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Dopaminergic degeneration induces early posterior cortical thinning in Parkinson's disease

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ABSTRACT

Background: Cognitive decline in Parkinson's disease (PD) is a highly prevalent condition with no effective treatment. Cortical atrophy is thought to promote its development but to design optimal therapeutic approaches in this clinical setting we need to understand the physiopathological mechanisms leading to this disorder.
Objective: To characterize the impact of dopaminergic degeneration on cortical integrity in early PD.
Methods: We studied 87 recently-diagnosed PD patients and 38 healthy controls from the Parkinson's Progression Marker Initiative who underwent I123-ioflupane SPECT (DATSCAN) and T1-MRI imaging. Using Freesurfer 6.0, we characterized baseline and longitudinal (one-year) correlations between striatal DAT uptake and cortical thickness. We also addressed the association between these imaging biomarkers and cognitive measures.
Results: Reduced DAT uptake in PD patients was associated with cross-sectional and longitudinal cortical thinning in frontal and posterior-cortical brain regions. Imaging parameters correlated with cognitive indicators in multiple domains that extend beyond frontal-executive tasks. Dopaminergic medication attenuated the longitudinal loss of cortical integrity in frontal and a subset of parietal regions, but not in other key regions such as the precuneus.
Discussion: To date, posterior cortical alterations in PD, known to play a major role in the development of PD-dementia, have mainly been attributed to a cholinergic degeneration occurring in later stages of the disease. Our results suggest that dopamine loss also promotes posterior-cortical atrophy from the very early stages of Parkinson's disease, which may have potential clinical and therapeutic implications.

1. Introduction

Mild cognitive impairment is an inherent non-motor feature of Parkinson's disease (PD-MCI). Because as many as half the patients with PD develop dementia (PDD) within 10 years of diagnosis, cognitive deficits in this population are a major health issue. Whereas successful therapeutic approaches are available to manage motor symptoms in PD, effective treatments for PDD or its prodromal phase PD-MCI are lacking (Svenningsson et al., 2012). This may be partly due to an incomplete understanding of the underlying processes leading to cognitive deficits in PD. Further characterization of the physiopathological mechanisms involved in cortical deterioration is thus urgently needed to design and evaluate new disease-modifying therapeutics for PD-MCI and PDD.

Given the highly heterogeneous clinical course of cognitive decline in PD, a complex sequence of pathological events is likely to subserve this disorder (Aarsland et al., 2017). In recent years, the concept of an early dopamine-modulated frontal-striatal network dysfunction followed by a posterior-cortical compromise associated with cholinergic depletion has emerged (Williams-Gray et al., 2009; Pagonabarraga and Kulisevsky, 2012; Kehagia et al., 2013). Nonetheless, while the transition from a frontal-dysexecutive syndrome to posterior-cortical deficits heralding dementia appears consistent from a clinical point of view (Williams-Gray et al., 2009), the timing, overlap and interaction between these two neurodegenerative pathways are not fully understood.

On one hand, for instance, the temporal sequence of these syndromes is challenged by clinical and neuroimaging evidence of posterior-cortical alterations in early PD patients without a severe fronto-striatal compromise (Pagonabarraga and Kulisevsky, 2012; Dušek et al.,

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2012).On the other hand, a significant proportion of PD-MCI patients seem to revert to normal cognition after dopaminergic medication, showing improvements even in posterior-cortical domains (Kulisevsky et al., 2000; Wood et al., 2016; Pedersen et al., 2017). Lastly, cholinergic treatment has not proven to have a significant impact on PD-MCI nor to prevent its progression to dementia (Mamikonyan et al., 2015).

In view of these inconsistencies, we consider that a better characterization of the impact of dopaminergic depletion on cortical integrity in recently-diagnosed PD patients is needed to fully comprehend the complex dynamics of cognitive decline in this population. On the basis of the aforementioned observations, we hypothesize that, in addition to a fronto-striatal compromise, the inherent dopaminergic degeneration in early PD might play a causative role in posterior-cortical thinning. Thereafter, a possible cholinergic loss would aggravate and catalyze an already-existing posterior-cortical damage. Our hypothesis is supported by the presence of dopamine receptors and transporters in parietal and posteromedial brain regions, which have shown to modulate brain connectivity in healthy controls (Nagano-Saito et al., 2017).

