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Parkinson's disease patients with hallucinations exhibit dopaminergic degeneration and cortical thinning

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Introduction

Parkinson's disease (PD) is the fastest growing neurological condition (Aarsland & Kurz, 2010; Dorsey & Bloem, 2018).

The development of visual hallucinations in PD is a significant predictor of dementia and earlier nursing home placement (Pfeiffer, 2016; Schapira et al., 2017; Weintraub et al., 2004).

A reduction in striatal dopamine transporter (DAT) has been linked to posterior cortical atrophy and associated with the development of psychosis (Sampedro et al., 2019). Therefore, dopaminergic degeneration may be one mechanism of cortical atrophy associated with the development of hallucinations (Dave et al., 2020; Jaakkola et al., 2017). Alternatively, limbic degeneration has also been associated with the development of hallucinations in PD (Gallagher et al., 2011; Harding et al., 2002; Papapetropoulos et al., 2006).

The current study examines the relationship between DAT imaging, subcortical and cortical volumes, and the development of hallucinations in PD early in the disease course.

Methods

Participants

- PPMI cohort
- De novo at enrollment
- 423 participants with PD and 196 HCs in PPMI study
- Identified 41 patients with hallucinations (≥1 on Movement Disorder Society-Unified Parkinson's Rating Disease Scale (MDS_UPDRS) 1.2 at any visit)
- Of 41 patients with hallucinations (PD+hall), 34 had good structural MRI data
- Matched PD with no hallucinations (PD-ctrl) and healthy controls (HC) by age, sex, education and Hoehn and Yahr score

Table 1: Demographic and Clinical Information

	HC group	PD+hall	PD-ctrl	P-Value
Demographic Characteristics				
Mean age in years (SD)	63.74(7.8)	63.35(9.0)	61.0(9.1)	0.44
Mean age at diagnosis in years (SD)	N/A	62.76(9.1)	60.6(9.1)	0.33
Mean disease duration in years (SD)	N/A	0.53(0.7)	0.29(0.5)	0.15
Sex (M: F) (n, %)	10(0.3):24(0.7)	0:34	0:34	0.90
Non-Hispanic: Hispanic	34:0	34:0	34:0	0.37
Race (self-reported, white: non-white or not reported)	34:0	33(0.97):1(0.3)	34:0	0.33
Mean years of Education (SD)	14.71(2.8)	14.88(3.7)	15.09(2.9)	0.82
PD Measures				
MDS-UPDRS 3 Total Score	0.5(1.2)	14.41(5.9)	13.97(7.5)	<0.001
Hoehn & Yahr Score	0	1.62(0.5)	1.5(0.51)	<0.001
RBD	2.44(1.9)	4.82(3.1)	3.67(2.7)	0.001
DATSCAN SBR1.84				
Left Putamen	1.99(0.4)	0.74(0.4)	0.8(0.3)	<0.001
Right Putamen	1.99(0.4)	0.73(0.3)	0.71(0.3)	<0.001
Left Caudate	2.73(0.5)	1.74(0.6)	1.85(0.6)	<0.001
Right Caudate	2.65(0.4)	1.77(0.6)	1.77(0.5)	<0.001

Statistical Analysis

- Extracted longitudinal cortical thickness [figure 1] values from T1-weighted structural MRI and striatal binding ratios (SBRs) in the putamen and caudate from ^{123}I-ioflupane SPECT data [figure 2] for 34 HC, 34 PD-ctrl, and 34 PD+hall.
- Four 3 × 4 [group (PD+hall vs PD-ctrl) × Time (baseline, year 1, 2, and 4)] repeated measures analyses of variance were conducted with SBR values as the dependent variables to examine whether SBRs exhibited a greater decline over time in the PD+hall relative to PD-ctrl groups.
- General linear models were used to examine the relationship between SBRs and cortical thickness across time.

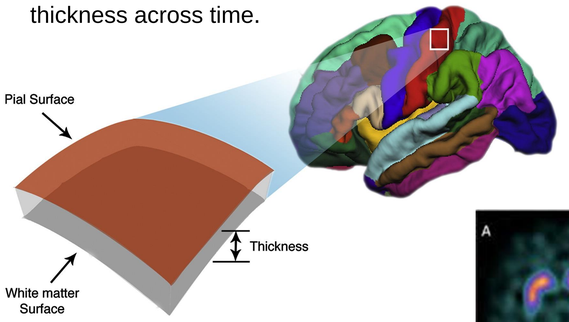


Fig. 1 Cortical thickness measured as the distance between white matter and pial surface (Wierenga et al., 2014).

