy controls (n=22)
	Pattern 1 (n=6) *	Pattern 2 (n=16)	Pattern 3 (n=22)	
Mean thickness, mm, mean (SD)				
Time 1	2.4 (0.1)	2.4 (0.1)	2.5 (0.1)	2.5 (0.7)
Time 2	2.4 (0.2)	2.4 (0.1)	2.4 (0.2)	2.5 (0.1)
Lateral ventricles, mm^3, mean (SD)				
Time 1	13,794.3 (7,381.0)	10,731.0 (4,664.2)	11,273.2 (6,970.8)	9,359.2 (4,167.1)
Time2	17,815.2 (9,865.6)	12,397.3 (5,857.7)	13,029.1 (7,903.5)	11,009.1 (4,837.8)
Total gray matter, mm^3, mean (SD)				
Time 1	412,884.6 (26,132.0)	457,530.6 (42,379.1)	435,619.7 (49,877.4)	442,086.2 (31,781.1)
Time 2	408,021.3 (35,260.5)	453,746.1 (46,130.0)	421,838.7 (49,118.0)	434,227.8 (33,086.1)
Cortical gray matter, mm^3, mean (SD)				
Time 1	591,136.9 (42,135.8)	642,346.8 (52,725.5)	605,341.1 (67,393.5)	612,253.5 (44,795.3)
Time 2	581,585.6 (55,598.3)	636,953.8 (57,142.7)	587,168.3 (59,403.5)	599,098.0 (45,617.0)
Subcortical gray matter, mm^3, mean (SD)				
Time 1	178,252.3 (17,724.7)	184,816.3 (17,956.6)	169,721.5 (22,292.9)	170,167.4 (19,916.5)
Time 2	173,564.3 (21,207.5)	183,207.7 (13,614.8)	165,329.6 (15,479.9)	164,870.2 (17,891.0)

* one PD patient was excluded due to motion artifacts.
SD, standard deviation.
Permutation tests were calculated with 10,000 iterations.
Pattern 1 patients were not included in the permutation testing due to small sample size.
There were significant time effects in total gray matter (pattern 2: t=3.226; P=.018; pattern 3: t=6.412; P<.001; controls: t=3.228; P=.005), in cortical gray matter (pattern 3: t=4.969; P<.001; controls: t=2.476; P=.032) and in subcortical gray matter (pattern 2: t=2.674; P=.053). There was an interaction group x time

between pattern 2 and pattern 3 patients in lateral ventricles (t=-2.827; P=.008), total gray matter (t=3.124; P=.003) and cortical gray matter (t=3.027; P=.004) volumes.

Supplementary Table 5 Demographical and clinical characteristics of completers and non-completers

	Parkinson's Disease subtypes			healthy controls
	Pattern1	Pattern2	Pattern3	
Age, y, median (IQ range)				
completers	76.0 (18.0)	57.5(13.0)	63.0 (10.0)	66.0 (13.0)
non-completers	73.0 (13.0)	64.0 (19.0)	66.0 (11.0)	65.0 (18.0)
Education, y, median (IQ range)				
completers	8.0 (6.0)	17.5 (8.0)	10.5 (6.0)	10.0 (8.0)
non-completers	7.0 (5.0)	9.0 (8.0)	10.0 (5.0)	9.0 (8.0)
Sex, male, n (%)				
completers	6 (86.7)	13 (81.3)	12 (54.5)	11 (50.0)
non-completers	9 (39.1)	7 (53.8)	4 (57.1)	5 (55.6)
Mini Mental State Examination, median (IQ range)				
completers	29.0 (4.0)	30.0 (1.0)	30.0 (1.0)	30.0 (0.0)
non-completers	29.0 (2.0)	29.0 (1.0)	30.0 (1.0)	29.0 (1.0)
Disease duration, y, median (IQ range)				
completers	4.0 (7.0)	6.0 (8.3)	6.0 (8.5)	NA
non-completers	9.0 (12.0)	8.0 (9.0)	5.0 (11.0)	NA
Age of onset, y, median (IQ range)				
completers	67.0 (19.0)	47.5 (14.6)	54.5 (12.8)	NA
non-completers	63.0 (22.0)	55.0 (12.5)	61.0 (21.0)	NA
UPDRS part III, median (IQ range)				
completers	13.0 (12.0)	12.0 (20.0)	11.5 (14)	NA
non-completers	17.0 (13.0)	12.0 (16.0)	15.0 (3.0)	NA

Hoehn&Yahr stage, n 1/1.5/2/2.5/3				
completers	2/0/5/0/0	5/1/7/2/1	11/0/8/1/2	NA
non-completers	0/3/11/4/5	4/1/6/1/1	0/0/6/1/1	NA
LEDD, mg, median (IQ range)				
completers	400.0 (450.0)	800.0 (1150.0)	485.0 (639.0)	NA
non-completers	780.0 (580.0)	1,000.0 (1,035.0)	1,033.0 (1,007.0)	NA
Beck Depression Inventory II, median (IQ range)				
completers	14.0 (6.0)	5.0 (7.0)	8.0 (5.0)	6.0 (9.0)
non-completers	15.5 (9.0)	11.5 (11.0)	7.0 (12.0)	2.0 (8.0)
Starkstein's Apathy Scale, median (IQ range)				
completers	17.0 (12.0)	8.0(11.0)	10.0 (10.0)	10.0 (11.0)
non-completers	14.0 (14.0)	13.5 (13.0)	11.0 (9.0)	9.0 (4.0)
Cummings' Neuropsychiatric Inventory, median (IQ range)				
completers	2.0 (26.0)	2.5 (6.0)	4.0 (9.0)	0.0 (3.0)
non-completers	3.5 (9.0)	1.0 (5.0)	7.0 (9.0)	0.0 (0.0)
MCI at time 1, n (%)				
completers	3 (42.9)	6 (37.5)	7 (31.8)	NA
non-completers	17 (73.9)	8 (61.5)	4 (57.1)	NA

IQ range, Interquartil range; LEDD, L dopa equivalent daily dose; MCI, mild cognitive impairment;NA, not applicable; UPDRS part III, Unified Parkinson's Disease Rating Scale motor section.

