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Short communication

Longitudinal intracortical diffusivity changes in de-novo Parkinson's disease: A promising imaging biomarker

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ABSTRACT

Cognitive impairment and dementia in Parkinson's disease (PD) are highly disabling non-motor symptoms with no effective treatment currently available. As cortical degeneration is thought to be involved in the development of these comorbidities, novel imaging biomarkers capable of detecting early cortical deterioration are needed. Recently, an increase in mean diffusivity (MD) within the cerebral cortex has been proposed as a highly sensitive imaging indicator of early microstructural cortical damage in neurodegenerative diseases. Using the Parkinson's Progression Markers Initiative (PPMI), we studied longitudinal changes in intracortical MD in recently-diagnosed and drug-naïve PD patients (n = 64). Compared to healthy controls (n = 20), de novo PD patients showed a higher one-year MD increase in frontal and occipital cortices ($p < 0.05$, corrected). These PD-specific MD changes correlated with changes in cognitive measures. Importantly, cortical MD increases were widespread in the PD group and loss of cortical thickness was only increased in a small parietal cluster. These results suggest that intracortical MD changes could be promising imaging biomarker in clinical trials targeting the prevention and treatment of early cortical degeneration in PD, but further research confirmation is needed.

1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder, representing a major health issue worldwide. Even though the disease is largely known for its motor symptoms, as the disease progresses a significant proportion of PD patients will also develop cognitive impairment (PD-MCI) or dementia (PDD), leading to debilitating consequences for patients and caregivers [1]. Critically, in contrast with motor symptoms, effective treatments for PD-MCI or PDD are currently lacking.

Whereas neuronal loss in the substantia nigra is the pathological hallmark of PD, a concomitant cortical degeneration is likely to occur and promote cognitive decline in this population [2]. To better characterize the neuropathological pathways leading to PD-MCI/PDD, neuroimaging indicators are needed to identify early cortical degeneration. The use of such indicators is of particular importance in clinical trials, especially in patient selection and treatment monitoring scenarios.

It has recently been suggested that an increase in mean diffusivity (MD) within the cerebral cortex reflects early cortical microstructural degeneration [3–5]. This novel surface-based imaging metric is derived from diffusion tensor imaging (DTI) scans and is thought to detect a regional increase in water mobility as a consequence of a recent neural death within the cerebral cortex. Compared to well-established indicators of cortical atrophy such as cortical thickness, intracortical MD has shown notably higher effect sizes and greater sensitivity to identify cortical neurodegeneration [4]. Therefore, tracking cortical MD changes could serve as a potential imaging biomarker of early cortical damage in PD, even in the absence of concomitant cortical thinning or significant cognitive decline.

Little is known about the role of this imaging measure in PD. In this short communication we characterize intracortical MD changes in recently-diagnosed and drug-naïve PD patients from the Parkinson's Progression Markers Initiative (PPMI). Our main objective was to investigate whether this novel imaging biomarker was able to identify incipient PD-specific cortical degeneration. As strong signs of cortical deterioration in very early disease stages are likely to be subtle in cross-sectional settings, we used a longitudinal approach to specifically assess dynamic MD changes. As a secondary and exploratory objective, we investigated the possible associations between the observed imaging differences and the patients' cognitive performance.

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2. Materials and methods

2.1. Sample and assessments

PD patients belonging to the de-novo PD PPMI cohort were considered in this study. By definition, these patients had a PD diagnosis for less than two years and were not taking PD medications. A healthy control (HC) group was also included. Inclusion criteria were the availability of baseline and longitudinal (one-year follow-up) T1-MRI and DTI data and error-free neuroimaging preprocessing (as specified in the neuroimaging methods subsection).

As cognitive assessments, we considered all neuropsychological tests that were administered at baseline and at one-year follow-up in PPMI. These included the Montreal Cognitive Assessment (MoCA) test as a global measure of cognitive performance, and domain-specific tests targeting frontal-dominant tasks (Symbol Digit Modality Test [SDMT], Letter Number Sequencing [LNS]), fronto-temporal dominant tasks (Semantic Fluency), posterior-cortical dominant tasks (Benton Judgment of Line Orientation [BJLO], and the Hopkins Verbal Learning Test [HVLT]). Motor status was inferred by the total motor score for the Unified Parkinson's Disease Rating Scale. Specific details regarding all the considered assessments are available at http://www.ppmi-info.org/ .

