Movement Disorders
CLINICAL PRACTICE

RESEARCH ARTICLE

The Relationship Between Serotonin-2A Receptor and Cognitive Functions in Nondemented Parkinson's Disease Patients with Visual Hallucinations

Sang Soo Cho, PhD,[1,2] Antonio P. Strafella, MD, FRCPC, PhD,[1,2,3] Sarah Duff-Canning, PhD,[3] Mateusz Zurowski, MD, MSc,[4] Anne-Catherine Vijverman, MD,[5] Veronica Bruno, MD, MPH,[3] Camila C. Aquino, MD, MSc,[3] Marion Criaud, PhD,[1,2] Pablo M. Rusjan, PhD,[2] Sylvain Houle, MD, PhD,[2] Susan H. Fox, MRCP(UK), PhD[3,]*

Abstract: **Background:** There is growing evidence that the serotonergic system, in particular serotonin 2A receptors, is involved in neuropsychiatric symptoms in Parkinson's disease (PD), including cognitive processing and visual hallucinations. However, the relationship between serotonin 2A receptor availability, visual hallucinations, and cognitive profile is unknown. The objective of this study was to investigate the level of serotonin 2A receptor availability in brain regions affected by visual hallucinations and to test the association with cognitive/behavioral changes in patients who have PD with visual hallucinations.

Methods: Nondemented patients who had PD with (n = 11) and without (n = 8) visual hallucinations and age-matched controls (n = 10) were recruited. All participants completed neuropsychological testing, which consisted of visuoperceptual, executive, memory, language, and frontal-behavioral function. Positron emission tomography scans using [^{18}F]setoperone, a serotonin 2A antagonist radioligand, were acquired in patients with PD, and a parametric binding potential map of [^{18}F]setoperone was calculated with the simplified reference tissue model using the cerebellum as a reference.

Results: Patients who had PD with visual hallucinations exhibited significantly lower scores on measures of executive and visuoperceptual functions compared with age-matched controls. These changes were paralleled by decreased [^{18}F]setoperone binding in the right insula, bilateral dorsolateral prefrontal cortex, right orbitofrontal cortex, right middle temporal gyrus, and right fusiform gyrus. The psychometric correlation analysis revealed significant relationships among tests associated with visuoperceptual function, memory and learning, and serotonin 2A binding in different prefrontal and ventral visual stream regions. There was also reduced serotonin 2A receptor binding in patients who had PD with depression.

Conclusions: These findings support a complex interaction between serotonin 2A receptor function and cognitive processing in patients who have PD with visual hallucinations.

Nonmotor symptoms, including cognitive decline and psychosis, are significant causes of morbidity and contribute to mortality in patients with Parkinson's disease (PD). Well-formed visual hallucinations (VHs), along with illusions and a sense of presence, are common psychotic symptoms in PD, affecting 22% to 30% of patients.[1,2] The cause of VHs in PD is

[1]Division of Brain, Imaging and Behavior-Systems Neuroscience, Krembil Research Institute, University Health Network, University of Toronto, Toronto, Ontario, Canada; [2]Research Imaging Center, Center for Addiction and Mental Health, University of Toronto, Toronto, Ontario, Canada; [3]Movement Disorder Unit and E. J. Safra Parkinson Disease Program, Toronto Western Hospital, University Health Network, University of Toronto, Toronto, Ontario, Canada; [4]Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada; [5]Division of Neurology, Onze-Lieve-Vrouw Hospital, Aalst, Belgium

***Correspondence to:** Dr. Susan H. Fox, Movement Disorders Centre, Toronto Western Hospital, University Health Network, University of Toronto, Toronto Ontario, Canada M5T2S8; E-mail: sfox@uhnresearch.ca
Keywords: cognitive decline, Parkinson's disease, positron emission tomography (PET), serotonin 2A (5-HT$_{2A}$) receptor, visual hallucinations.
Supporting information may be found in the online version of this article.
Relevant disclosures and conflicts of interest are listed at the end of this article.
Received 15 August 2016; revised 10 November 2016; accepted 1 December 2016.
Published online xx Xxxxx 2016 in Wiley InterScience (www.interscience.wiley.com). DOI:10.1002/mdc3.12466

doi:10.1002/mdc3.12466

multifactorial. Antiparkinsonian medications may be responsible for triggering VHs[3]; however, other neurotransmitters may also be implicated, because patients often continue to have symptoms despite the reduction or withdrawal of dopaminergic agents.[2,4] Evidence suggests that serotonin (5-HT) neurotransmission may also play a role in VHs. For example, the atypical antipsychotic agents clozapine and quetiapine reduce VHs in PD. Both agents are not only dopamine D_2 receptor antagonists but also 5-HT 2A and 2C (5-$HT_{2A/2C}$) receptor antagonists at the low doses employed in PD.[5] Using a serotonergic radioligand, [^{18}F]setoperone, with positron emission tomography (PET), we previously demonstrated that patients who have PD with VHs and normal cognitive performance have altered 5-HT_{2A} binding in several different cortical regions, particularly the visual ventral pathway, compared with those who have PD without VHs.[6] That study suggested a role for 5-HT_{2A} in the pathophysiology of VHs in PD.

Basic mechanisms underlying the generation of VHs in PD include dysfunction in "top-down" systems (i.e., orbitofrontal prefrontal cortex and dorsolateral prefrontal cortex [DLPFC]), which may implicate executive and attentional cognitive impairment, as well as a "bottom-up" (i.e., occipitotemporal cortex) defect in visual processing, which may implicate visuospatial dysfunction.[7,8] Growing numbers of studies provide evidence that patients who have PD with VHs may exhibit greater cognitive impairment than those without VHs in multiple areas, from attention to executive, visuospatial, learning, and memory functions, although findings are not consistent (see Table S1). In addition, neuroimaging studies have shown alterations in brain regions associated with cognitive performance in patients who have PD with VHs. For example, cortical and subcortical regional atrophy in the prefrontal and visual areas as well as in the limbic structure have been reported in patients with PD who experience VHs.[9,10] Hippocampal pathology with disrupted visuospatial memory has also been associated with VHs in PD[11] along with disrupted default-mode network.[12] These functional and anatomical changes may be associated with alterations in "top-down" and "bottom-up" information proposed to underlie the development of VHs.

The neural mechanisms underlying VH phenomena are complex and are the results of poorly understood interactions between cognitive changes and several neurotransmitter abnormalities, such as acetylcholine and dopamine as well as serotonin. Understanding patterns of 5-HT_{2A} receptor binding associated with cognitive dysfunction and VHs may enable a better understanding of the pathophysiology of neuropsychiatric issues in PD and possibly may also allow for the future identification of individuals who are at risk of VHs using PET imaging. The purpose of the current study is to investigate the interaction between cognitive function and 5-HT_{2A} receptor availability in cortical regions associated with "top-down" and "bottom-up" processing in patients with PD who experience VHs. We hypothesized that: (1) patients who have PD with VHs have visuoperceptual deficits mediated by the right inferotemporal cortex, (2) patients who have PD with VHs exhibit alterations of 5-HT_{2A} receptor function in the right inferior temporal (RIT) cortex, and (3) 5-HT_{2A} receptor availability in top-down/bottom-up network-related areas is associated with the performance of visuoperceptual function in patients who have PD with VHs.

Patients and Methods

Patients

Right-handed patients with idiopathic PD (age range, 30–80 years; UK Brain Bank criteria) were recruited from the Movement Disorders Clinic, Toronto Western Hospital. For patients who had PD with VHs, the proposed diagnostic criteria for PD-associated psychosis[13] were used. Thus, eligible patients had illusions, a sense of presence, and/or intermittent, well-formed VHs with maintained insight; but they had no delusions, paranoia, or persistent hallucinations, and these had to occur at least once a week and be present for at least 1 month. All antiparkinsonian and concomitant medications had to be stable for at least 1 month before study enrolment.