Mann-Whitney pairwise test for continuous variables and chi-squared test for categorical variables were calculated.

There were significant differences between completers and non-completers of pattern 1 in sex (chi=4.658; P=.031) and Hoehn & Yahr stage (chi=10.784; P=.029). There were significant differences between completers and non-completers of pattern 2 in education (U=40.500; P=.004), Mini Mental State Examination (U=58.500; P=.045) and Beck Depression Inventory-II (U=108.000;

P=.026). There were significant differences between completers and non-completers of pattern 3 in LEDD (U=122.000; P=.021).

Supplementary Table 6 Gottfries-Brane-Steen scale results

	Pattern1 (n=12)	Pattern2 (n=4)	Pattern3 (n=6)	Test stats / *P*-value
GBS-I, median (IQ range)	14.5 (25.5)	3.5 (5.5)	5.5 (2.8)	15.240/<.001
GBS-E, median (IQ range)	5.5 (10.0)	1.0 (2.3)	1.0 (0.8)	9.861/.007
GBS-ADL, median (IQ range)	16.5 (14.3)	1.0 (2.8)	2.0 (1.8)	15.082/.001
GBS-S, median (IQ range)	9.0 (10.3)	1.5 (5.3)	4.0 (3.5)	11.939/.003
GBS total score, median (IQ range)	43.5 (50.3)	6.0 (12.3)	12.0 (6.5)	15.791/<.001

GBS-I, intellectual impairment; GBS-E, emotional impairment; GBS-ADL, impairment of Activity Daily Living performance; GBS-S, symptoms common in dementia.

Two familiars refused to complete the interview and 14 were impossible to contact for telephonic interview. From these 14, two patients were still working.

P-values are from Kruskal-Wallis test followed by Mann-Whitney pairwise test and Bonferroni correction.

There were significant differences between pattern 1 and pattern 2 in GBS-I (P=.004), GBS-ADL (P=.007), GBS-S (P=.017) and GBS total score (P=.005). There were significant differences between pattern 1 and pattern 3 in GBS-I (P=.007), GBS-E (P=.021), GBS-ADL (P=.004), GBS-S (P=.016) and GBS total score (P=.004).

Chapter 5

Discussion

The present thesis aimed to identify different patterns of brain atrophy in PD patients at different stages of the disease from a data-driven approach. Distinct regional atrophy would contribute differently to clinical manifestations such as cognitive impairment. Moreover, we were interested in following the progression of the described patterns over time in order to identify which cerebral pattern was a better predictor of progression to dementia.

The regional patterns of atrophy identified via cluster analysis will be discussed: firstly, concerning the *de novo* PD sample (Study 2) and secondly results from the medicated PD sample (Study 1) with its correspondent longitudinal follow-up (Study 3). Such organization, despite the *anachronism*, follows a temporal continuum of the disease evolution. Posteriorly, clinical manifestations with special emphasis to cognitive profiles will be commented, and the possible neuropathological underpinnings of the described patterns. At last but not the least, methodological strengths and limitations of the cluster analysis technique will be discussed.

PD cortical atrophy patterns

Two patterns of cortical atrophy were identified in the early drug-naïve sample of PD patients (Study 2): 1) one with orbitofrontal involvement, anterior cingulate and temporal atrophy and 2) a second involving occipital and parietal atrophy. In the medicated PD sample (Study 1), we found: 1) a pattern mainly involving parietal and temporal atrophy; 2) a second pattern with frontal and occipital atrophy and finally, 3) a third group of patients that did not have any overt atrophy compared with controls of similar age.

The atrophic groups identified were not identical between the two samples. As hypothesized, the *de novo* PD sample had more specific focal atrophy than the medicated PD sample, where the two first patterns showed wider extension of cortical thinning in temporal, parietal and occipital lobes as well as in the prefrontal cortex. In Study 1, the 2- and 3-cluster solutions were reported while in Study 2 the 2-cluster solution was the most optimal classification.

Cortical thickness comparisons between patterns confirmed the differences found when comparing them with controls. In Study 2 (*de novo* sample), there was clearly a differentiation between the anterior predominant pattern 1 and the posterior atrophy reported in pattern 2 patients. In Study 1 (medicated sample),

the posterior/anterior regional thinning observed in the patterned patients in comparison with healthy controls was also seen between them.

PD *de novo* regional patterns

Orbitofrontal involvement in *de novo* PD patients (i.e., newly diagnosed drug naïve) has not been previously described. Preserved cerebral blood flow through arterial spin labeling (ASL) was reported in the right prefrontal cortex whereas reduced precuneus perfusion and cortical thinning in parietal regions took place (Madhyastha et al., 2015) in early staged PD patients (i.e., disease onset < 5 years). In the same line, in a pooled sample of early-to-moderate PD patients ASL hypoperfusion was found in posterior regions ranging from the occipital cortex, through the superior parietal and the superior frontal cortex but not in the prefrontal cortex (Fernández-Seara et al., 2012). Nevertheless, such orbital atrophy has been recently reported in early staged patients (i.e., disease onset < 5 years) when comparing them with controls (Wilson et al., 2019), and in PD-MCI newly-diagnosed patients at an uncorrected threshold (S. W. Noh et al., 2014).

In Study 2, pattern 1 *de novo* patients had orbitofrontal thinning extending to the anterior cingulate and also anterior temporal thinning compared with controls. It would be interesting to follow-up these patients to see if they have any memory progressive decline, although at the time of diagnosis they did not differ in any neuropsychological tests from controls or pattern 2 patients. Indeed, worsened neuropsychological performance has been mainly linked to the medial temporal cortex (Squire et al., 2004) and not to lateral parts.