Few studies have addressed this issue by using cross-sectional gray matter volume (GMV) voxel-based-morphometry (VBM) and dopaminergic imaging (Choi et al., 2016; Maekawa et al., 2017; Zeighami et al., 2015). Importantly, their results are in line with our hypothesis, suggesting a correlation between GMV in posterior brain regions and dopaminergic loss. However, these works had severe limitations in terms of sample size, heterogeneous disease stage, use of PD medication, cross-sectional design and lack of a control group. Besides, consideration was not given to important confounders of brain atrophy such as amyloid plaque accumulation and neurofibrillary tangle aggregation, or to the specific relationship between structural cortical changes and cognition.

Here, we overcame these limitations by selecting a relatively large, well-characterized and cognitively homogeneous sample of early PD patients and healthy controls from the Parkinson's Progression Markers Initiative (PPMI) project (Marek et al., 2011). Furthermore, we investigated both cross-sectional and longitudinal cortical thickness (Cth) patterns associated with the dopaminergic state using a surface-based model instead of VBM, since this technique has shown increased sensitivity for characterizing subtle changes in cortical atrophy (Mak et al., 2015).

2. Materials and methods

The main objective of this work was to study the possible impact of early dopaminergic loss in PD on cortical atrophy. As a biomarker of dopaminergic degeneration we used striatal I^{123}-ioflupane SPECT (DATSCAN) uptake, and cortical thickness derived from T1-MRI scans was used as a measure of cortical integrity.

Characterizing neurodegeneration during the transition from normal cognition to cognitive impairment in PD is especially relevant to further comprehend and prevent or delay its onset. Accordingly, we investigated the association between baseline and one-year changes in dopaminergic loss, cortical thinning and cognitive indicators in recently-diagnosed PD patients with normal cognition (PD-NC).

2.1. Sample and assessments

This analysis included a group of 87 PD-NC patients and 38 healthy controls (HC). Inclusion criteria for PD participants were: de-novo PD ($\leq$2 years from diagnosis), cognitively preserved [MoCA $\geq$26 (Marras et al., 2013)] and untreated at baseline, and available baseline and one-year follow-up DATSCAN and T1-MR imaging. All PD patients belonged to the de-novo PD PPMI cohort and not to the genetic cohort. The majority of participants were Caucasian (94%).

Table 1 shows the clinical, socio-demographic and neuropsychological data, DAT imaging quantification, and biomarker information known to be linked to cognitive status in this sample(Kim et al., 2012; Deck et al., 2017; Choi et al., 2014; Ashraghi et al., 2016; Anang et al., 2014). We grouped the set of neuropsychological test into frontal-dominant (verbal fluency [executive], SDMT [processing speed], LNS [working memory]), posterior-cortical-dominant (BJLO [visuospatial], HVLT [memory]) and fronto-temporal-dominant (semantic fluency [executive]).

In addition, even though all PD patients were drug-naïve at baseline, a significant proportion (73%) received dopaminergic treatment during the follow-up year. Since dosages, prescription schemes and starting dates were highly variable, the accumulated levodopa-equivalent dose (accLED) during the follow-up year was calculated for each patient (Tomlinson et al., 2010).As we used accLED values instead of the daily LED at the end of follow-up, we were able to take both the dosage and timing of the medication into account. Details regarding all the considered assessments are available at http://www.ppmi-info.org/ .

2.2. T1-MRI neuroimaging methods

Cortical thickness (Cth) analysis was performed using the FreeSurfer 6.0 software package (https://surfer.nmr.mgh.harvard.edu/). The procedure of cortical reconstruction of structural MRI images has been fully described elsewhere (Fischl and Dale, 2000). On visual inspection, no major surface reconstruction errors were observed in our sample.

We studied the association between striatal DAT uptake and Cth both cross-sectionally (at baseline) and longitudinally (relative changes over a one-year follow-up period). Using the Freesurfer's longitudinal pipeline, changes in Cth 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 is defined as:

$$\mathrm{SPC} = \text{atrophy rate/average Cth} = [(\mathrm{Cth}_{\mathrm{follow-up}} - \mathrm{Cth}_{\mathrm{baseline}}) /(\mathrm{time2} - \mathrm{time1})]/[0.5^{*}(\mathrm{Cth}_{\mathrm{follow-up}} + \mathrm{Cth}_{\mathrm{baseline}})]$$

Therefore, negative SPC values represent a longitudinal reduction of cortical thickness. After applying a vertex-wise Cth and SPC smoothing of 15 mm FWHM, we performed a set of generalized linear models (GLM) to investigate whether striatal dopaminergic integrity modulated cortical thinning. In particular, we studied continuous correlations between Cth/SPC and DAT uptakes (average putamen, caudate or striatal).