A group of age-matched and education-matched healthy controls were recruited from the community for neuropsychological testing (spouses/relatives of patients in the clinic and through advertisements in the hospital and on a website). Other detailed exclusion criteria are included in the online supporting information.

Patients with PD were evaluated for parkinsonian disability using the Unified Parkinson's Disease Rating Scale (UPDRS). A neuropsychiatric evaluation was conducted, and VHs were characterized according to phenomenology and severity using the Neuropsychiatric Inventory (NPI) (caregiver reported) and the Parkinson Psychosis Questionnaire (PPQ) (patient reported). For screening general cognitive abilities, the Montreal Cognitive Assessment (MoCA) was used. Mood was evaluated using the Beck Depression Inventory (BDI-II) and the Hospital Anxiety and Depression Scale due to potential confounder of mood issues on 5-HT_{2A} binding.

The study was approved by the Center for Addiction and Mental Health and University Health Network Research Ethics Boards. For each patient, written informed consent was obtained.

Neuropsychological Testing

Full neuropsychological evaluation was performed on all participants and included tests for: (1) *estimated premorbid intellectual function* (the Wechsler Test of Adult Reading[14]), (2) *attention* (the Brief Test of Attention[15]), (3) *processing speed* (the Trail Making Test [Part A][16]), (4) *language* (verbal fluency subtests of the Delis-Kaplan Executive Function System [D-KEFS][17] and the 30-item Boston Naming Test-odd version[18]), (5) *visuoperceptual function* (the Visual Object and Space Perception [VOSP] battery [incomplete letter, silhouettes, object decision, and progressive silhouettes[19]], the Benton Facial Recognition Test [FRT[20]], the Rey Complex Figure Test [RCFT[21]], and Judgment of Line Orientation [JLO[22]]), (6) *learning and memory* (the

doi:10.1002/mdc3.12466

California Verbal Learning Test [CVLT[23]] and the Recognition Memory Test [RMT[24]]), (7) *executive function* (the Trail Making Test [Part B-A][16]), the Golden version of the Stroop test,[25] the Modified Conditional Associative Learning Test [MCALT[26]], and the Visual Verbal Test abbreviated 10-item version.[27] The Frontal Systems Behavior (FrSBe) Scale,[28] which includes apathy, disinhibition, and executive dysfunction as subscales, was used to measure symptoms often associated with frontal dysfunction that may affect day-to-day functioning (only for patients with PD).

Imaging Scans

PET scans were obtained only for patients with PD. We used a high-resolution PET/computed tomography, Siemens mCT scanner (Siemens Medical Solutions USA, Inc.) with the same PET acquisition protocol that was used in our previous study.[6] Detailed PET acquisition and reconstruction procedures are described in Data S1.

To rule out structural lesions in the brain and to provide anatomical reference for the analysis, a T1-weighted MRI image was obtained from each participant using high-resolution MRI (GE Discovery MR750 3T; T1-weighted images, fast spoiled gradient echo with repletion time = 6.7 msec, echo time = 3.0 msec, flip angle = 8 mm, slice thickness = 1 mm, number of excitations = 1, matrix size = 256 × 192). Patients received their usual medication regimens for the duration of imaging.

Statistical Analysis

The clinical characteristics of patients who had PD with and without VHs were compared using appropriate parametric and nonparametric tests. To compare patterns of cognitive impairment between patients who had PD without VHs (PD-VH−) and with VHs (PD-VH+), each participant's score for the dependent variable of each test was converted to a z score on the basis of data from the normal control group. As a second outcome, domain-specific composite scores were calculated by averaging z scores of the tests within a domain. Domain-specific composite scores are a common approach when full profiles of cognitive function are tested. Using an appropriate composite minimizes the number of outcomes employed, the risk of Type I error,[29] and the impact of measurement error due to idiosyncratic single items or subdomains.[30] Furthermore, the composite score reportedly is more sensitive than using a single task list or battery to track cognitive decline.[29] In this analysis, attention (z scores for the Brief Test of Attention), processing speed (z scores for Trail Making Test Part A), language (average of z scores for the Boston Naming Test, D-KEFS–letter fluency, and D-KEFS–category fluency), memory (average of z scores for CVLT-long delay free recall, RMT-words, and RMT-faces), visuoperceptual (average of z scores for VOSP subtests, RCFT copy, and JLO), and executive function domains (average of z scores for Stroop interference, Visual Verbal Test-shift score, MCALT-memory errors, and Trail Making Test B-A) were calculated for group analysis.

Given the laterality differences in cognition, along with our data indicating laterality differences of serotonin binding in the inferior temporal cortex,[6] composite scores were calculated for left inferior temporal (LIT)-dependent and RIT-dependent cognitive tests. To create RIT composite score, z scores were averaged across the FRT, RMT-faces, and subtests of the VOSP, all tasks that are sensitive to the integrity of RIT cortical areas. Similarly, an LIT composite score was created by averaging z scores on the Boston Naming Test, CVLT–total learning trials, and RMT-words, tasks that are sensitive to the integrity of LIT cortical areas.

Statistical comparisons among groups were conducted using a nonparametric Kruskal-Wallis test at each assessment, the Mann-Whitney U test was for comparisons between PD groups, and subsequent post-hoc analyses of nonparametric Kruskal-Wallis tests with Dunn-Sidak corrections. For within-subjects comparisons (i.e., RIT vs. LIT composite), a nonparametric Wilcoxon test was used. Spearman's rho (r) test was used to test the relationship between demographic measurement and regional [^{18}F]setoperone binding potential (BP). The significance level for all statistical analyses was set at $P < 0.05$, and statistical analyses were performed in SPSS version 16.0 for Windows (IBM Corp., Somers, NY).

PET Image Analysis

The frame-based, motion-corrected PET data were analyzed using the in-house image analysis platform ROMI.[31] Detailed image-preprocessing procedures using ROMI are described in Data S1. After the ROMI procedure, a parametric [^{18}F]setoperone BP map was calculated in the native PET space with a simplified reference tissue method[32] using the cerebellar time activity curve value as reference. For statistical analysis, parametric BP images were transformed into standardized stereotaxic space using individual MRIs. Finally, normalized images were smoothed with a Gaussian function at 8 mm full width half-maximum.

The image preprocessing for the statistical analysis was done with SPM 8 (Wellcome Department of Imaging Neuroscience, London, UK). For within-group comparisons, uncorrected P values (<0.01; with an extent threshold [k] of at least 20 contiguous voxels) were used to generate an initial t-map to determine the predicted peaks and visualization. Furthermore, to partially address the reduced power of the whole-brain analysis, a secondary, small-volume correction analysis (i.e., 8-mm sphere, with fixation point at the local maxima) was performed for those clusters within a priori brain regions (including the bilateral inferior-occipital gyrus, right fusiform gyrus, inferior temporal cortex, bilateral DLPFC, orbitofrontal cortex, and insula) that were selected based on our previous study.[6] To measure the psychometric correlation of visuospatial function of PD-VH+ with 5-HT$_{2A}$ receptor availability, we applied a voxel-based correlation method (uncorrected P value <0.005; with an extent threshold [k] of at least 20 contiguous voxels).

doi:10.1002/mdc3.12466

Results

PD Clinical Features

The demographics and clinical characteristics of each group are provided in Table 1.[33] There was no significant difference between the 3 groups with respect to age, years of education, or MoCA scores. The PD-VH+ group had higher depression scores than the PD-VH− group and the normal control group (H = 12.5; $P = 0.002$). There was no significant difference between the PD-VH− and PD-VH+ groups with respect to PD motor disability, including disease duration, daily levodopa (L-dopa)-equivalent dose (LEDD), ON-drug Hoehn and Yahr stage, or ON-drug UPDRS motor part (part III) scores. The groups were well matched with respect to estimated premorbid intellectual ability based on a reading test. None of the patients were taking antipsychotic medications. Because of the common association of depression and anxiety with PD, 3 patients were taking antidepressants at the time of the study, including 1 in the PD-VH− group (a serotonin and norepinephrine reuptake inhibitor) and 2 in the PD-VH+ group (a selective serotonin reuptake inhibitor).