More remarkably, the *de novo* PD sample (Study 2) had occipital involvement in pattern 2 patients. To the best of our knowledge, such atrophy has not been previously reported at this early stage of the disease. Indeed, PD-MCI *de novo* patients had medial occipital-temporal thinning in the left lingual compared with controls but no primary order visual regions was observed (Pereira et al., 2014). This finding is very interesting since regional lateral occipital thinning could underlie the color deficits described in prodromal stages of PD such as REM sleep behavior disorders (Postuma et al., 2015). In addition to the occipital thinning, pattern 2 patients also showed lateral parietal atrophy. Similar parietal thinning has been reported in *de novo* PD-MCI patients (Pereira et al., 2014).

PD medicated regional patterns

In Study 1 with more advanced medicated PD patients, pattern 2 patients presented a cortical thinning pattern involving the medial orbitofrontal cortex and rostral middle frontal areas.

Prefrontal and occipital hypometabolism using PET MRI techniques have been described in advanced PD patients of more than 10 years of disease evolution (Garcia-Garcia et al., 2012; González-Redondo et al., 2014; Huang et al., 2007).

Reduced ^{18}F-fluorodeoxyglucose (FDG)-PET uptake was reported in PD-MCI and PDD patients in bilateral orbitofrontal areas extending to other regions of the prefrontal cortex (Garcia-Garcia et al., 2012; González-Redondo et al., 2014). Hypometabolism in the orbital gyrus was accompanied of GM atrophy in the demented PD but not in PD-MCI patients (González-Redondo et al., 2014). The authors suggested that GM atrophy and hypometabolism are two steps of the same process. Firstly, a reduction on the cortical glucose uptake would take place in the orbitofrontal cortex evolving to a reduction in GM volume (González-Redondo et al., 2014). Thus, it would possibly explain why cortical atrophy has not been found in previous studies of non-demented patients using structural MRI techniques such as VBM (González-Redondo et al., 2014; Pereira et al., 2012) or cortical thickness (Pereira et al., 2014, 2012; Segura et al., 2014).

Contrarily to the focal degeneration described in the *de novo* patients, this pattern also displayed distinct occipital thinning in the cuneus and the lateral occipital and lateral inferior and superior parietal thinning similar to the hypometabolism pattern previously described in PD-MCI (Garcia-Garcia et al., 2012) and demented PD patients (González-Redondo et al., 2014). GM volume reductions in lateral occipital, fusiform and lateral orbitofrontal have been recently reported to be predictors of cognitive impairment in the *de novo* PPMI sample over 3-years follow-up (Caspell-Garcia et al., 2017). Indeed, lateral occipital atrophy would be linked to cognitive impairment in PD (Segura et al., 2014). Pattern 2 patients of Study 1 did not differentiate from the other two patterns in the proportion of MCI although they showed worse visuospatial, speed processing, working memory and attention performance when compared with controls.

Pattern 1 patients (Study 1) displayed distinctive medial temporal thinning in comparison with HC. Lateral and medial temporal lobe atrophy has been reported in PD-MCI patients (Danti et al., 2015; Garcia-Diaz et al., 2018; Kunst et al., 2019; Pereira et al., 2014; Segura et al., 2014) and PDD patients (Burton et al., 2004; Tam et al., 2005). Indeed, higher Lewy body densities in the temporal lobe is a marker of PDD patients (Halliday et al., 2014; Harding and Halliday, 2001).

Patients grouped in Pattern 1 and 2 in Study 1 presented parietal atrophy. Such atrophy has been previously described in PD-MCI *de novo* (Pereira et al., 2014) and medicated (Segura et al., 2014) patients. Indeed, differences between cognitively preserved and PD-MCI patients were found in the medial parietal cortex located in the cuneus (Garcia-Diaz et al., 2018; Pereira et al., 2014; Segura et al., 2014) and laterally in the supramarginal (Garcia-Diaz et al., 2018; Segura et al., 2014) and both the superior (Garcia-Diaz et al., 2018) and inferior (Danti et al., 2015) parietal gyri. The main difference between pattern 1 and 2 patients concerning the parietal lobe is that the pattern 1 group had more widespread atrophy, especially in middle regions that extended to the middle temporal lobe. On the other hand, the parietal contribution in pattern 2 patients was mainly

lateral, extending from the occipital thinning previously described through the superior parietal cortex.

From the prospective longitudinal Study 3, cortical thickness revealed sensitive to time effects among the PD patterned patients and in normal aging. Over four years, pattern 2 and 3 patients and controls had cortical thinning mainly in parieto-temporal regions, as well as global gray matter atrophy.

Patterned 2 patients, initially identified as the frontal and occipital atrophy pattern, showed focal increases in the symmetrized percent of change of cortical thinning measures mainly in temporal and occipital lobe and posterior cingulate gyrus. Such progressive atrophy was consistent with the cognitive evolution that PD patients suffered.

Non-atrophic patients, a distinct subtype?

In PD, it has been reported no manifest brain atrophy in cognitively normal patients (Garcia-Diaz et al., 2018) or modest results (Hanganu et al., 2013) with significant small cluster sizes over the cortical mantle (S. W. Noh et al., 2014; Pagonabarraga et al., 2013), especially in early (Tessa et al., 2014) PD patients when comparing them with age-matched controls.