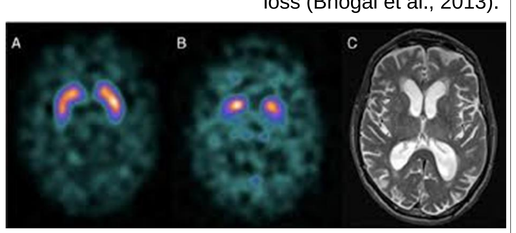


Fig. 2 HC DAT scan (a) for comparison. DAT scan of patient with neurological condition (b) showing lack of tracer uptake in the putamen. Axial T2-weighted image (c) of same patient shows generalized volume loss (Bhogal et al., 2013).

Results

- PD+hall showed greater reduction in SBR in the left and right caudate over time relative to PD-ctrl [figure 3].
- A greater reduction in caudate SBR values was associated with reduced cortical thickness over time in the left lateral occipital (p = 0.01), right superior parietal (p = 0.001), and precentral gyri (p = 0.01) in the PD+hall group only [figures 4 and 5].
- Reduced right putamen SBR was associated with cortical thinning in the PD+hall group in the right precentral gyrus (p = 0.04).

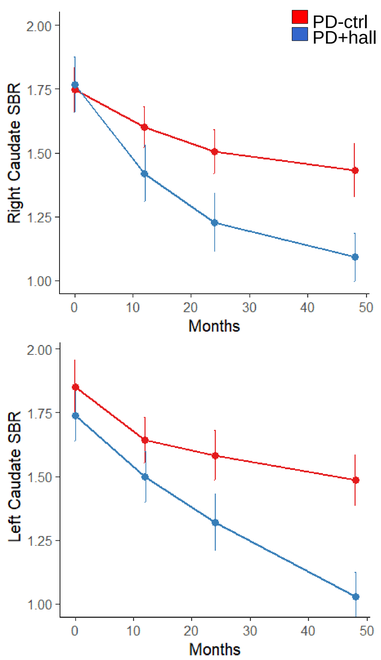
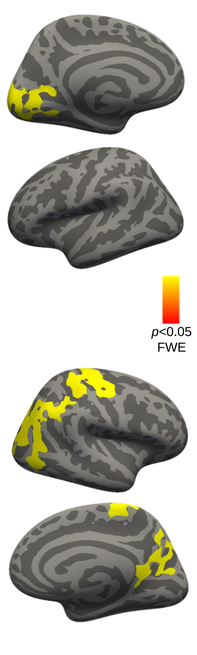


Fig. 3 Striatal Binding Ratios (SBRs) over time. PD+hall exhibited a greater decline in SBRs in the right and left caudate relative to PD-hall across four study visits (baseline, year 1, year 2, and year 4). Baseline visits occurred within two years of PD diagnosis.



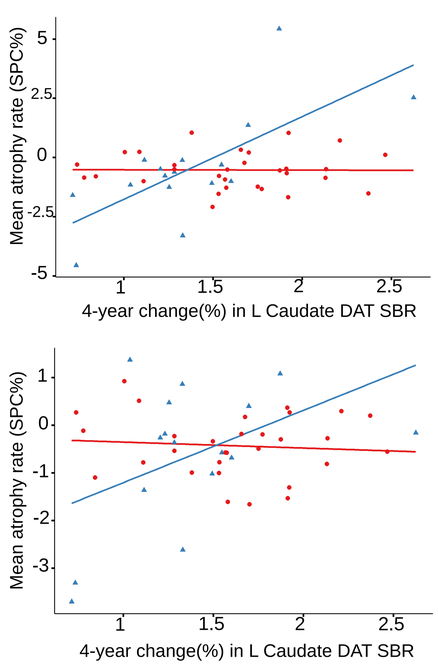


Fig. 4 Association between left caudate DAT and RH atrophy rate. PD+hall group had greater atrophy over time in the right precentral gyrus and superior parietal gyrus compared to PD-ctrl group in relation to reduced dopaminergic uptake

Fig. 5 Association between left caudate SBR and LH atrophy rate. PD+hall group had significantly greater symmetrized percent change (atrophy) over time in the left lateral occipital cortex compared to PD-ctrl group in relation to reduced dopaminergic uptake.

Discussion

- People with Parkinson's disease who experience hallucinations exhibit a greater decline in striatal dopamine binding. Striatal dopamine binding is associated with posterior cortical thinning in the left lateral occipital, right superior parietal, and precentral gyri in these patients.
- This suggests dopamine degeneration may play a role in posterior cortical thinning and the development of hallucinations in Parkinson's disease.
- Understanding these relationships can inform treatment practices as well as identify novel avenues for interventions

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