All 11 participants who had PD with VHs had stable, well-formed VHs (mean duration of VHs, 3.5 years; range, 1–10 years). As expected, the PD-VH+ group had significantly higher NPI total scores (U = 13.0; $P = 0.009$) and NPI hallucination subscale scores (U = 4; $P = 0.0004$) as well as PPQ total scores (U = 12; $P = 0.014$) and PPQ-hallucination subscale scores (U = 0; $P = 0.0001$) compared with the PD-VH− group.

Cognitive Profile in Patients Who Had PD With and Without VHs

In the PD-VH+ group, we tested the relationship between the severity of VHs using the NPI hallucinations subscore and a global cognitive screen using the MoCA total score. There was a significant negative correlation between hallucination severity and MoCA scores ($r = -0.71$; $P = 0.014$) (Fig. 1); a higher level of hallucinations was associated with lower overall cognitive function in these nondemented patients with PD.

Neuropsychological tests using z-transformed outcome scores were compared across the 3 groups (Table 2). We observed group effects on measures of executive function (i.e., Trail Making Test B-A [H = 7.61; $P = 0.022$]), visual-perceptual function (i.e., JLO [H = 6.61; $P = 0.04$]) and FRT [H = 9.52; $P = 0.009$]), and verbal recognition memory (i.e., RMT-words [H = 6.44; $P = 0.04$]). In the post-hoc analysis, scores were significantly lower on Trail Making Test B-A (U = 15.0; $P = 0.004$; Dunn-Sidak corrected), the JLO (U = 20.0; $P = 0.01$; Dunn-Sidak corrected), and the FRT (U = 12.50; $P = 0.002$; Dunn-Sidak corrected) in the PD-VH+ group compared with age-matched controls but not compared with the PD-VH− group. The PD-VH− group had lower RMT-word scores compared with controls (U = 15.50; $P = 0.03$). The difference between the groups in RMT-words scores did not pass the correction of multiple comparisons (Dunn-Sidak method), although it still trended toward the level significance. The PD-VH+ group had greater self-rated symptoms of executive dysfunction on the FrSBe relative to the PD-VH− group (U = 16.0; $P = 0.04$; Dunn-Sidak corrected). There were no other significant changes in any cognitive tests between the PD-VH+ and PD-VH− groups.

TABLE 1 Demographic and clinical characteristics

Characteristic	Mean Score ± SD			*P* value
	Controls	PD-VH−	PD-VH+	
No. of patients	10	8	11	
Percentage of men	20	100[a]	60[b]	0.003
Age, y	64.2 ± 7.1	63.0 ± 6.4	64.1 ± 9.1	0.75
Education, y	18.5 ± 1.8	15.9 ± 2.9	16.2 ± 2.5	0.09
MoCA score	27.9 ± 1.9	26.9 ± 1.9	26.0 ± 1.8	0.16
Estimated premorbid IQ	117.8 ± 5.2	116.33 ± 7.8	112.9 ± 9.6	0.44
BDI	3.4 ± 3.8	7.9 ± 6.5	13.1 ± 6.8[a,b]	0.002
NPI total score[a]	—	2.1 ± 4.6	13.7 ± 10.6	0.009
NPI hallucination subscale score[a]	—	0 ± 0	4.27 ± 2.7	0.0004
PPQ total score[b]	—	2.0 ± 1.6	4.9 ± 2.3	0.014
PPQ hallucination subscale score[b]	—	0 ± 0	2.2 ± 0.9	0.0001
Disease duration, y	—	6.7 ± 4.0	8.7 ± 4.6	0.71
MDS-UPDRS III	—	14.3 ± 7.0	24.5 ± 15.1	0.55
H&Y	—	1.87 ± 0.4	2.09 ± 0.7	0.72
LEDD	—	687.1 ± 437.0	965.2 ± 677.3	0.27
Antidepressant drug use	—	Venlafaxine, n = 1	Citalopram, n = 1	

SD, standard deviation; PD-VH−, Parkinson's disease without visual hallucinations; PD-VH+, Parkinson's disease with visual hallucinations; MoCA, Montreal Cognitive Assessment; BDI, Beck Depression Inventory; NPI, Neuropsychiatry Inventory; PPQ, Parkinson Psychosis Questionnaire; MDS-UPDRS III, on-drug Unified Parkinson's Disease Rating Scale, Part III (motor part); H&Y, on-drug Hoehn and Yahr rating scale; LEDD, total levodopa equivalent daily dose (see Tomlinson et al.,[33]).
[a]Compared with normal controls.
[b]Compared with patients who had PD-VH−.

doi:10.1002/mdc3.12466

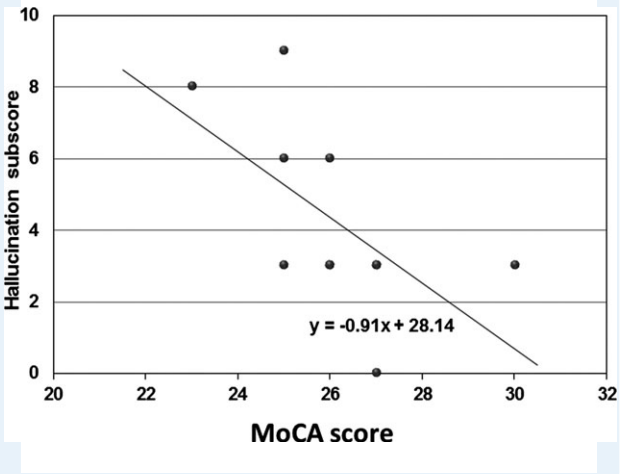

Figure 1 Correlation between the Neuropsychiatric Inventory Hallucination subscore and the Montreal Cognitive Assessment (MoCA) total score in patients who had Parkinson's disease with visual hallucinations (Pearson correlation coefficient [r] = −0.61; P = 0.048; 2-tailed).

Among the cognitive composite scores, there was a significant group effect for the executive domain (H = 7.99; P = 0.018), with the PD-VH+ group exhibiting significantly lower scores than the normal control group (U = 18.0; P = 0.009; Dunn-Sidak corrected). There were no significant group differences in the other domain composite scores.

With respect to inferotemporal cortical function, there were significant group effects for the LIT (H = 10.16; P = 0.006) but not for the RIT (H = 4.35; P = 0.12). In the post-hoc analysis, PD-VH− patients scored significantly lower than normal controls on the LIT measure (U = 4.0; P = 0.002; Dunn-Sidak corrected). The PD-VH+ group did not differ from the normal control group or the PD-VH− group on this composite score. Laterality effects within each patient group were examined by comparing RIT and LIT scores using a nonparametric Wilcoxon test. The PD-VH+ group exhibited significantly lower scores on the RIT composite compared with the LIT composite (z = −2.76; P = 0.006). In contrast, neither the PD-VH− group (z = −0.11; P = 0.92) nor the normal control group (z = −1.79; P = 0.074) showed a significant difference between the right and left composite scores.

5-HT$_{2A}$ Receptor PET Imaging Results

The injected [^{18}F]setoperone dose (4.92 ± 0.33 mCi/μmol vs. 4.87 ± 0.29 mCi/μmol; P = 0.78) and specific activity (2605.49 ± 1819.9 vs. 2884.28 ± 2251.69; P = 0.74) between the 2 PD groups were the same.