Age, sex, and education were used as nuisance variables in all GLM models. Additionally, we included basal CSF $A\beta_{1-42}$ and CSF phospho-tau as covariates to control for the possible effect of an underlying comorbid preclinical Alzheimer's disease (Lin and Wu, 2015). Finally, we also aimed to adjust all GLM models for a heterogeneous cholinergic depletion within the PD group, which could act as a confounding factor on the association between dopaminergic depletion and brain atrophy. To do so, in the absence of available biomarkers of cholinergic integrity, we added RBD scores as a covariate the analyses. This clinical indicator has been suggested to infer the brain's cholinergic status in PD using acetylcholinesterase ([^{11}C]PMP) PET imaging as a reference (Müller et al., 2015).

Clusters obtained from GLM models that survived $p < 0.05$ and family-wise error (FWE) correction for multiple-comparison by a Monte-Carlo simulation with 10,000 repeats were considered significant. Mean Cth or SPC values at the identified clusters were computed for each patient to perform further correlation analyses with other clinical parameters.

2.3. Scalar statistical analyses

Scalar statistical analyses were performed using SPSS15 software. To examine differences across groups, we used *t*-test analyses for continuous variables and X^2 for categorical measures. Additionally, we

Table 1
Baseline and longitudinal sample characteristics. Values are expressed as mean ± standard deviation.

	PD-NC	HC	Significance (*p*-value)
n	87	38	
Age at baseline [years]	59.2 ± 8.8	60.2 ± 11.2	0.62
Sex [% of male]	64.3%	68.4%	0.66
Education at baseline[years]	15.2 ± 2.9	16.1 ± 2.8	0.11
Disease duration at baseline [months]	7.6 ± 8.1		
Laterality [% left]	46%		
UPDRS III (baseline, Δabs)	20.3 ± 8.4, 2.1 ± 9.0	0.7 ± 1.6,0.4 ± 1.6	< 0.001*,0.27
DATSCAN SBR			
Avg Putamen (baseline, Δrel%)	0.8 ± 0.3, −12.7 ± 27.4	1.9 ± 0.4, NA	< 0.001*, NA
Avg Caudate (baseline, Δrel%)	1.9 ± 0.5, −9.7 ± 10.9	2.7 ± 0.4, NA	< 0.001*, NA
Avg Striatum (baseline, Δrel%)	1.3 ± 0.4, −11.1 ± 13.0	2.3 ± 0.4, NA	< 0.001*, NA
accLED	29,527.8 ± 30,109.1		
MoCA (baseline, Δrel%)	28.3 ± 1.3, −2.9 ± 8.6	28.3 ± 1.1, −3.7 ± 6.6	0.99,0.52
HVLT (baseline, Δrel%)	25.3 ± 5.1, −2.1 ± 21.0	25.5 ± 4.5, 3.3 ± 15.9	0.79,0.07
LNS (baseline, Δrel%)	11.1 ± 2.6, 0.7 ± 24.4	11.1 ± 2.4, 2.6 ± 24.0	0.99,0.69
SDMT (baseline, Δrel%)	42.6 ± 9.1, −0.7 ± 16.7	48.0 ± 12.4, 0.03 ± 23.7	0.008*,0.85
BJLO (baseline, Δrel%)	13.1 ± 1.8, −0.7 ± 16.4	13.2 ± 1.9, −0.6 ± 16.6	0.80,0.96
Semantic fluency (baseline, Δrel%)	21.1 ± 5.0, 4.0 ± 22.1	22.0 ± 4.6, 6.0 ± 19.8	0.33,0.69
Phonetic verbal fluency (baseline, Δrel%)	12.8 ± 4.4, 19.8 ± 82.3	13.8 ± 3.8, 17.5 ± 43.3	0.24,0.83
GDS15 (baseline, Δrel%)	5.2 ± 1.4, 9 ± 58.9	5.1 ± 1.1, −4 ± 25.6	0.57,0.08
RBD score at baseline	3.9 ± 2.6	2.7 ± 2.0	0.006*
CSF $A\beta_{1-42}$ at baseline [pg/ml]	376.9 ± 100.4	356.5 ± 80.6	0.23
CSF p-tau_{181p} at baseline [pg/ml]	17.1 ± 10.5	19.2 ± 13.1	0.37
BMI at baseline [kg/m^2]	27.1 ± 4.7	27.1 ± 4.4	0.95
MAP at baseline [mmHg]	95.5 ± 9.1	98.3 ± 10.9	0.18
History of DM [%]	2.3%	2.6%	0.91
Statin use at baseline [%]	18.4%	10.5%	0.27
Thyroid medication at baseline [%]	8.1%	7.9%	0.97