We addressed cross-sectional clinical data (at baseline) and one-year longitudinal relative changes (post-pre/pre) in cognitive performance. The rationale behind this approach is to appropriately compare and correlate relative changes in cognitive indicators with longitudinal changes in imaging indicators, as the latter have shown increased sensitivity than cross-sectional alternatives at detecting early cortical deterioration [6].

2.2. Neuroimaging methods

As of November 2018, we downloaded T1-MRI (labeled “T1-anatomical”) and DTI (labeled “DTI_gated”) scans from https://www.ppmi-info.org/access-data-specimens/download-data/. All participants belonging to the de novo PD cohort or the control PPMI cohorts were selected if their baseline and one-year follow-up T1-MRI and DTI data were available. One hundred and thirty-seven participants met these criteria.

Vertex-wise cortical thickness (Cth) information from T1-MRI scans was computed using the FreeSurfer 6.0 software package (https://surfer.nmr.mgh.harvard.edu/). The procedure of surface-based cortical reconstruction of structural MRI images and the derivation of Cth data has been fully described elsewhere [7].

Vertex-wise intracortical MD information was derived from DTI scans using the following procedure. First, MD maps were obtained using the dtifit tool from the FSL software package (https://www.fmrib.ox.ac.uk/fsl). MD maps were then co-registered with the associated T1-MRI scans. On continuation, after applying partial volume correction (PVC) using FreeSurfer's mri_gtmpvc tool, we sampled MD values halfway between the white and pial cortical surfaces.

We studied Cth and MD differences between de-novo PD and HC both cross-sectionally (at baseline) and longitudinally (relative changes over a one-year follow-up period). Longitudinal changes were measured in terms of symmetrized percent change (SPC), a robust measure recommended by FreeSurfer developers that has shown increased statistical power in this context. SPC values of a measure (Cth or intracortical MD) are defined as:

$$SPC_{measure} = [(Measure_{follow\text{-}up}\text{-}Measure_{baseline})/(time2\text{-}time1)]/\ [0.5*(Measure_{follow\text{-}up} + Measure_{baseline})]$$

Therefore, negative SPC_{Cth} values indicate a longitudinal reduction of cortical thickness, and positive SPC_{MD} values indicate a longitudinal increase of MD. For their computation, we used the longitudinal FreeSurfer pipeline, designed to increase reliability and statistical power in this setting through the use of an unbiased within-subject template space [8].Finally, and for the sake of completeness, we also computed subcortical volumetric and PVC-MD information using standard FreeSurfer procedures. These data were then compared across groups to further investigate the role of this imaging metric in the caudate, putamen, accumbens, pallidum, amygdala, thalamus, and hippocampus regions.

The following exclusion criteria related to preprocessing errors were applied: poor image quality (in either baseline T1, follow-up T1, baseline DTI, or follow-up DTI), inaccurate Freesurfer T1 segmentation (baseline or follow-up), poor longitudinal T1 registration, poor MD map estimated by tensor fitting (baseline or follow-up), or poor T1-MD registration. We were particularly strict when detecting local surface reconstruction and co-registration defects so as not to introduce inaccurate vertex-wise measures. Consequently, and given the relatively high number of preprocessing steps (11) where poor quality results could have occurred, we considered only 84 participants in the final analyses.

2.3. Statistical analyses

Clinical and sociodemographic data were compared across groups using two-sample *t*-test analysis for continuous variables and X^2 for categorical variables. Differences were considered significant at $p < 0.05$.

Cortical vertex-wise measures (Cth,SPC_{Cth},MD, SPC_{MD}) were first smoothed using a Gaussian kernel of 15 mm full-width-at-half-maximum to increase the signal-to-noise ratio. A generalized linear model (GLM) was then performed to compare these measures across groups, using age, sex and education as covariates of no interest. Clusters surviving $p < 0.05$ and family-wise error (FWE) correction for multiple-comparison using a Monte-Carlo simulation with 10000 repeats were considered significant.