Comparisons between the PD-VH+ and PD-VH− groups disclosed BP differences in several brain regions. The PD-VH+

TABLE 2 Neuropsychological tests

Test	Mean Score ± SD			*P* value
	Controls	PD-VH−	PD-VH+	
Wechsler Test of Adult Reading	117.80 ± 5.16	116.25 ± 8.28	113.30 ± 9.15	0.426
Brief Test of Attention	0.27 ± 0.35	0.13 ± 0.54	0.13 ± 0.28	0.680
Trail Making Test A	−0.53 ± 1.72	−1.49 ± 1.56	−1.83 ± 1.47	0.174
Trail Making Test B-A	0.46 ± 1.48	−0.31 ± 1.55	−2.59 ± 3.73[a]	0.022
Boston Naming Test	0.74 ± 0.82	0.66 ± 0.67	0.42 ± 0.83	0.644
D-KEFS, letter fluency	1.28 ± 0.93	0.22 ± 1.31	0.28 ± 1.05	0.065
D-KEFS, category fluency	0.85 ± 1.38	−0.21 ± 0.94	−0.06 ± 1.06	0.188
RCFT, copy	−0.67 ± 0.92	−1.16 ± 1.10	−1.07 ± 1.10	0.473
JLO	0.42 ± 1.18	−0.34 ± 1.12	−1.09 ± 1.34[a]	0.037
VOSP, total	0.27 ± 0.86	0.19 ± 0.67	−0.29 ± 0.94	0.343
FRT	0.85 ± 0.82	0.20 ± 1.07	−0.70 ± 0.93[a]	0.009
CVLT, total learning trials	0.97 ± 1.03	−0.08 ± 1.25	0.29 ± 1.10	0.114
CVLT, long-delay free recall	0.45 ± 0.73	0.00 ± 0.85	0.68 ± 0.84	0.187
CVLT, total learning slope	0.02 ± 0.10	−0.19 ± 0.53	0.32 ± 0.93	0.345
RMT, words	1.39 ± 0.47	0.20 ± 1.16	0.91 ± 0.67	0.040
RMT, faces	0.27 ± 1.10	−0.33 ± 1.13	−0.50 ± 1.51	0.491
Stroop interference	0.29 ± 0.64	−0.12 ± 0.44	−0.37 ± 0.64	0.223
CALT, working memory error	0.21 ± 0.90	−0.05 ± 0.97	−0.82 ± 1.94	0.291
VVT, correct shifts	−0.53 ± 0.93	−1.63 ± 1.53	−1.38 ± 2.07	0.393
FrSBe Se, executive dysfunction	NA	−0.22 ± 0.92	1.41 ± 1.56[b]	0.044
FrSBe Fe, executive dysfunction	NA	0.50 ± 1.07	1.83 ± 1.38	0.056

SD, standard deviation; PD-VH−, Parkinson's disease without visual hallucinations; PD-VH+, Parkinson's disease with visual hallucinations; D-KEFS, Delis-Kaplan Executive Function System verbal fluency subtest; RCFT, Rey-Osterrieth Complex Figure Test; JLO, Judgment of Line Orientation; VOSP, Visual Object and Space Perception; FRT, Benton Facial Recognition Test; CVLT, California Verbal Learning Test; RMT, Recognition Memory Test; CALT, Conditional Associative Learning Test; VVT, Visual Verbal Test; FrSBe Se, Frontal Systems Behavior Scale-Self Rating; NA, not applicable; FrSBe Fe, Frontal Systems Behavior Scale-family rating.
All scores are shown as z scores (mean = 0, SD = 1), with the exception of Estimated Full-Scale IQ scores, which are shown as standardized scores (mean = 100, SD = 15).
[a]Compared with normal controls.
[b]Compared with patients who had PD-VH−.

doi:10.1002/mdc3.12466

group had decreased BP in the right insula, bilateral DLPFC, right orbitofrontal cortex, right middle temporal gyrus (mTG), and right fusiform gyrus (Fig. 2A, Table 3). The extracted BP values confirmed the differences in 5-HT$_{2A}$ receptor availability between the PD-VH+ and PD-VH− groups (Fig. 2B).

In the psychometric correlation analysis, some tests associated with visuoperceptual function were correlated with 5-HT$_{2A}$ binding. In particular, the FRT score showed a significant positive correlation with [^{18}F]setoperone BP in the right anterior cingulate cortex (ACC), left DLPFC, and inferior temporal gyrus (Fig. 3A, Table 4). The VOSP total score was also significantly positively correlated with [^{18}F]setoperone BP, mainly in the right ACC and other prefrontal brain regions (Fig. 3B, Table 4). These correlations implied that lower (worse) visuoperceptual function was associated with reduced binding in prefrontal regions. A positive relationship was noticed as well between the CVLT learning slope and [^{18}F]setoperone BP in the left frontal region, including the DLPFC, the precentral and postcentral gyri, and the insular region (Fig. 3C, Table 4), implying an association also with memory and learning functions. However, negative correlations were also observed between 5-HT$_{2A}$ binding and RCFT copy scores in the middle/inferior temporal gyrus (Fig. 4A, Table 4) and JLO scores in the occipital cortex (Brodmann area [BA] 18), regions considered part of the ventral visual stream within the bottom-up information processing network (Fig. 4B, Table 4).

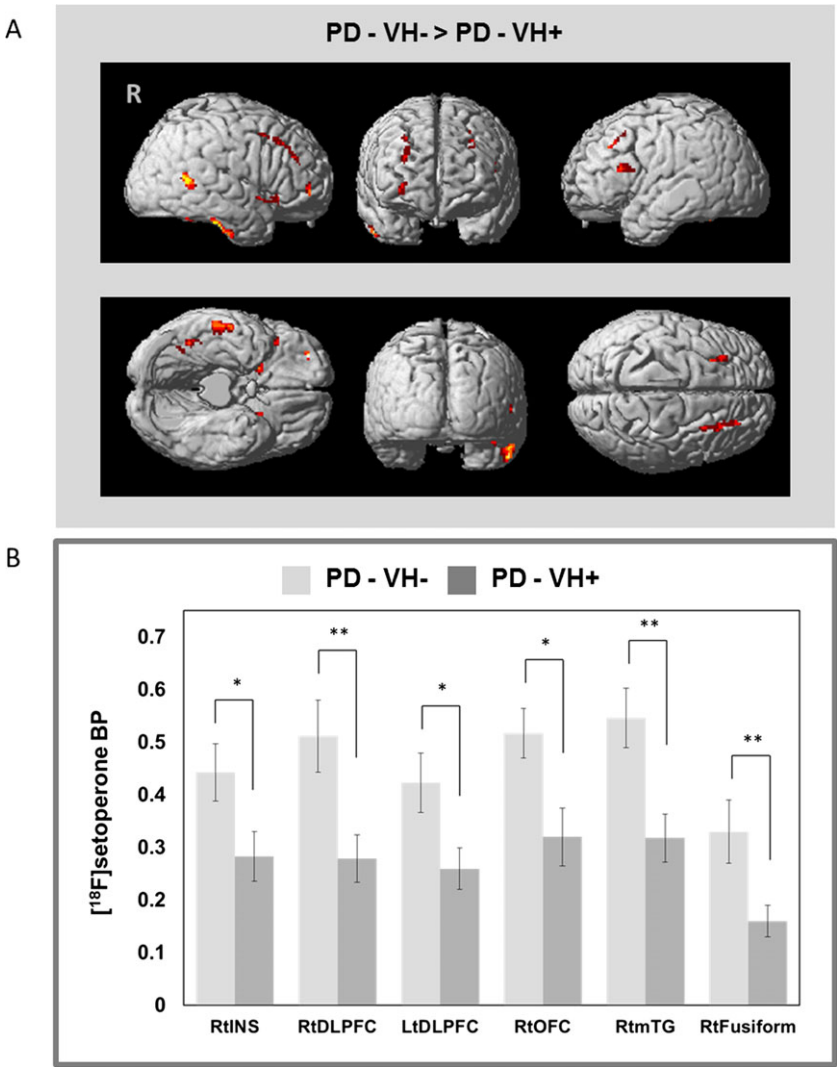

Figure 2 Results from statistical analyses using SPM software comparing patients who had Parkinson's disease (PD) with and without visual hallucinations (PD-VH+ and PD-VH−, respectively). (A) Rendered brain images indicate reductions in binding potential (BP) among patients with PD-VH+. (B) Bars display BPs extracted from statistically significant clusters in the SPM analysis. Decreased [^{18}F] setoperone BP was observed in the right insula (RtINS), bilateral dorsolateral prefrontal cortex (RtDLPFC), right orbitofrontal cortex (RtOFC) and middle temporal gyrus (RtmTG), and fusiform gyrus (RtFusiform). Error bars represent the standard errors of the mean. *$P < 0.05$; **$P < 0.01$ (Student t test).

doi:10.1002/mdc3.12466

The LEDD had a significant negative correlation with 5-HT_{2A} level in the right mTG ($r = -0.47$; $P = 0.04$). Lower 5-HT_{2A} receptor availability in the right DLPFC was associated with higher depression scores ($r = -0.55$; $P = 0.015$).