UPDRS-III: total motor score for the Unified Parkinson's Disease Rating Scale, DATSCAN SBR: DATSCAN Striatal Binding Ratio, 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, GDS: Geriatric Depression Scale, RBD: Rapid Eye Movement Sleep Behavior Disorder Questionnaire. BMI: Body Mass Index, MAP: Mean Arterial Pressure, DM: Diabetes Mellitus, NA: Not available, Δrel%: Percentage relative change at one-year (follow-up-baseline), Δabs: Absolute one-year change. One-year follow-up missing data: UPDRSIII (three PD-NC patients), MoCA (two PD-NC patients), neuropsychological battery (one PD-NC patient).* $p < 0.05$

performed an exploratory correlation analysis between imaging parameters and clinical measures such as cognitive tests and medication using Pearson's correlation coefficients. A probability value (p-val) < 0.05 was considered significant.

3. Results

Table 1 summarizes the demographic, clinical, neuropsychological, DAT imaging and CSF data of the sample.

3.1. Dopaminergic depletion and cognitive indicators

Several significant correlations were found between striatal DAT uptake and cognitive measures. Within the PD-NC group, baseline caudate DAT uptakes correlated with the following basal scores: HVLT ($r = 0.24$, $p = 0.024$), LNS (r = 0.24, p = 0.024), SDMT($r = 0.23$,$p = 0.034$), Verbal Fluency (r = 0.23, $p = 0.029$) and GDS15 ($r = -0.22$, $p = 0.045$). Additionally, annual DAT uptake loss correlated with a longitudinal reduction of HVLT scores, both in the caudate ($r = 0.29$, $p = 0.008$) and in the putamen ($r = 0.35$, $p = 0.001$†) regions.

In the HC group, only two significant cross-sectional correlations at baseline were found: putamen DAT uptake and SDMT ($r = 0.42$, $p = 0.009$†) and caudate DAT uptake and LNS ($r = 0.36$,$p = 0.027$). Fig. 3a shows the subset of correlations marked with a cross (†).

3.2. Dopaminergic depletion and cortical thinning

Fig. 1 shows a pattern of cortical thinning associated with a reduction in putamen DAT uptake, observed both in PD-NC and HC subjects. Similar atrophy patterns were also related to a reduced caudate DAT uptake, but their statistical maps did not survive multiple comparison correction.

In the PD-NC group, mean Cth values at the identified clusters in the temporal lobe correlated with executive, visuospatial and memory scores: left temporal – HVLT ($r = 0.21$, $p = 0.048$), right temporal – BJLO ($r = 0.22$, $p = 0.041$) and LNS (r = 0.22, $p = 0.037$). No correlations were found between cortical integrity at the clusters identified in HC subjects and their cognitive measures.

Within the PD-NC group, Fig. 2 illustrates patterns of longitudinal cortical thinning associated with both baseline and one-year changes of putamen DAT uptake. In the HC group, however, there was no association between baseline DAT uptake and longitudinal cortical thinning. Longitudinal DATSCAN data were not available in the HC group.

Lower baseline DAT uptake in the caudate was also associated with an increased loss of Cth in the precuneus/posterior cingulate region ($p < 0.05$ FWE, not shown). However, there was no significant longitudinal pattern of cortical thinning associated with longitudinal changes of caudate DAT uptake.

The longitudinal loss of Cth at the identified frontal clusters was associated with a loss in BJLO scores (left frontal: $r = 0.22$, $p = 0.042$; right frontal: $r = 0.23$, $p = 0.036$†). Also, reduced basal semantic fluency was associated with increased longitudinal cortical thinning at the identified left supramarginal cluster (r = 0.23,$p = 0.032$). Moreover, atrophy rates at some of the identified clusters were attenuated by dopaminergic treatment: i.e. increased accLED was associated with lower Cth loss in the right frontal cluster ($r = 0.27$, $p = 0.012$†) and in the right inferior parietal cluster ($r = 0.26$, $p = 0.015$). Correlations marked with a cross (†) are displayed in Fig. 3b. None of the presented results changed significantly when potential outliers were removed.