In Study 1 using the medicated sample, we described a third pattern of non-atrophic patients when they were compared with a group of similar age and education. The lack of regional cortical thinning in this PD subgroup does not mean patients had no brain atrophy at all. Indeed, patients were compared with a group of controls with similar ages and years of education. This means that, at least, pattern 3 patients did not have further cortical degeneration associated to PD at baseline and that they followed a normal aging pattern. The lack of differences in PD patients' pattern 3 with aged healthy control participants could be due to the actual existence of a specific subgroup that is called the benign tremulous subtype, introduced in the first section of the present thesis. Unfortunately, in Study 1 we did not calculated the motor phenotypes of the patients; and UPDRS-III total scores as well as L-DOPA doses as measures of motor severity alongside with the disease duration did not differed from the other two patients' groups.

At the 2-cluster level solution in Study 1, non-atrophic PD patients (pattern 3) were grouped with patients showing frontal and occipital thinning. Our data-driven free-hypothesis results could partially overlap the dual syndrome hypothesis. Pattern 2 patients alongside with patients in Pattern 3 would have mainly fronto-striatal involvement, suggesting a more benign form of PD.

Surprisingly, we did not find a non-atrophic group of *de novo* PD patients in Study 2 as we could expect to be more prevalent at early stages of the diagnosis than

in more advanced PD. This *non-finding* would be in contrast with the benign subtype, since all patients at the time of diagnosis show specific non-aging related neocortical atrophy. The differences found between patterns in Study 1 and 2 could also be possibly explained due to methodological differences between both studies, which will be discussed in a posterior section.

Longitudinally, pattern 3 and healthy controls that initially were identified as the less atrophic groups in Study 1, they showed an extensive cortical thinning effect in bilateral parietal and temporal regions. This time effect in pattern 3 was similar to cortical atrophy previously detected in pattern 1 at baseline.

Group comparisons of the symmetrized percent of cortical thickness change showed that pattern 3 patients had greater cortical degeneration compared with healthy controls and pattern 2, in spite of the absence of manifest atrophy at baseline. After a four-year period, pattern 3 patients differed from normal aging in right frontal lobe and showed higher symmetrized percent of change in the left occipital lobe than pattern 2 PD patients that already showed atrophy in this region at baseline. As introduced in this thesis and discussed above, occipital thinning compared to controls has been observed in cross-sectional (Burton et al., 2004) and longitudinal studies in demented PD patients (Ramírez-Ruiz et al., 2005), in PD-MCI (Hanganu et al., 2014) and in PD with visual hallucinations (Goldman et al., 2014; Ramírez-Ruiz et al., 2007). However, these studies also reported more widespread atrophy including other lobes.

Global atrophy measures also revealed higher volume decrements in pattern 3 patients than in pattern 2, as well as increased ventricular enlargement. Previous literature has reported an association between global atrophy measures (Apostolova et al., 2012; Burton et al., 2005) with cognitive impairment. However, the proportion of MCI was not significantly different between pattern 2 and 3. From the prospective four-years follow-up we can conclude that pattern 3 patients did not follow a benign course of the disease. In fact, such PD pattern depicted a similar cortical progression than normal aging but with the presence of PD-related features.

Clinical manifestations underlying neuroanatomical correlates

In Study 1 of unmedicated patients, pattern 2 patients were younger at the disease onset than pattern 1 and 3 patients. In addition, pattern 1 patients were less educated than controls and pattern 2 patients and the oldest among the PD subgroups. These demographical differences could partially explain the greater extent of atrophy observed in pattern 1 patients. For this reason, in all statistical group comparison analyses age and education were considered as variables of no interest. Based on previous findings, age would substantially contribute to PD

degeneration (Williams-Gray et al., 2009a), although pattern 3 patients with no overt atrophy would be expected to be the youngest. At baseline, medicated pattern 2 patients were initially younger, with higher education and younger age at onset, probably as indicators of better prognosis. In the longitudinal Study 3, patients from pattern 2 who dropped out of the study had less years of education, more global cognitive impairment and had more depressive symptoms. Thus, patients from pattern 2 who completed the follow-up assessment probably represent a PD group with better progression of these disease aspects.

Despite the different patterns of regional thinning described in PD patients, patterned groups in Study 1 (medicated patients) did not differentiate in their motor severity. Instead, in Study 2 (*de novo* patients), pattern 2 patients had more severe motor impairment than pattern 1 patients although patients did not show motor phenotypical differences. We would expect that pattern 2 *de novo* patients would show a greater proportion of PIGD subtype as they also showed worse cognitive performance. However, the instability of motor-feature diagnosis in the first year of the disease might explain the lack of a motor predominance between patterns (Simuni et al., 2016).

We would also expect an increased proportion of patients with visual hallucinations in medicated pattern 2 patients as previous GM volume decrements (Ramírez-Ruiz et al., 2007) and activity reductions (Meppelink et al., 2009) have been reported in occipital regions. Similarly, the proportion of PD-MCI patients was not different between PD subgroups. In spite of that, we did find some neuropsychological distinct characteristics between patterns. Overall, we found that in both studies the patterns with the more widespread posterior-dominant atrophy had the worse cognitive performance.

In Study 1, medicated pattern 1 and 2 patients had worse visuospatial performance than controls. Specifically, pattern 1 patients showed manifest impairment in the VFD and the JLO tests whereas pattern 2 patients only had significant worse performance in the JLO test. Previous neuroanatomical correlates on VFD have linked a worse performance to thinning in posterior middle temporal regions and JLO to thinning in temporal and parietal regions (Garcia-Diaz et al., 2018). Such correlates partially overlap the cortical thinning observed in our patterned groups. Additionally, SDMT worse performance was observed in both pattern 1 and 2 groups in Study 1 and in pattern 2 patients of Study 2. SDMT has been found to be a suitable marker of lateral temporal and parietal regions (Garcia-Diaz et al., 2018). Overall, neuropsychological posterior cortical-based instruments have been reported to be markers of the risk to dementia (Williams-Gray et al., 2009a).