Discussion

This study adds to the growing evidence of a role for 5-HT_{2A} receptors in the pathophysiology of VHs in PD. In the PD-

TABLE 3 Brain regions that had significantly decreased [^{18}F]setoperone (serotonin 2A receptor) binding potential in patients who had Parkinson's disease with visual hallucinations compared with those who had Parkinson's disease without visual hallucinations

Laterality	Region	BA	Coordinate*			T value	SVC *P* value	No. of clusters
			X	Y	Z			
Left	Inferior frontal gyrus	BA 45	−46	22	15	4.21	0.007	29
Right	Middle temporal gyrus	BA 39/22	50	−50	12	3.80	0.02	78
Right	Middle frontal gyrus (DLPFC)	BA 9	30	27	37	3.64	0.02	64
Right	Fusiform gyrus	BA 20	55	−23	−28	3.31	0.03	89
Right	Insula cortex	BA 13	42	9	−7	3.08	0.04	26
Left	Middle frontal gyrus	BA 9	−28	28	35	3.04	0.05	28
Right	Orbitofrontal cortex	BA 10	30	50	−3	3.21	0.04	21

BA, Brodmann area; SVC, small-volume correction; DLPFC, dorsolateral prefrontal cortex.
*The Talairach coordinates X, Y, and Z describe the maxima within a cluster; an SVC was applied using a reporting criterion of $P < 0.05$ for multiple comparisons.

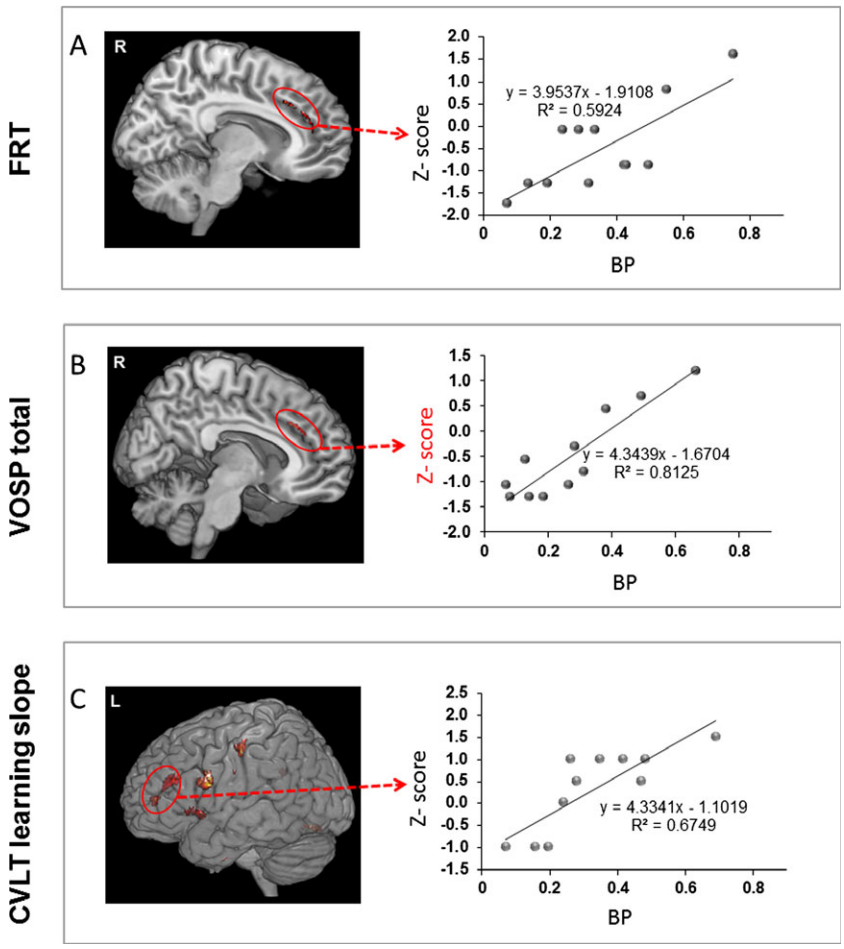

Figure 3 Positive correlation between [^{18}F]setoperone binding potential (BP) and cognitive tasks, including (A) the Benton Facial Recognition Test (FRT), (B) the Visual Object and Space Perception (VOSP) battery total score, and (C) the California Verbal Learning Test (CVLT) learning slope.

doi:10.1002/mdc3.12466

TABLE 4 Correlations between [^{18}F]setoperone binding potential and neuropsychological tests according to brain regions in patients who had Parkinson's disease with visual hallucinations

Test	Region	BA	Coordinate*			T value	No. of clusters
			X	Y	Z		
Positive correlation							
FRT							
Right	Anterior cingulate gyrus	BA 32	6	40	15	3.90	33
Left	Middle frontal gyrus	BA 22	−38	41	5	3.84	28
		BA 9	−36	29	30	3.77	24
Left	Supramarginal gyrus	BA 40	−55	−22	21	3.69	28
Left	Inferior temporal gyrus	BA 20	−57	−45	−8	3.54	51
Left	Precentral gyrus	BA 44	−50	11	20	3.53	28
VOSP total score							
Right	Anterior cingulate gyrus	BA 32	6	34	22	3.87	53
CVLT learning slope							
Left	Lingual gyrus	BA 18	−17	−72	−10	1.66	55
Left	Middle frontal gyrus	BA 9	−44	9	25	4.45	106
		BA 46	−40	34	19	3.53	142
Left	Precentral gyrus	BA 4	−42	−15	43	4.30	64
Left	Insula	BA 13	−37	11	−6	3.64	94
Left	Posterior cingulate gyrus	BA 31	−6	−45	26	3.40	45
Negative correlation							
JLO							
Bilateral	Middle occipital gyrus (cuneus)	BA 18/19	6	−92	10	3.19	163
RCFT copy							
Right	Middle temporal gyrus	BA 21	58	−25	−9	4.69	292
		BA 22	48	−53	16	4.68	77
Right	Middle frontal gyrus	BA 10	35	50	−8	4.18	65
Right	Postcentral gyrus	BA 43	57	−15	19	3.57	66

BA, Brodmann area; FRT, Benton Facial Recognition Test; VOSP, Visual Object and Space Perception; CVLT, California Verbal Learning Test; JLO, Judgment of Line Orientation; RCFT, Rey-Osterrieth Complex Figure Test.
*The Talairach coordinates describe the maxima within a cluster.

VH+ group, we observed a significant positive correlation of visuoperceptual dysfunction with 5-HT$_{2A}$ receptor availability mainly in right prefrontal regions (i.e., ACC, DLPFC), implying that lower visuoperceptual function was associated with reduced binding in brain regions associated with "top-down" control. These observations add further insights to the current belief that VHs in PD may be a result of impaired inhibition in the top-down network (i.e., orbitofrontal prefrontal cortex, DLPFC, and insula), accounting for worse executive function, attention, and limbic system function,[7] interfering with the emotional/cognitive processing of visual information.