Lastly, we explored the possible cognitive translation of the observed neuroimaging differences. To do so, we first computed average Cth/MD values at the regions showing significant differences between groups. Using Pearson's coefficients, we then performed correlation analyses between the imaging indicators and the cognitive indicators. A $p < 0.05$ was considered significant.

3. Results

Table 1 summarizes the sample's sociodemographic and clinical data. Significant differences between groups were only found for motor symptoms.

Regarding cortical imaging differences, cross-sectionally at baseline, no significant regions showed either reduced Cth or increased MD in de novo PD patients with respect to HC. However, with respect to HC, de-novo PD patients showed an increased one-year loss of Cth in the right supramarginal gyrus, and a higher one-year increase in intracortical MD in bilateral frontal and left occipital regions (Fig. 1). Significant longitudinal intracortical MD increases were 6.4 times more extensive than the longitudinal Cth decreases. Additionally, a vertex-wise effect size analysis revealed there were 3.15 times more vertices showing Cohen's d larger than 0.5 in the longitudinal MD analysis than in the long-

Table 1
Baseline and longitudinal sample characteristics. Values are expressed as mean ± standard deviation. UPDRS-III: total motor score for the Unified Parkinson's Disease Rating Scale, MoCA: Montreal Cognitive Assessment (MoCA) [total score], HVLT: Hopkins Verbal Learning Test, LNS: Letter-Number Sequencing, SDMT: Symbol Digit Modality Test, BJLO: Benton Judgment of Line Orientation. Longitudinal changes are expressed as (follow-up – baseline)/baseline, except for UPDRS-III scores, which are expressed as follow-up– baseline to avoid division by zero.

	de-novo PD		HC		Significance (p-value)	
	Baseline	One-year change	Baseline	One-year change	Baseline	One-year change
n	64		20			
Age [years]	60.4 ± 9.1		59.8 ± 9.9		0.81	
Sex	19/64 female		6/20 female		0.98	
Education [years]	14.9 ± 3.1		15.2 ± 2.7		0.69	
Months since PD diagnosis	5.7 ± 7.6		-		-	
UPDRS III	19.6 ± 9.3	2.3 ± 7.6	1.1 ± 2.1	0.5 ± 2.2	< 0.001	0.09
MoCA	27.4 ± 2.3	−0.01 ± 0.1	28.0 ± 1.0	−0.03 ± 0.05	0.22	0.29
HVLT	24.8 ± 5.6	−0.02 ± 0.2	25.3 ± 3.4	0.004 ± 0.2	0.76	0.66
LNS	10.9 ± 2.7	0.03 ± 0.2	10.1 ± 2.3	0.06 ± 0.2	0.17	0.64
SDMT	42.1 ± 10.1	.001 ± 0.2	46.5 ± 12.6	0.04 ± 0.2	0.17	0.51
BJLO	12.9 ± 2.0	0.01 ± 0.2	13.2 ± 2.1	0.01 ± 0.1	0.69	0.94
Semantic fluency	21.6 ± 4.6	0.03 ± 0.2	20.9 ± 4.2	0.10 ± 0.2	0.48	0.20

itudinal Cth analysis.

Concerning subcortical differences between groups, de-novo PD patients only showed larger one-year volume loss than the HC group in the right caudate ($p = 0.013$) and in the left hippocampus ($p = 0.012$).

In the set of cortical and subcortical regions where differences between the groups were significant, the corresponding imaging metrics showed the following correlations with cognitive indicators in the PD group: longitudinal MD increases at the left frontal cortex correlated with a longitudinal reduction in Letter Number Sequencing scores ($p = 0.035$); lower semantic fluency scores at baseline correlated with larger longitudinal MD increases in the left occipital cortex ($p = 0.043$); and lower BJLO scores at baseline correlated with an increased loss of left hippocampal volume ($p = 0.022$).

4. Discussion

We found that despite the absence of cross-sectional imaging differences, recently-diagnosed and drug-naïve PD patients showed a higher one-year increase in intracortical diffusivity than healthy controls with a similar sociodemographic profile. Whereas MD increases spanned both frontal lobes and the left occipital cortex, loss of cortical thickness in the PD group was only increased in a small parietal cluster.