We repeated all neuroimaging analyses in the PD-NC group using age and sex as covariates of a base-model and adding one confounder at a time (CSF $A\beta_{1-42}$, CSF p-tau_{181p}, RBD, BMI, MAP, DM, statin use and thyroid medication). Only one or two clusters in some models failed to

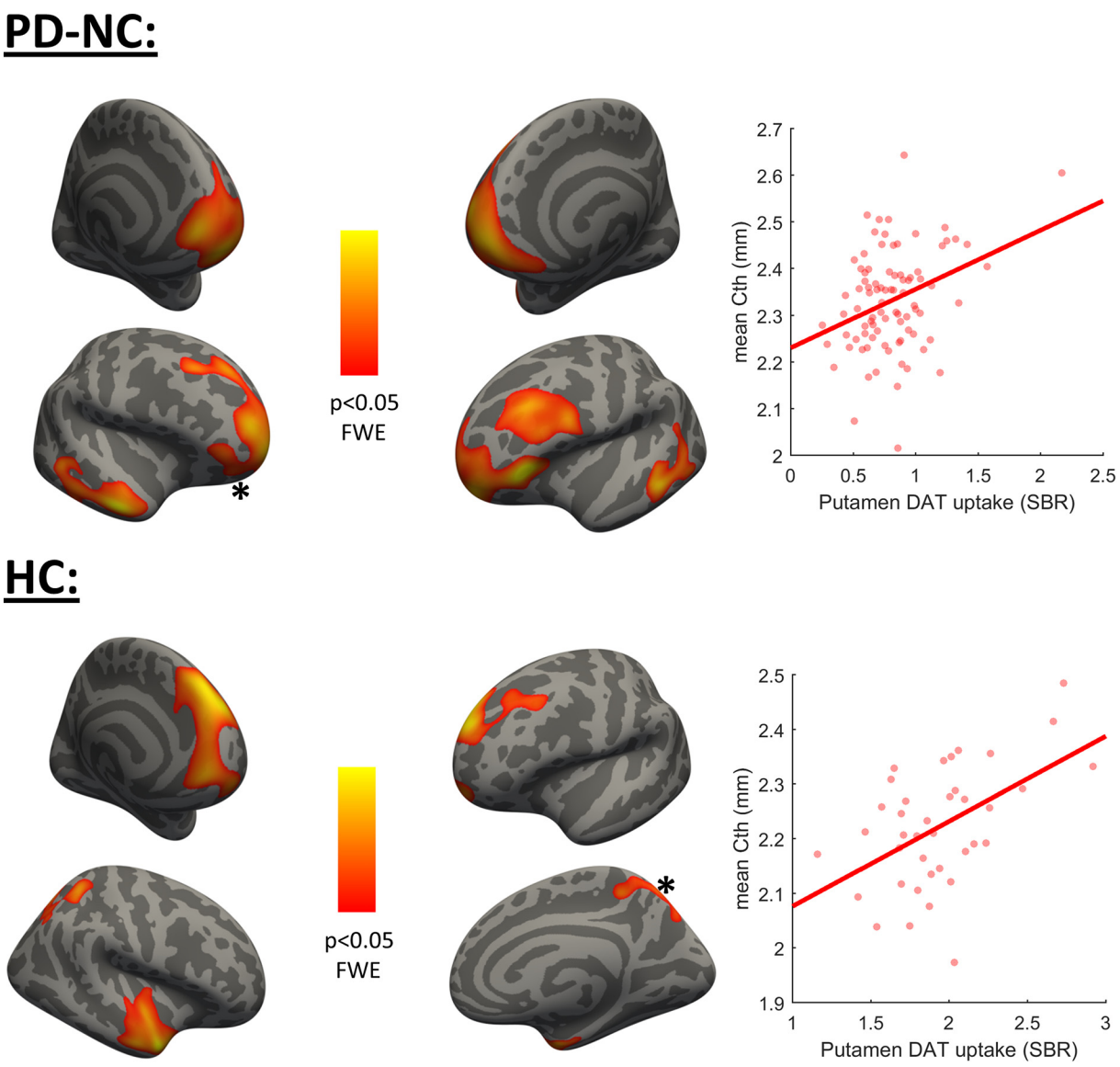

Fig. 1. Baseline cross-sectional cortical thinning patterns associated with reduced putamen DAT uptake in PD-NC (top) and HC (bottom) subjects. The adjacent scatter plots illustrate the direction of the correlation in the clusters marked with an asterisk. Age, sex, education, amyloid accumulation, tangle aggregation and inferred cholinergic status were used as covariates within the vertex-wise statistical models.

survive multiple comparison correction with respect to the presented results. These clusters were variable across models and still held uncorrected significance. Moreover, additional FWE-corrected clusters appeared in similar regions in some models.

Finally, Supplementary Figs. S1 and S2 show the set of cortical vertices where PD-NC patients had lower Cth at baseline and increased one-year Cth loss with respect to the HC group, respectively. Note that all cortical regions showing significant associations with dopaminergic status (Figs. 1 and 2) appeared compromised in the PD-NC group when compared to HC. Notice that as studying PD-NC vs HC differences in Cth was not the main objective of the study, the resulting vertexwise maps are presented in the supplementary material using a less-stringent statistical criterion.