In contrast, negative psychometric correlations of visuoperceptual function with 5-HT$_{2A}$ receptor binding were observed in the middle/inferior temporal gyrus and the occipital cortex, regions considered part of the ventral visual stream within the bottom-up information processing network. The inferior temporal cortex and other cortical regions constitute the "ventral visual processing stream" involved in visual processing of complex features related to recognition of people and objects,[8,34] thus making this region a likely candidate for mediating the typical complex VHs characteristic of PD. Prior neuroimaging studies have also emphasized the importance of these cortical regions in PD-VH+.[35–37] Other cognitive associations with 5-HT$_{2A}$ receptors were suggested. Thus a positive relationship was noticed between the CVLT learning slope and 5-HT$_{2A}$ receptor availability in the left DLPFC, implying an association also with memory and learning functions.[38]

Overall, we demonstrated that the severity of hallucinations in PD is related to lower general cognitive function. Similarly, previous studies have also reported lower scores[39] and steeper cognitive decline on measures of general cognitive function in patients who had PD with VHs.[40] However, when comparing individual cognitive domains, our study showed that, in nondemented patients with PD, there may not be major significant differences between those with and without VHs. Impaired executive function[41] and visuoperceptual function[42] in PD-VH+ have been previously reported. However, in those prior studies, the clinical stage of the PD-VH+ group was not matched with that of the control PD group; thus, differences in cognitive function could be due to effects of ongoing disease pathology rather than VHs. In our study, nondemented patients with PD-VH− had performance levels that were equivalent to those in non-PD, age-matched controls; whereas patients with PD-VH+ had significant differences compared with age-matched controls. This indicates that the presence of VHs per se is not associated with significant impairment of cognitive function in individuals with PD. However, progression of cognitive decline may be faster in those with PD-VH+, especially in tasks that require visuospatial process and executive modulation. To date, few longitudinal studies have evaluated nondemented patients with PD to determine effect of VHs on cognition. One study evaluated patients who had PD with mild cognitive impairment (PD-MCI); for example, in a longitudinal study, Gasca-Salas et al.[36] showed that patients who had PD-MCI and VHs exhibited more severe cerebral hypometabolism

doi:10.1002/mdc3.12466

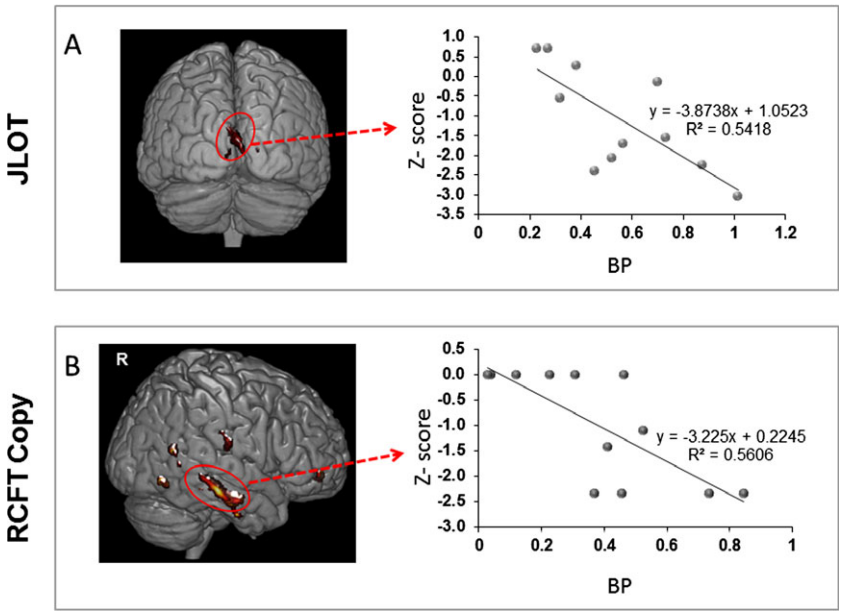

Figure 4 Negative correlation between [^{18}F]setoperone binding potential (BP) and cognitive tasks on (A) the Judgment of Line Orientation Test (JLOT) score and (B) the Rey Complex Figure Test (RCFT) copy score.

and a higher rate of progression to dementia than VH-negative patients with PD-MCI. Further studies are needed to evaluate longitudinal progression and associated cognitive function contemplating psychiatric symptoms in patients with PD-VH+ over time.

We also showed a significant decline of right inferotemporal region-dependent function compared with left inferotemporal region-dependent function in PD-VH+. Right ventral visual hemisphere-oriented laterality effects on visuoperceptual function have been previously noted.[43] In addition, functional laterality of temporal lobe function in PD with VHs has been reported, including increases in blood flow in the temporal cortex[44] and hypometabolism in temporoparietal regions limited to the right hemisphere.[36]

The study confirmed links between depression and 5-HT$_{2A}$ receptors. The PD-VH+ group had higher depression scores (using the BDI) than both the control group and the PD-VH− group, a finding in keeping with previous studies.[45,46] However, we did not find any significant correlation between the level of hallucination and BDI scores. Instead, there was lower 5-HT$_{2A}$ receptor availability in the right DLPFC, a cortical region known to play an important role in mood modulation,[47,48] that correlated with higher depression scores ($r = -0.61$; $P = 0.006$). Based on this, VHs are not a direct factor in depression, but decreased 5-HT$_{2A}$ levels in the prefrontal region may explain the level of depression in patients with PD-VH+. Our additional analysis excluding patients who were taking antidepressant medication confirmed that antidepressant medication did not affect our observations. Results of parametric [^{18}F]setoperone PET image analysis showed no major changes; we found an additional significant cluster in the left precentral gyrus (BA 6) (Fig. S1). This brain region is related to motor function rather than function likely linked to VHs. We also conducted group analysis of neurocognitive tests after excluding the 2 patients on antidepressant medication. There were no major changes from the results of our original analysis. Among the cognitive composite scores, executive domain remained significant ($H = 8.94$; $P = 0.01$). With respect to individual neurocognitive tests, only JLO did not pass the statistical inference, but there was a trending level of significance ($P = 0.051$); all other tests showed significant group differences consistent with our original analysis.

The present findings are in contrast with our previous observations of increased [^{18}F]setoperone 5-HT$_{2A}$ receptor PET[6] in PD-VH+. In our previous study, however, cognitive functioning was not formally evaluated; patients were assessed with the MoCA for screening purposes only. These study differences implicate the influence of altered cognitive processing on serotonergic neurotransmission. Changes in 5-HT$_{2A}$ receptor binding, as measured using PET, reflect changes in actual receptor number that can be reduced due to loss of synaptic receptors secondary to neurodegeneration or up-regulation/down-regulation caused by lower or higher levels of endogenous ligands (5-HT or dopamine), respectively. The degree of neurodegeneration with consequent atrophy and loss of 5-HT$_{2A}$ receptor (i.e., disease severity) between the 2 cohorts overall is similar. In the prior study, although disease severity and duration were

doi:10.1002/mdc3.12466

not statistically matched, patients with PD-VH+ had significantly higher UPDRS III scores and longer disease duration than those with PD-VH−. In our current study, although nonsignificant, the PD-VH+ group also had higher motor disability according to MDS-UPDRS III scores, compared with the PD-VH− group. In both cohorts, the PD-VH+ groups had overall similar scores for disease severity and duration. To explore the possible effect of greater disease burden (and consequent neurodegeneration with 5-HT$_{2A}$ loss), we performed a post-hoc subanalysis using gray matter cortical thickness as a surrogate measure (with a prior cohort of normal controls) and showed significant cortical thinning in the right prefrontal, temporal, and fusiform cortical regions in the PD-VH+ group compared with the PD-VH− group (data not shown).