On the other hand, the orbital pattern described in the *de novo* sample did not show any specific neuropsychological deficit, although global cognition scores

were lower than controls performance. Most of the studies that have investigated the structural MRI correlates associated to PD have divided the patients according to their cognitive outcome either in *de novo* patients (Danti et al., 2015; Pereira et al., 2014), early staged patients (Hanganu et al., 2013) and in more advanced staged patients (Pagonabarraga et al., 2013; Segura et al., 2014) including PET studies (Garcia-Garcia et al., 2012; González-Redondo et al., 2014; Huang et al., 2007). However, PD-MCI diagnostic criteria have never included specific tools sensitive to the orbital function. Indeed, the prefrontal cortex has always been assessed non-specifically using the classical neuropsychological tests that supported the classical hypotheses of the frontostriatal cognitive deficits in PD (Dubois and Pillon, 1997). In Study 1 (medicated sample) we found specific facial emotion recognition deficits in pattern 2 patients supporting previous findings of the bilateral orbital gyrus as neural correlate of facial emotion recognition (Ibarretxe-Bilbao et al., 2009).

In our results, we found specific memory deficits associated to posterior cortical involvement (Study 1 and 2) and medial temporal atrophy (only in Study 1). Memory impairment and semantic fluency deficits have been postulated as markers of progression to dementia (Levy et al., 2002; Williams-Gray et al., 2009a, 2007). Indeed, both cognitive performances are thought to be related to the temporal lobe functioning (Henry and Crawford, 2004; Squire et al., 2004).

In Study 1, although neither the proportion of PD-MCI nor the proportion of memory impairment significantly differed from other patterns; pattern 1 patients had the worse verbal memory performance in both RAVLT total learning and delayed recall tests that significantly differed from that observed in controls. This patients' subgroup presented middle temporal atrophy including the parahippocampal gyrus. Regional thinning in temporal regions was not observed in the posterior-based pattern 2 patients of the *de novo* sample. In that case, we found a predominant regional thinning in posterior regions including the parietal and occipital lobes and these patterned patients showed worse memory performance than the controls group.

The non-atrophic medicated PD subgroup described in Study 1 had similar cognitive profile to that observed in the other PD subgroups, although only performance in Stroop words test significantly differed from controls performance. These results are in line with previous cluster analysis works that reported a cluster of PD patients with no manifest MCI although with lowered speed processing (Dujardin et al., 2013).

Clinical progression of the patterns

Patients in pattern 1 with initial extensive parieto-temporal atrophy (Study 1) showed a higher attrition rate and for that reason they were not included in the quantitative MRI analyses (Study 3). This group showed higher severity of motor symptoms measured by the H&Y scale at baseline, more ADL, and more cognitive impairment assessed by telephone interview at follow-up. Previous longitudinal studies also reported that patients who were lost to follow-up were older, had higher age at disease onset, more axial impairment, scored higher on H&Y and showed higher percentage of PD dementia (Broeders et al., 2013b). Considering the initial sample, we estimated that 15% of PD patients converted to dementia during the follow-up period. This percentage was similar to other population-based studies (Broeders et al., 2013a, 2013b; Mahieux et al., 1998; Williams-Gray et al., 2009a).

Regarding the cognitive evolution of the PD patients, our results identified that semantic fluency, TMT, SDMT and Stroop tests were sensitive to time effect. This result agrees with previous findings in longitudinal studies showing processing speed impairment in PD over time assessed by Digit Symbol Test and TMTA (Broeders et al., 2013b; Muslimović et al., 2009). Contrarily to the expected results accounted by aging effects, we did not find memory decline. This could be due to a test-retest effect. In favor of this interpretation, we can see that, although non-significant, the healthy control group showed a slight increase in their performance. Other longitudinal studies reported memory loss but the follow up was longer (Broeders et al., 2013b; Muslimović et al., 2007).

After four years, patients from patterns 2 and 3 showed reduced semantic fluency performance. At baseline, semantic fluency test differentiated the parieto-temporal pattern (pattern 1) from other PD subtypes. In light of our new findings, such worsened performance could be related to the progressive posterior parietal and temporal thinning observed in PD.

Heterogeneity in PD: a matter of time or distinct symptomatologic entities?

Two possible theories concerning the disease subtypes have been recently proposed (Fereshtehnejad and Postuma, 2017). PD could be a single entity with all patients having the same brain degeneration but with different slopes of progression or, there is no uniform disease progression and patients can progress over time in different ways. These authors have demonstrated that even in *de novo* PD patients (from the PPMI database, like Study 2 patients sample), there exists a *diffuse-malignant* subtype that showed different symptomatology (Fereshtehnejad et al., 2017).

The first two studies that compose the present thesis aimed to subtype PD patients in two different stages of the disease progression. Based on our results, we can hypothesize that at the very moment of the PD diagnosis, there already exist at least two distinct patterns of cortical progression regardless the dopaminergic effects. These two subtypes, although they share some common regional atrophy, they represent two distinct patterns of cortical degeneration, regardless PD-MCI diagnosis.

In fact, the two patterned atrophic groups of patients would partially be in accordance of the neurobiological dual syndrome hypothesis (Kehagia et al., 2012). One group of patients would predominantly manifest prefrontal thinning already present at the diagnosis (pattern 1, Study 2). In more advanced stages, thinning would progress to occipital and parietal regions but not in medial parietal and temporal regions (pattern 2, Study 1). This progression would be accompanied with a progressive development of impairment in speed processing, attention and working memory and visuospatial function. This group of patients would have a better disease evolution and less progressive cortical atrophy, with modest decrements in temporal and parietal regions and no significant to the degeneration observed in normal aging.

