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

A.I. Garcia-Diaz [a, b], B. Segura [a, b], H.C. Baggio [a, b], C. Uribe [a, b], A. Campabadal [a, b, c], A. Abos [a, b], M.J. Marti [c, d, e], F. Valldeoriola [c, d, e], Y. Compta [b, c, d, e], N. Bargallo [b, c, f], C. Junque [a, b, c, d, e, *]

[a] Department of Medicine, Faculty of Medicine and Health Science, University of Barcelona, Barcelona, Catalonia, Spain
[b] Institute of Neurosciences, University of Barcelona, Barcelona, Catalonia, Spain
[c] Institut D'Investigacions Biomèdiques August Pi I Sunyer (IDIBAPS), Barcelona, Catalonia, Spain
[d] Centro de Investigación Biomédica en Red Sobre Enfermedades Neurodegenerativas (CIBERNED), Hospital Clinic de Barcelona, Barcelona, Catalonia, Spain
[e] Movement Disorders Unit, Neurology Service, Hospital Clínic de Barcelona, Barcelona, Catalonia, Spain
[f] Centre de Diagnostic per La Imatge, Hospital Clinic, Barcelona, Catalonia, Spain

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ABSTRACT

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

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

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

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

1. Introduction

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

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

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

* Corresponding author. Department of Medicine, Faculty of Medicine and Health Sciences, University of Barcelona, Casanova 143, 08036, Barcelona, Spain.
E-mail address: cjunque@ub.edu (C. Junque).

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

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

2. Methods

2.1. Participants

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

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

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

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

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

2.2. Visuospatial and visuoperceptual assessment

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

2.3. MRI acquisition

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

2.4. Longitudinal cortical thickness

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

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

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