One factor that may have altered 5-HT$_{2A}$ binding is the L-dopa dose; thus, the average total LEDD was higher in the PD-VH+ group (mean LEDD, 965 mg/day) in our current study compared with the prior study (mean LEDD, 778 mg/day), although, in both studies, LEDD levels did not differ between the groups with and without VHs. There is evidence that, in advancing PD, due to loss of nigrostriatal dopamine terminals, conversion of L-dopa to dopamine occurs in relatively preserved 5-HT terminals in the striatum[49]—and possibly in other frontal cortical projection regions.[50] Thus, 1 hypothesis is that higher L-dopa levels converted to dopamine could possibly lead to increased levels of synaptic dopamine, which may bind to postsynaptic 5-HT$_{2A}$ receptors and result in the down-regulation of 5-HT$_{2A}$ receptor numbers. In addition, the VH−PD+ group had an overall higher LEDD and a significant negative correlation between LEDD and BP in the right mTG, suggesting a potential interaction between 5-HT$_{2A}$ receptor availability and dopaminergic medication.

The small sample size and male dominance in our PD-VH− group represent limitations of our study, and further investigations are needed to validate current findings using larger sex-matched samples. We attempted to match the 2 groups of patients who had PD with and without VHs as far as possible for confounding factors known to affect 5-HT$_{2A}$ binding and cognitive profile, including age, duration of PD, parkinsonian disability using UPDRS part III, handedness, and drugs. The male dominance of the non-VH group was unfortunate; but comparisons between clinical and imaging variables for only men with PD (VH+ vs. VH−) did not show any differences compared with the full analysis set (data not shown). Thus, we do not believe that this sex imbalance impacted the findings. In addition, recent studies have suggested that the known age-related decline in cortical 5-HT$_{2A}$ receptor binding is not affected by sex.[51]

In summary, brain regions associated with cognitive performance may be significantly impaired in patients who have PD with VHs and contribute to the development of these complications. The observed impairment in visuoperceptual and executive function and associated cortical regions in patients who have PD-VH+ may interfere with serotonergic neurotransmission in prefrontal and ventral visual regions that play a role in VHs.

Author Roles

1. Research Project: A. Conception, B. Organization, C. Execution; 2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique; 3. Manuscript Preparation: A. Writing the First Draft, B. Review and Critique.

S.S.C.: 1B, 1C 2A, 2B, 2C, 3A, 3B
A.P.S.: 1A, 2B, 2C, 3A, 3B
S.D.-C.: 1A, 1B, 2A, 2B, 2C, 3A, 3B
M.Z.: 1A, 1B, 2C, 3B
A.-C. V.: 1C, 2C, 3B
V.B.: 1C, 2C, 3B
C.C.A.: 1C, 2C, 3B
M.C.: 1C
P.M.R.: 2B, 2C, 3B
S.H.: 3B
S.H.F.: 1A, 1B, 2A, 2C, 3A, 3B

Acknowledgements

Generous support from Dr. and Mrs. W Bentham (Toronto Western Foundation) to Susan H. Fox for clinical studies is gratefully acknowledged. The assistance of Dr. Naomi Visanji with statistical analysis and Dr. Melanie Cohn with neuropsychological studies is greatly appreciated. As always, the enthusiasm and help of patients and participants was greatly appreciated.

Disclosures

Ethical Compliance Statement: We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

Funding Sources and Conflicts of Interest: The authors report no conflicts of interest.

Financial Disclosures for the previous 12 months: Antonio P. Strafella received funding for research from the Canadian Institutes of Health Research and the National Parkinson Foundation; the has been employed with the Department of Medicine, University Health Network, Toronto. Sarah Duff-Canning has received funding for research from the Canadian Institutes of Health Research. Veronica Bruno received a Clinical Research Fellowship sponsored by the American Academy of Neurology, the American Brain Foundation, and Allergan. Marion Criaud received a Research Fellowship sponsored by the Center for Addiction and Mental Health, Toronto. Sylvain Houle has received research funding from the US National Institutes of Health, the Canada Foundation for Innovation, the Canadian Institutes for Health Research, and the Ontario Ministry of Industry and Research Innovation and has been employed by the Center for Addiction and Mental Health and the University of Toronto. Susan H. Fox has served on the advisory boards of Orion and C2N and as a consultant to Astra Zeneca; she has been employed with the Department of Medicine, University Health Network, Toronto; has signed contracts

doi:10.1002/mdc3.12466

with Adamas, Merck, Kyowa, and Avanir; has received honoraria from Teva and Novartis; has received royalties from Oxford University Press; and has been awarded grants from the National Institutes of Health, Parkinson Society Canada, and the Michael J. Fox Foundation for Parkinson's Research. San Soo Cho, Mateusz Zurowski, Camila C. Aquino, and Pablo M. Rusjan reported no sources of funding and no conflicts of interest.