On the other hand, a second group of patients would have a predominantly posterior patterned atrophy associated to worse memory and speed processing performance already present at the time of the diagnosis (pattern 2, Study 2). This posterior-predominant atrophy would evolve to degeneration of medial and lateral parietal regions and medial temporal atrophy in turn associated to the worse performance in neuropsychological evaluation: visuospatial, semantic fluency and memory impairment (pattern 1, Study 1). Therefore, these patients would have dopaminergic and non-dopaminergic disturbances that potentially would evolve to dementia. Patients would eventually evolve to dementia or at least, they would present a greater compromise of the ADL (pattern 1 patients in Study 3).

Less certain is the existence of a third group of non-atrophic patients that arise from the group with prefrontal involvement in Study 1 based on the the 2-cluster solution. This group follows a similar evolution to normal aged controls but with progressive atrophy in the prefrontal cortex and worsened performance in processing speed in comparison with controls progression over time.

From a neurobiological point of view, the pathological meaning of the differences between the patterns is unclear. As stated in the introduction of the present thesis, Braak stages (Braak et al., 2006a, 2003) and the synergistic effect between α-synuclein and amyloid-β deposition in PD are still controversial (Halliday et al., 2014). Indeed, Braak staging pathology has revealed useful to describe neuropathological evolution of PD (Jellinger, 2004) although is insufficient in

advanced stages (V and VI) of the disease (Jellinger, 2009), especially in dementia (Jellinger, 2008) and in patients with rapid disease progression (Halliday et al., 2008). We could speculate that pattern 1 patients in Study 1 could have abnormal amyloid-β depositions since they showed medial temporal and parietal atrophy. In normal aging, these regions have been reported as sensitive to progressive cortical thinning in cognitively preserved Pittsburgh compound B (PiB) positive participants (Doré et al., 2013).

In the first study, Patterns 1 and 2 medicated patients differed in the degree of atrophy in the posterior cingulate, isthmus of the cingulate, and precuneus. In this line, it has been reported that in non-demented PD patients, higher PiB retention in the precuneus seems to contribute to cognitive decline over time although no baseline differences were reported between PD-MCI and noMCI patients (Gomperts et al., 2013). Of high relevance is the temporal atrophy observed distinctively in Pattern 1 patients of Study 1. Densities in the temporal lobe differentiated PDD patients from non-demented patients (Halliday et al., 2014; Harding and Halliday, 2001).

Methodological implications in cluster analysis

Cluster analysis techniques have revealed sensitive for detecting regional cortical thinning even at early stages of the disease. Indeed, unsupervised machine learning techniques has allowed us to detect distinct atrophy patterns from a hypothesis-free data-driven approach at different stages of the disease using objective imaging data rather than clinical data that is examiner-dependent.

Interest in machine learning techniques has increased with big data management that can allow training large data sets to predict future outcomes or to group data sets according to multiple features such as clustering techniques. However, algorithms perform better when the number of features does not overcome the number of observations (i.e., subjects in our case). Methodology between Study 1 and 2 was improved to overcome multicollinearity and the *curse of multidimensionality*. Multicollinearity is a phenomenon in which one predictor variable can be linearly predicted from the others (Farrar and Glauber, 1967). The problem with dimensionality is that when the later increases, the volume of the space increases so fast that the available data become sparse (Trunk, 1979). In Study 2, we extracted the means of the recently published atlas from the Human Connectome Project (Glasser et al., 2016) in order to reduce the three-dimensionality of the whole-brain vertex-wise approach. Indeed, in Study 1 we used all vertex information as features of the clustering analysis as previously described (Y. Noh et al., 2014). However, when we performed the Principal Component Analysis (PCA) to validate the cluster groups, we did reduce the matrix. We discarded vertices with values of 0 and vertices that correlated highly with others. The result was a PCA with 4,150 vertices.

The decision of including all vertex-wise information in the clustering was from the idea of the hypothesis-free data-driven methodology. At that time, we could not find a well-defined cytoarchitectonic atlas that could allow us to reduce vertex information without losing too much topographical information. The atlas HCP-MMP1.0 was published posteriorly to Study 1. For Study 2, we decided to take advantage of such multi-modal cortical parcellations (Glasser et al., 2016).

Although the data-driven nature of unsupervised methodologies, it is always important to contrast the findings with the literature state-of-the-art. For this reason, in Study 1 both 2-level and 3-level cluster solutions were reported, and patterned groups did make sense with the classical findings in PD. In Study 2, we only reported the 2-cluster solution given the small number of patients clustered in the third group. Similarly, in Study 1 the 4-cluster solution was not considered due to small sample size.

This does not mean that there must exist two patterns of atrophy related to PD pathology. Indeed, the choice of a hierarchical cluster analysis technique was based on the lack of preconceived number of possible PD subtypes. Inside the 2-cluster solution presented in Study 2, there could exist subgroups with more specific focal atrophy. However, small sample sizes in comparison with the features prevented us to further characterize subgroups. In fact, in Study 1 the 2-cluster solution already identified two different patterns: one mainly posterior and another with an anterior atrophy involvement. Inside pattern 2 (frontal-occipital thinning) there were two distinct groups: 1) one with a younger onset that mainly contributed to the prefrontal-occipital thinning observed in pattern 2, and 2) a third group that was not as young but did not present overt atrophy.

Final remarks

This thesis has helped clarify the heterogeneity of cortical atrophy in non-demented PD patients at different stages of the disease. The data-driven hypothesis free approach has contributed to establish distinct patterns of atrophy that possibly explain the differences found across studies investigating neuroanatomical correlates in PD cognition and other clinical manifestations. In addition, we had available the followed-up sample of the medicated PD patients that, despite the high attrition rate, allowed us to describe the progressive brain degeneration that took place in the patterned patients over 4 years. Indeed, the high percentage of dropouts in pattern 1 patients is informative of the worse prognosis in patients with predominant posterior atrophy. Together all these findings should help elucidate which PD patients are more likely to evolve to dementia. For this, longitudinal large-multicentric samples are required.