Because as many as half the patients with PD develop dementia (PDD) within 10 years of diagnosis [1], the ability to identify very early signs of cortical alterations – which are strongly associated with PDD – is of interest to the medical community. We found that intracortical MD changes were able to detect incipient cortical microstructural degeneration in PD patients whose cognitive performance was still similar to healthy controls.

Besides showing a more consistent neurodegenerative pattern than Cth changes in terms of frontostriatal circuitry, the increases we observed in cortical MD yielded significant correlations with cognitive changes. In particular, we found that MD increases in the left frontal cortex correlated with a decrease in LNS scores, a frontal-dominant test. Additionally, semantic fluency scores in the PD group correlated with temporo-occipital MD increases. This is noteworthy because impaired semantic fluency has shown to predict PDD [9], and occipital involvement in this cognitive indicator is well-documented [10]. Indeed, one recent review on PDD highlighted the importance of finding imaging techniques able to detect early occipital degeneration in this clinical context [11].

The lack of significant cross-sectional differences in our sample highlights the importance of a longitudinal neuroimaging approach in this context, as longitudinal changes may be more sensitive and specifically-related to active neurodegeneration in predementia disease stages [6,12]. Overall, our results suggest that monitoring intracortical MD changes in clinical trials could provide a useful imaging biomarker of early cortical deterioration in PD.

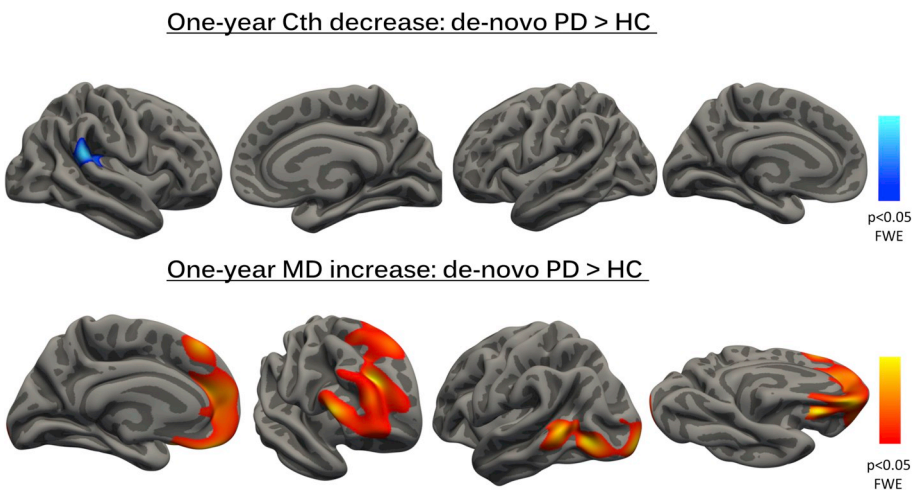

Fig. 1. Cortical regions where de-novo PD patients showed a higher one-year loss of Cth (top) and a higher one-year increase of intracortical MD (bottom) with respect to HC, $p < 0.05$ FWE controlling for age, sex, and education. Longitudinal changes were measured in terms of vertex-wise symmetrized percent change (SPC).

The main strength of this study is the application, for the first time in PD, of a novel neuroimaging technique within a longitudinal framework. This approach yielded significant FWE-corrected vertex-wise results with higher effect sizes than standard approaches. However, the exploratory nature of the subsequently observed clinical-imaging associations may limit their interpretation. Hence, further research is needed to establish the relationship between this imaging biomarker and the development of cognitive impairment and dementia in PD.

To conclude, using a longitudinal surface-based analysis of mean diffusivity within the cerebral cortex, we observed early widespread cortical microstructural degeneration in de-novo PD patients. Alterations in this novel imaging metric were found in the absence of pronounced cortical thinning, and they correlated with cognitive indicators. This imaging biomarker could thus be useful to monitor early cortical deterioration in PD trials targeting the prevention or treatment of cognitive decline, but further research confirmation is needed.

Authors' roles

FS: Project conception, project execution, manuscript writing.
SMH, JP, JML: Statistical analysis, manuscript review.
JK: Project organization, manuscript review and critique.

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