4. Discussion

In recently-diagnosed PD patients, our results first show an exploratory association between dopaminergic depletion and cognitive performance in multiple domains that extend beyond frontal-execute tasks. Importantly, memory scores (e.g. HVLT) and also depressive symptomatology (GDS-15) were related to dopaminergic status in this population. In healthy controls, normal-range dopamine levels were only associated with the performance of two frontal-executive measures (SDMT and LNS).

Dopaminergic integrity was also associated with a cross-sectional reduction of cortical thickness in frontal and posterior-cortical regions, both in PD and HC subjects. However, the observed structural brain alterations were only associated with neuropsychological measures in PD patients. Furthermore, in PD patients, dopaminergic loss was associated with an increased longitudinal atrophy rate in frontal and posterior-cortical territories, which was in turn related to longitudinal changes in neuropsychological scores.

These data suggest that the pathological loss of dopaminergic neurons in PD is related to a cortical neurodegeneration that extends beyond frontal regions and impacts cognitive performance. In contrast, non-pathological variability of dopamine levels in healthy controls only seems to drive developmental differences in their brain structure.

Notably, the observed posterior-cortical degeneration associated with dopaminergic loss appeared to be independent of direct and indirect markers of other underlying neurodegenerative processes such as

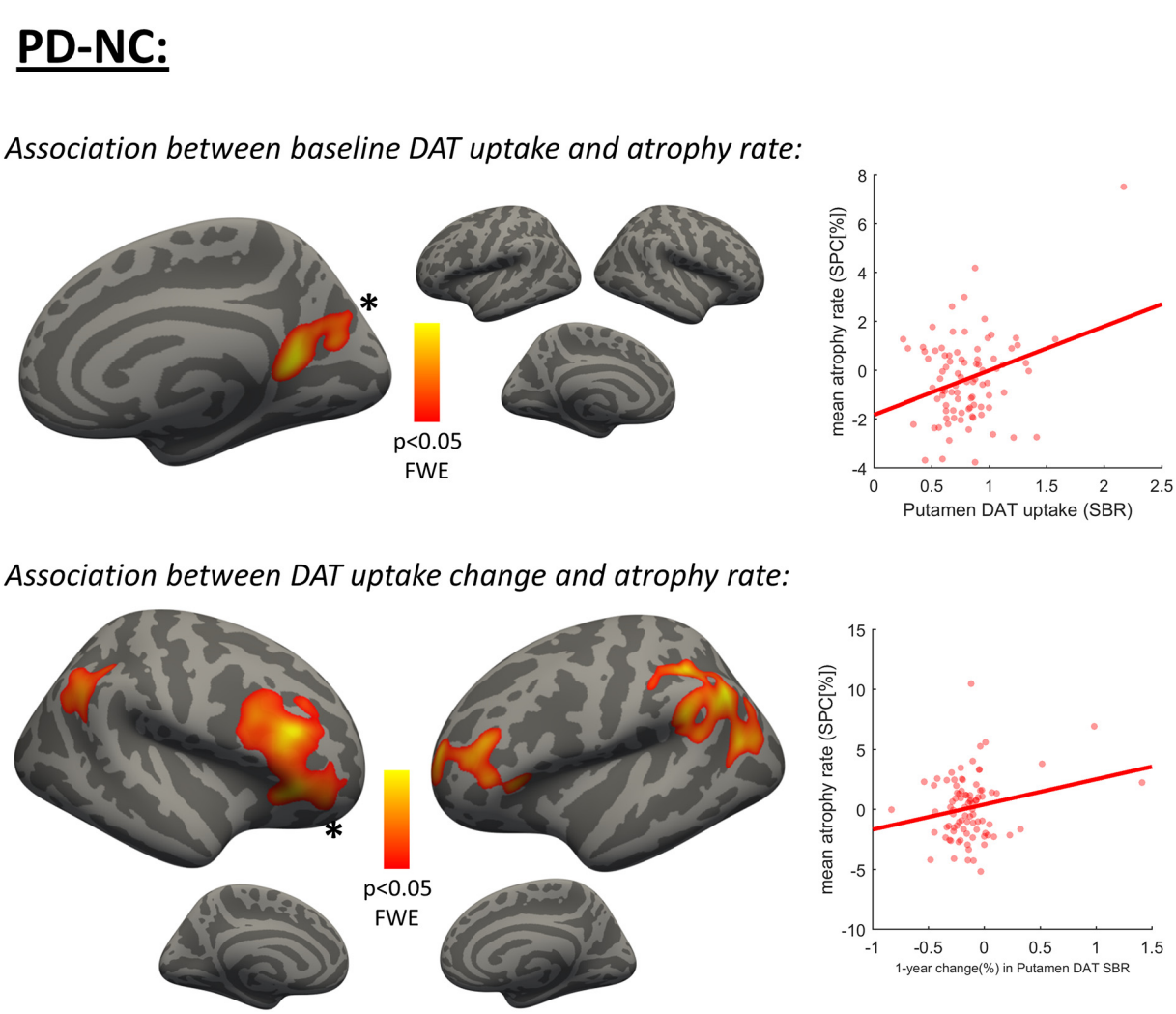

Fig. 2. Longitudinal Cth analyses in the PD-NC group. Top: brain regions where a reduced baseline putamen DAT uptake was associated with an increased one-year loss of cortical thickness ($p < 0.05$ FWE). Bottom: brain regions where a larger one-year loss in putamen DAT uptake was associated with an increased one-year loss of cortical thickness ($p < 0.05$ FWE). Adjacent scatter plots illustrate the direction of the correlation in the clusters marked with an asterisk. Age, sex, education, amyloid accumulation, tangle aggregation and inferred cholinergic status were used as covariates within the vertexwise statistical models.

amyloid plaque accumulation, neurofibrillary tangle aggregation and cholinergic depletion. Noteworthy, higher dosages of dopaminergic medication correlated with a lower longitudinal loss of cortical thickness, but only in a subset of brain regions. In particular, atrophy rates at the precuneus/posterior-cingulate cortex and left supramarginal gyrus did not show an association with standard medication profiles.