Chapter 6

Conclusions

From the two cross-sectional studies we can conclude that:

1) In medicated PD patients, three patterns of cortical thinning were identified. One with prefrontal and occipital predominance, another with widespread posterior temporo-parieto-occipital atrophy and a third pattern with similar atrophy to healthy aging subjects. Clinically, the first pattern is characterized by younger disease onset. Both PD subtypes with cortical thinning have significant cognitive decline and a similar proportion of PD-MCI patients. However, the posterior-based pattern is associated with specific semantic fluency deficits.
2) In newly diagnosed untreated PD patients, cortical thinning is already present, and two patterns of atrophy were identified. One pattern with medial orbitofrontal and lateral temporal thinning and another with occipital and parietal predominance. Cortical thickness differences in comparison with controls seem to be less extensive and more focal than that observed in medicated PD patients.
3) Both patterns of *de novo* PD patients had global cognitive decline. However, patients with posterior predominance had more severe motor symptoms; worse verbal memory learning and delayed recall performance, as well as visuospatial and processing speed deficits.
4) Structural MRI findings based on hypothesis free data-driven methodologies stress the importance to review neuropsychological tools for the diagnosis of PD-MCI. Specific orbital function assessment should be included.

From the longitudinal study we can conclude that:

5) Cortical thinning is an MRI measure sensitive to aging effects and to specific cortical degeneration in PD. It is observed in all PD patients, although the three Parkinson's disease phenotypes identified via clustering analysis displayed different progressions over time.
6) Initial temporo-parietal atrophy was linked to worsening of functional ADL and patients were more likely to progress to dementia. In contrast, the pattern with initial prefrontal and occipital thinning and younger disease onset was linked to a better disease evolution.

Overall, data-driven analyses are able to classify PD patients according to patterns of cortical degeneration. Such patterns had clinical and

neuropsychological distinct characteristics and different evolution. Thus, PD prognosis could be characterized by MRI data.

Abstract

Background and objectives. Parkinson's disease is a heterogenous neurodegenerative disorder. To characterize homogeneous groups of PD patients, PD phenotypes have been described based on clinical data including motor and non-motor manifestations. This thesis is presented as a compendium of three research studies. The aim was to identify different PD subtypes based on objective MRI measures of cortical thickness. We hypothesized that different patterns of regional brain atrophy would be associated to distinct clinical and cognitive features.

Methods. We have used T1-weighted MRI images acquired with 3T Siemens scanners in two sample of PD patients at different times of the disease evolution: a sample of medicated PD patients (n = 88; disease duration: 8 ± 5.7 years) and a second sample from the Parkinson Progression Marker Initiative (PPMI, https://www.ppmi-info.org/) that enrolled 119 PD newly diagnosed drug naïve patients (n = 77; disease duration: 0.9 ± 1.0 years) with available MRI and neuropsychological assessments. Additionally, the medicated sample was followed-up after four years (n = 45). Both PD samples were compared with two similar groups of healthy elders. Cortical thickness estimation was performed with the FreeSurfer suite v5.1 (https://surfer.nmr.mgh.harvard.edu/). An agglomerative hierarchical cluster analysis technique was used to classify patients from a hypothesis-free data driven approach using Matlab (release 2014b, The MathWorks, Inc., Natick, Massachusetts). For the longitudinal assessment, we computed the symmetrized percent of change of the cortical thickness estimation of both times.

Results. In Study 1, we firstly classified patients of the medicated sample according to the vertex-wise cortical thickness data. Three patterns of regional thinning were obtained when comparing them with a sample of healthy controls with similar age and education: (1) a pattern mainly involving temporal and parietal atrophy; (2) a second pattern with frontal and occipital and younger age at disease onset; (3) a third pattern with no manifest atrophy in comparison with controls and reduced processing speed.

In Study 2, we classified the PD *de novo* patients according to their cortical thickness information from the 360 parcellations of the Human Connectome Project Multi-Modal Parcellation version 1.0. Two PD patterns were identified: (1) one pattern with anterior predominance including orbitofrontal, anterior cingulate and temporal atrophy with no cognitive deficits and (2) a posterior-based pattern with lateral occipital and parietal atrophy with associated verbal memory learning and delayed recall deficits as well as visuospatial and processing speed impairment.

In Study 3, we assessed the progression of the cortical patterns identified in Study 1 over four years. Pattern 1 patients with initial temporal and parietal widespread

atrophy had worse compromise in the activities of daily living. Regarding the other two patterns and the controls group, all groups displayed temporo-parietal progressive decline and reduced processing speed. However, pattern 2 patients with initial prefrontal involvement and younger disease onset had better evolution and focal cortical thinning changes. Pattern 3 patients and controls, that at baseline were the less atrophic groups, displayed extensive symmetrized percent of change in temporal and parietal regions. Despite the similar progression of pattern 3 with controls, pattern 3 patients had more atrophy in the prefrontal cortex over time than controls and more decline in semantic fluency, processing speed and visuospatial function.

Conclusions. PD patients showed different patterns of cortical thinning even at the time of diagnosis, regardless the presence of mild cognitive impairment and medication doses. Our patterned groups of patients based on hypothesis free data-driven methodologies stress the importance to review neuropsychological tools for the diagnosis of PD-MCI. Cortical thickness measures of percent of change revealed sensitive to aging and specific cortical degeneration in PD. Different regional atrophy patterns progress differently over time. It has been observed that initial posterior-based atrophy had worse compromise in the activities of daily living and patients were more likely to progress to dementia, whereas initial prefrontal involvement is linked to a better clinical evolution.

Overall, data-driven analyses were able to classify PD patients based on their cortical degeneration depicting distinct clinical manifestations and different progressions. Thus, PD prognosis can be characterized by structural MRI data.

