Dopamine and Functional Connectivity in Patients With Parkinson's Disease and Visual Hallucinations

Visual hallucinations (VH) are the most common symptom of Parkinson's disease (PD) psychosis,[1] are difficult to treat, impact on quality of life, and increase the likelihood of institutionalization.[1] Dopaminergic medications have been implicated in VH and are often reduced in patients experiencing this symptom. Despite this common practice, the relationship between dopamine and VH remains unclear. VH have been reported in drug-naïve patients,[2] and the intravenous infusion of levodopa fails to reliably trigger VH in PD hallucinators.[3]

Previous functional magnetic resonance imaging studies utilizing the Bistable Percept Paradigm, a computerized behavioural task that reliably identifies clinically assessed VH in PD,[4] have highlighted the role of altered neural connectivity between attentional and visual networks. In brief, VH are proposed to arise because of impaired coupling between distributed brain networks, such as the dorsal attention and default mode network, which in turn could result in intrusions from the default mode network entering into perceptual consciousness as hallucinatory episodes.[4,5]

To examine the effect of dopamine on network connectivity, 14 PD hallucinators underwent clinical and imaging assessment twice: both *on* and *off* dopaminergic medication (interscan interval ≤ 2 weeks). Demographic and clinical data are reported in Table 1.

Neuroimaging was conducted on a 3-Tesla magnetic resonance imaging (General Electric, Milwaukee, WI). Functional images were preprocessed according to a standard pipeline, and statistical parametric maps were calculated for each patient using a general linear model analysis within an event-related design to assess differences under task conditions and with medication status. A whole-brain map was generated to compare any differences in activation with correct perceptions or misperceptions of single images *on* and *off* dopaminergic medication utilizing a paired *t* test. Then, a region of interest (ROI)-to-ROI analysis involving the attentional and visual neural networks was performed (seeds were defined according to a previous study).[5]

TABLE 1. Clinical and demographic features and *on* versus *off* comparison

Details			
Age, mean ± SD			71.1 ± 5.7
Female:male			5:9
Disease duration in years (mean ± SD)			8.4 ± 6
UPDRS motor (III) *on* (mean ± SD)			38.4 ± 15.2
Hoehn & Yahr stage *on* (mean ± SD)			2.4 ± 0.6
LED in mg (mean ± SD)			818.9 ± 283.5
Dopamine agonist use (%)			50%
Other psychotropic medications			
Fluoxetine (n = 2)			
Dothiepin (n = 1)			
Amitriptyline (n = 1)			
MMSE (mean ± SD)			28.1 ± 1.9
MoCA (mean ± SD)			25.1 ± 2.7
RBD-Q (mean ± SD)			6.6 ± 3.5
SCOPA-PC questions 1–4 (mean ± SD)			2.3 ± 2.5
UPDRS question 2 (mean ± SD)			1 ± 1
BDI-II (mean ± SD)			13 ± 11.7
	On	*Off*	*P* Value
BPP misperceptions (%)			
Patient			
1	63	88	
2	21	6	
3	80	87	
4	63	50	
5	61	68	
6	58	58	
7	56	35	
8	35	82	
9	36	40	
10	61	45	
11	50	43	
12	70	66	
13	20	31	
14	15	36	
Mean ± SD	49 ± 20.3	53 ± 23.7	0.46
BPP misses (% mean ± SD)	31 ± 19.4	34 ± 26.1	0.52
Visual contrast sensitivity (mean ± SD)	1.0 ± 0.2	1.1 ± 0.2	0.18

SD, standard deviation; UPDRS, Unified Parkinson's Disease Rating Scale; LED, levodopa equivalent dose; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; RBD-Q, Rapid Eye Movement Behavior Disorder Questionnaire; SCOPA-PC, Scales for Outcome in PD–Psychiatric Complications; BDI-II, Beck Depression Inventory; BPP, Bistable Percept Paradigm.

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Contrary to traditional clinical practice, dopaminergic medication status did not affect behavioral performance on the Bistable Percept Paradigm (all P values >0.05). In addition, we observed no overall difference in the whole-brain or ROI–ROI analyses when comparing the correct and incorrect perception of single images on the Bistable Percept Paradigm comparing *on* and *off* dopaminergic medication states (all P values >0.05).

Our results augment accumulating evidence suggesting that dopaminergic medication status is unlikely to be the primary factor regulating the complex pathogenesis of VH in PD. Indeed, PD patients with VH will almost certainly demonstrate idiosyncratic patterns and degrees of neurodegeneration and different risk factor profiles and medication combinations. This suggests that the individual effect of dopamine may be mediated by several other factors. The impacts of degeneration across other nondopaminergic neurotransmitter pathways, such as serotonin, noradrenaline, and acetylcholine, and medications that affect these pathways should be considered in future studies. In addition, dynamic functional magnetic resonance imaging studies techniques that can probe the degree of integration and segregation across the whole-brain network[6] and have been shown to be sensitive to neuromodulatory tone[7] may also provide unique viewpoints into this troubling symptom of PD.

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Genome-Wide Association Study of Pain in Parkinson's Disease Implicates *TRPM8* as a Risk Factor

Chronic pain affects 60% to 85% of people with Parkinson's disease (PD) and has a strong negative effect on quality of life.[1] Genetic factors are significantly associated with a variety of chronic pain conditions.[2] Identifying additional genetic modifiers of pain in people with PD is of high scientific and clinical interest and could open avenues for novel treatments. Here, we report the results of the first genome-wide association study of pain in PD.

PD patients were recruited from the UK Parkinson's Pain Study, which included patients from the Tracking Parkinson's and the Oxford Parkinson's Disease Centre cohorts. The clinical assessment of pain in these patients has been previously reported.[1] PD patients were stratified into 2 groups that represented individuals with no/low pain (McGill score < 3 and Visual Analog Scale severity <2) and high pain (McGill Score ≥ 3 and Visual Analog Scale severity ≥2).

DNA extracted from each sample was genotyped using either the Illumina Human ExomeCore-12 v1.1 array, Illumina, Cambridge, UK (Tracking Parkinson's) or the InfiniumCoreExome-24 v1.1, Illumina, Cambridge, UK (Oxford Parkinson's Disease Centre). Genotype data from both cohorts underwent the same conventional processing, quality control, and imputation procedures as described elsewhere.[3]

We performed a genome-wide association study of 6,655,232 autosomal single nucleotide polymorphisms (SNPs) that compared a total of 898 patients with PD who were classed as suffering high levels of pain to 420 PD patients who were not experiencing pain. After including covariates for age, gender, and ancestry in the association analysis there was no evidence of genomic inflation attributable to population stratification ($\lambda = 1.00$).

This analysis identified 2 SNPs (rs11563208 and rs12465950) that were associated with pain in PD at genome-wide

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