Biological and clinical plausibility of these results should be discussed. First, evidence suggests a dopamine involvement in the functional activation of the supramarginal and precuneus regions, which in PD patients seems to be influenced by medication (Dušek et al., 2012; Landau et al., 2009). Combining this information with our observation that the structural cortical compromise occurring in these areas is only partially influenced by medication could explain the incomplete response of both dopaminergic and cholinergic agents on PD cognition (Kulisevsky et al., 2000; Mamikonyan et al., 2015). In other words, the functional amelioration but only partial structural neuroprotection of dopamine therapy in posterior-cortical regions may underlie the set of complex cognitive progression profiles observed in clinical practice, and might challenge current therapeutic strategies. Second, basal striatal DAT uptake and cortical thickness in temporo-parieto-occipital regions of PD-NC patients have shown to predict their longitudinal conversion to PD-MCI (Melzer et al., 2012; Hanganu et al., 2014; Delgado-Alvarado et al., 2016; Caspell-Garcia et al., 2017). In the light of our findings, showing reduced cortical integrity in these regions at baseline, either pathologically-driven by dopaminergic depletion or due to physiological (e.g. demographic) variability, would aggravate the clinical consequences of the described underlying neurodegeneration.

This work has potential implications in therapeutics and clinical trials. Predicting patient trajectories is a challenge for clinicians, and the mechanisms underlying variations in progression to dementia remain elusive. To date, posterior-cortical alterations leading to PDD have been mainly attributed to cholinergic influences. We argue instead that the presence and severity of posterior-cortical atrophy are also –and perhaps mainly– driven by dopaminergic denervation. Although we could not establish a causal association, our data also suggest that initiation of dopamine replacement therapy may partially slow down a subsequent inherent cortical degeneration occurring in PD. Further research is needed to elucidate the possible mechanisms by which current dopaminergic medications seem to show an incomplete neuroprotective effect on cortical integrity. Our study design also propounds that monitoring annual cortical thinning in these regions and studying whether treatments are able to modulate its progression could be useful to preventing or delaying the onset of PDD.

The strengths of this study include the use of a relatively large, homogeneous, well-characterized and biomarker-rich sample of recently-diagnosed PD patients with preserved cognition. Additionally,