Resum

Antecedents i objectius. La malaltia de Parkinson és una malaltia neurodegenerativa molt heterogènia. Per a caracteritzar grups homogenis de malalts, s'han descrit fenotips de pacients basats en manifestacions motores i no motores de la malaltia. Aquesta tesi s'ha elaborat en format de compendi de tres estudis de recerca. L'objectiu va ser identificar diferents subtipus de malaltia de Parkinson basat en mesures objectives de gruix cortical (imatge estructural). Vam hipotetitzar que diferents patrons d'atròfia regional estarien associats a diferents manifestacions clíniques i cognitives de la malaltia.

Mètodes. S'han utilitzat imatges potenciades en T1 de ressonància magnètica estructural amb escàners Siemens de 3T en dues mostres de pacients amb diagnòstic de malaltia de Parkinson en diferents moments evolutius de la malaltia: una mostra de pacients medicats (n = 88; duració de la malaltia: 8 ± 5.7 anys) i una segona mostra extreta de *Parkinson Progression Marker Initiative* (PPMI, https://www.ppmi-info.org/). Aquesta base de dades pública inclou pacients amb malaltia de Parkinson recent diagnosticats que encara no prenien medicació dopaminèrgica per al maneig de la malaltia (n = 77; duració de la malaltia: 0.9 ± 1.0 anys) i que tenien disponibles imatges de ressonància magnètica i avaluació neuropsicològica. Addicionalment, la mostra de pacients medicats es va seguir després de quatre anys (n = 45). Les dues mostres de pacients esmentades es van comparar amb dos grups de controls amb envelliment sa de característiques demogràfiques similars. L'estimació de gruix cortical es va fer amb el *software* FreeSurfer versió 5.1 (https://surfer.nmr.mgh.harvard.edu/). La tècnica de l'anàlisi de *clustering* jeràrquic aglomeratiu es va utilitzar per a classificar els pacients des d'una aproximació lliure d'hipòtesis prèvies i guiat per les pròpies dades. Per a l'anàlisi longitudinal, vam calcular una mesura de percentatge de canvi simètric dels valors de gruix cortical en els dos temps.

Resultats. En l'estudi 1, primerament vam classificar els pacients medicats d'acord amb la informació de cada un dels vèrtexs que conformen el mantell cortical. Es van obtenir tres patrons d'atròfia regional comparant-los amb la mostra de controls d'edat i educació similars: (1) un patró amb atròfia majoritàriament temporal i parietal; (2) un segon patró amb atròfia frontal i occipital i una edat de debut de la malaltia més precoç; (3) un tercer patró sense atròfia cerebral diferent als controls envellits sans i una reducció en la velocitat de processament.

En l'estudi 2, vam classificar els pacients recent diagnosticats i sense medicació (*de novo*) segons la informació obtinguda de les mitjanes de les 360 parcel·lacions de l'atles *Human Connectome Project Multi-Modal Parcellation* versió 1.0. Es van identificar dos patrons: (1) un patró amb atròfia predominantment anterior que incloïa regions orbitofrontals, anterior cingulat i temporals i sense alteracions cognitives i (2) un segon patró de base posterior

amb atròfia a l'occipital i el parietal laterals i amb alteracions associades en l'aprenentatge i el record de la memòria verbal així com en les habilitats viso-espacials i en la velocitat de processament.

En l'estudi 3, vam valorar la progressió dels patrons corticals identificats en l'estudi 1 després de quatre anys de progressió. Els pacients classificats en el patró 1 amb atròfia inicial generalitzada en els lòbuls temporal i parietal van tenir la major proporció de casos de demència i compromís de les activitats de la vida diària. En referència als altres dos patrons d'atròfia i al grup de controls, tots els grups van patir un declivi progressiu en regions temporo-parietals i una reducció en la velocitat de processament.

No obstant, els pacients classificats en el patró 2 amb atròfia inicial en el còrtex prefrontal i una edat d'inici de la malaltia més jove, van mostrar la millor evolució i atròfia focal progressiva al llarg del temps. Els pacients en el patró 3 i els controls, que en l'estudi 1 primerament van ser descrits com els menys atròfics, van mostrar atròfia extensa al llarg del temps. Tot i la progressió similar entre aquests dos últims grups esmentats, els pacients en el patró 3 van patir més deteriorament en regions del còrtex prefrontal que els controls i en l'occipital medial en comparació a l'evolució dels pacients en el patró 2. Cognitivament, els pacients del patró 3 van presentar pitjors puntuacions en fluència semàntica, velocitat de processament i habilitats viso-espacials al llarg del temps.

Conclusió. Els pacients amb malaltia de Parkinson es poden classificar segons diferents patrons de gruix cortical fins i tot en el moment del diagnòstic i independentment de la presència de deteriorament cognitiu lleu i la medicació dopaminèrgica per al maneig de la malaltia. Els nostres grups de pacients identificats a partir de dades objectives lliures d'hipòtesis a priori posen de manifest la rellevància de revisar les eines neuropsicològiques per al diagnòstic de deteriorament cognitiu en la malaltia de Parkinson. Les mesures de percentatge de canvi en el gruix cortical es van mostrar sensibles a l'envelliment sa i també a processos de degeneració cortical específics de la malaltia de Parkinson. Diferents patrons d'atròfia regional progressen de forma diferent al llarg del temps. Hem mostrat que els pacients amb una atròfia inicial de base posterior mostren més compromís en activitats de la vida diària i tendeixen a evolucionar més probablement cap a demència mentre que una atròfia inicialment prefrontal va lligada a una millor evolució clínica.

En definitiva, els anàlisis guiats per les dades (data-driven) lliures d'hipòtesis van ser capaços de classificar pacients amb malaltia de Parkinson en base a la seva degeneració cerebral, mostrant diferents manifestacions clínics i progressions al llarg del temps. Per tant, l'evolució de la malaltia es pot caracteritzar a partir de dades de neuroimatge estructural.

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