References

1. Pappert EJ, Goetz CG, Niederman FG, Raman R, Leurgans S. Hallucinations, sleep fragmentation, and altered dream phenomena in Parkinson's disease. *Mov Disord* 1999;14:117–121.
2. Fenelon G, Mahieux F, Huon R, Ziegler M. Hallucinations in Parkinson's disease: prevalence, phenomenology and risk factors. *Brain* 2000;123(Pt 4):733–745.
3. Manford M, Andermann F. Complex visual hallucinations. Clinical and neurobiological insights. *Brain* 1998;121(Pt 10):1819–1840.
4. Merims D, Shabtai H, Korczyn AD, Peretz C, Weizman N, Giladi N. Antiparkinsonian medication is not a risk factor for the development of hallucinations in Parkinson's disease. *J Neural Transm* 2004;111:1447–1453.
5. Meltzer HY. Dimensions of outcome with clozapine. *Br J Psychiatry Suppl* 1992;17:46–53.
6. Ballanger B, Strafella AP, van Eimeren T, Zurowski M, Rusjan PM, Houle S, Fox SH. Serotonin 2A receptors and visual hallucinations in Parkinson disease. *Arch Neurol* 2010;67:416–421.
7. Collerton D, Perry E, McKeith I. Why people see things that are not there: a novel perception and attention deficit model for recurrent complex visual hallucinations. *Behav Brain Sci* 2005;28:737–757; discussion 757–794.
8. Ffytche DH, Howard RJ. The perceptual consequences of visual loss: 'positive' pathologies of vision. *Brain* 1999;122(Pt 7):1247–1260.
9. Watanabe H, Senda J, Kato S, et al. Cortical and subcortical brain atrophy in Parkinson's disease with visual hallucination. *Mov Disord* 2013;28:1732–1736.
10. Pagonabarraga J, Soriano-Mas C, Llebaria G, Lopez-Sola M, Pujol J, Kulisevsky J. Neural correlates of minor hallucinations in non-demented patients with Parkinson's disease. *Parkinsonism Relat Disord* 2014;20:290–296.
11. Yao N, Cheung C, Pang S, et al. Multimodal MRI of the hippocampus in Parkinson's disease with visual hallucinations. *Brain Struct Funct* 2016;221:287–300.
12. Franciotti R, Delli Pizzi S, Perfetti B, et al. Default mode network links to visual hallucinations: a comparison between Parkinson's disease and multiple system atrophy. *Mov Disord* 2015;30:1237–1247.
13. Ravina B, Marder K, Fernandez HH, et al. Diagnostic criteria for psychosis in Parkinson's disease: report of an NINDS, NIMH work group. *Mov Disord* 2007;22:1061–1068.
14. Wechsler D. *Wechsler Test of Adult Reading: Manual*. San Antonio, TX: The Psychological Corporation; 2001.
15. Schretlen D. *The Brief Test of Attention*. Lutz, Fla: Psychological Assessment Resources; 1989.
16. Strauss E, Sherman EMS, Spreen O, Spreen O. *A Compendium of Neuropsychological Tests: Administration, Norms, and Commentary*. 3rd ed. New York: Oxford University Press; 2006.
17. Delis DC, Kaplan E, Kramer JH. *The Delis-Kaplan Executive Function System: Examiner's Manual*. San Antonio, TX: The Psychological Corporation; 2001.
18. Williams BW, Mack W, Henderson VW. Boston Naming Test in Alzheimer's disease. *Neuropsychologia* 1989;27:1073–1079.
19. Warrington EK, James M. *The Visual Object and Space Perception Battery*. Burry St. Edmunds, UK: Thames Valley Test Company; 1991.
20. Benton AL. *Contributions to Neuropsychological Assessment: A Clinical Manual*. 2nd ed. New York: Oxford University Press; 1994.
21. Meyers J, Meyers K. *Rey Complex Figure Test and Recognition Trial—Professional Manual*. Odessa, FL: Psychological Assessment Resources; 1995.
22. Mitrushina MN. *Handbook of Normative Data for Neuropsychological Assessment*. 2nd ed. New York: Oxford University Press; 2005.
23. Delis DC, Kramer JH, Kaplan E, Ober BA. *California Verbal Learning Test: Adult Version*. San Antonio, TX: The Psychological Corporation; 1987.
24. Warrington E. *Recognition Memory Test Manual*. Windsor, UK: NFER-Nelson; 1984.
25. Golden CJ, ed. *The Stroop Color and Word Test: A Manual for Clinical and Experimental Uses*. Chicago, IL: Stoelting; 1978.
26. Taylor AE, Saint-Cyr JA, Lang AE. Memory and learning in early Parkinson's disease: evidence for a "frontal lobe syndrome". *Brain Cogn* 1990;13:211–232.
27. Cools R, Barker RA, Sahakian BJ, Robbins TW. Mechanisms of cognitive set flexibility in Parkinson's disease. *Brain* 2001;124(Pt 12):2503–2512.
28. Grace J, Malloy PF. *Frontal Systems Behavior Scale Professional Manual*. Odessa, FL: Psychological Assessment Resources; 2001.
29. Ayutyanont N, Langbaum JB, Hendrix SB, et al. The Alzheimer's prevention initiative composite cognitive test score: sample size estimates for the evaluation of preclinical Alzheimer's disease treatments in presenilin 1 E280A mutation carriers. *J Clin Psychiatry* 2014;75:652–660.
30. Crane PK, Carle A, Gibbons LE, et al. Development and assessment of a composite score for memory in the Alzheimer's Disease Neuroimaging Initiative (ADNI). *Brain Imaging Behav* 2012;6:502–516.
31. Rusjan P, Mamo D, Ginovart N, et al. An automated method for the extraction of regional data from PET images. *Psychiatry Res* 2006;147:79–89.
32. Lammertsma AA, Hume SP. Simplified reference tissue model for PET receptor studies. *Neuroimage* 1996;4(3 Pt 1):153–158.
33. Tomlinson CL, Stowe R, Patel S, Rick C, Gray R, Clarke CE. Systematic review of levodopa dose equivalency reporting in Parkinson's disease. *Mov Disord* 2010;25:2649–2653.
34. Mishkin M, Ungerleider LG, Macko KA. Object vision and spatial vision: two cortical pathways. *Trends Neurosci* 1983;6:414–417.
35. Goldman JG, Stebbins GT, Dinh V, Bernard B, Merkitch D, deToledo-Morrell L, Goetz CG. Visuoperceptive region atrophy independent of cognitive status in patients with Parkinson's disease with hallucinations. *Brain* 2014;137(Pt 3):849–859.
36. Gasca-Salas C, Clavero P, García-García D, Obeso JA, Rodríguez-Oroz MC. Significance of visual hallucinations and cerebral hypometabolism in the risk of dementia in Parkinson's disease patients with mild cognitive impairment. *Hum Brain Mapp* 2016;37:968–977.
37. Boecker H, Ceballos-Baumann AO, Volk D, Conrad B, Forstl H, Haussermann P. Metabolic alterations in patients with Parkinson disease and visual hallucinations. *Arch Neurol* 2007;64:984–988.
38. Tulving E, Kapur S, Craik FI, Moscovitch M, Houle S. Hemispheric encoding/retrieval asymmetry in episodic memory: positron emission tomography findings. *Proc Natl Acad Sci USA* 1994;91:2016–2020.
39. Sanchez-Ramos JR, Ortoll R, Paulson GW. Visual hallucinations associated with Parkinson disease. *Arch Neurol* 1996;53:1265–1268.
40. Ibarretxe-Bilbao N, Ramirez-Ruiz B, Junque C, et al. Differential progression of brain atrophy in Parkinson's disease with and without visual hallucinations. *J Neurol Neurosurg Psychiatry* 2010;81:650–657.
41. Barnes J, Boubert L. Executive functions are impaired in patients with Parkinson's disease with visual hallucinations. *J Neurol Neurosurg Psychiatry* 2008;79:190–192.
42. Barnes J, Boubert L, Harris J, Lee A, David AS. Reality monitoring and visual hallucinations in Parkinson's disease. *Neuropsychologia* 2003;41:565–574.
43. Tranel D, Vianna E, Manzel K, Damasio H, Grabowski T. Neuroanatomical correlates of the Benton Facial Recognition Test and Judgment of Line Orientation Test. *J Clin Exp Neuropsychol* 2009;31:219–233.
44. Oishi N, Udaka F, Kameyama M, Sawamoto N, Hashikawa K, Fukuyama H. Regional cerebral blood flow in Parkinson disease with nonpsychotic visual hallucinations. *Neurology* 2005;65:1708–1715.
45. Ramirez-Ruiz B, Junque C, Marti MJ, Valldeoriola F, Tolosa E. Neuropsychological deficits in Parkinson's disease patients with visual hallucinations. *Mov Disord* 2006;21:1483–1487.
46. Hepp DH, da Hora CC, Koene T, et al. Cognitive correlates of visual hallucinations in non-demented Parkinson's disease patients. *Parkinsonism Relat Disord* 2013;19:795–799.

doi:10.1002/mdc3.12466

47. Chen J, Zhou C, Wu B, et al. Left versus right repetitive transcranial magnetic stimulation in treating major depression: a meta-analysis of randomised controlled trials. *Psychiatry Res* 2013;210:1260–1264.

48. Stern WM, Tormos JM, Press DZ, Pearlman C, Pascual-Leone A. Antidepressant effects of high and low frequency repetitive transcranial magnetic stimulation to the dorsolateral prefrontal cortex: a double-blind, randomized, placebo-controlled trial. *J Neuropsychiatry Clin Neurosci* 2007;19:179–186.

49. Carta M, Carlsson T, Kirik D, Bjorklund A. Dopamine released from 5-HT terminals is the cause of L-DOPA-induced dyskinesia in parkinsonian rats. *Brain* 2007;130(Pt 7):1819–1833.

50. Navailles S, Carta M, Guthrie M, De Deurwaerdere P. L-DOPA and serotonergic neurons: functional implication and therapeutic perspectives in Parkinson's disease. *Cent Nerv Syst Agents Med Chem* 2011;11:305–320.

51. Moses-Kolko EL, Price JC, Shah N, et al. Age, sex, and reproductive hormone effects on brain serotonin-1A and serotonin-2A receptor binding in a healthy population. *Neuropsychopharmacology* 2011;36:2729–2740.

Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article:

Data S1. Supplemental Methods.

Table S1. Summary table of prior studies reporting cognitive profile in nondemented patients who had PD with visual hallucinations

Figure S1. Decreased receptor bindings in PD with VHs compared with PD without VHs after excluding patients who were taking serotonergic medication.

doi:10.1002/mdc3.12466