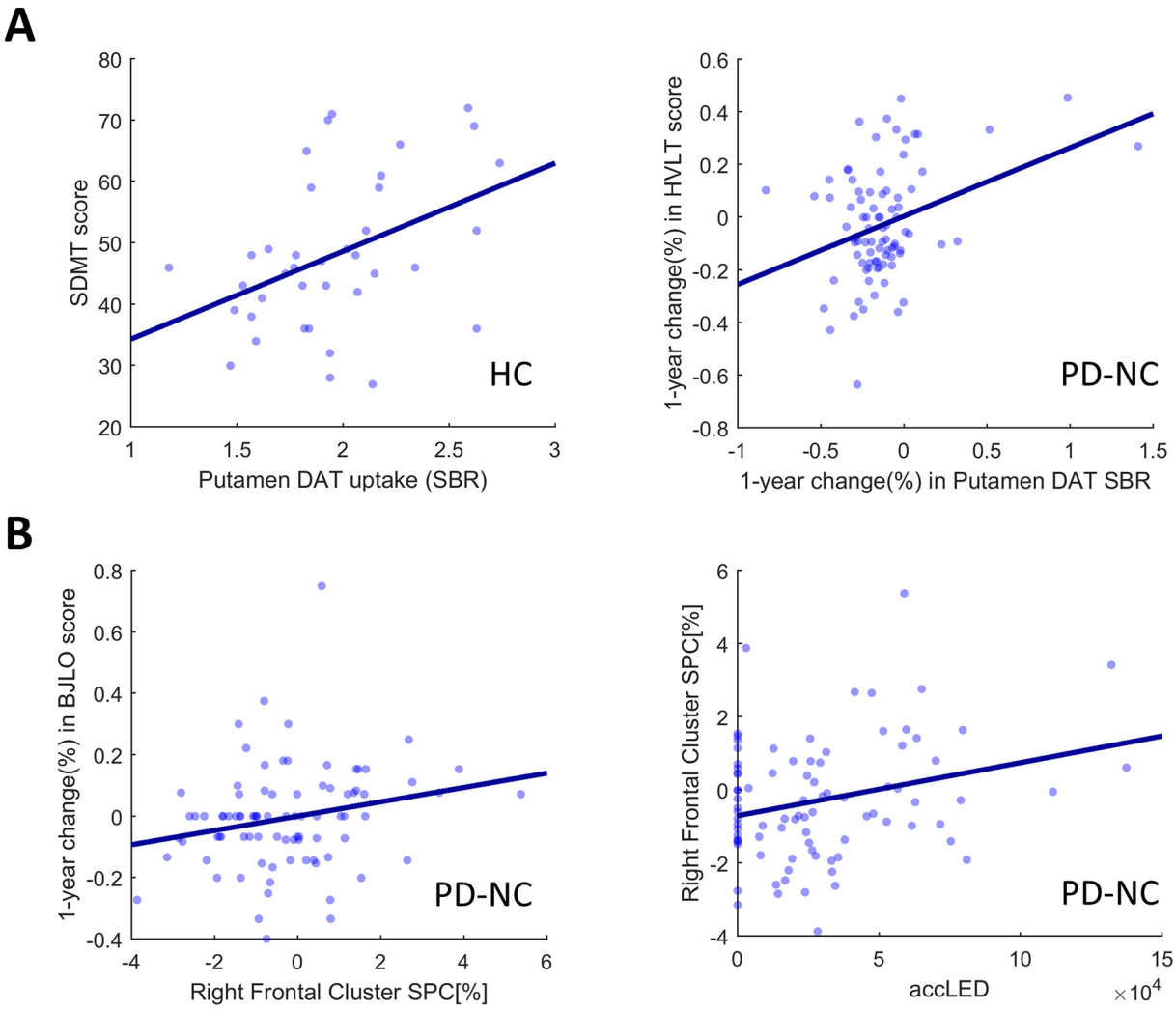

Fig. 3. Illustrative scatter plots of a subset of the significant correlations described in the text.

this study allowed direct assessment of early longitudinal changes in dopaminergic and cortical deterioration, thereby characterizing the preclinical dynamics of cortical PD neurodegeneration. Limitations of this work comprise, on one hand, the use of DATSCAN SPECT instead of 18F-DOPA PET as an imaging biomarker, impeding a robust topological characterization of dopaminergic deficiency (Picco et al., 2015). On the other hand, we are aware that the clinical inference of cholinergic status by RBD scores is far from optimal. The unavailability of longitudinal DATSCAN data in the control group also limits our results. Furthermore, the significant associations between cognitive tests and imaging parameters had modest correlation coefficients, although this would be expected in a highly homogeneous sample of cognitively-preserved and recently-diagnosed PD patients. Finally, it remains unclear whether the relationship between dopaminergic degeneration and posterior cortical integrity is causal or merely correlational.

In conclusion, our findings extend previous knowledge on the pathogenesis of cognitive decline in PD. The fact that the inherent dopaminergic loss in early PD patients already affects posterior-cortical brain integrity should be taken into consideration in future clinical and therapeutic settings.

Author's roles

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

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Appendix A. Supplementary data

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