Background: Complex visual hallucinations (VHs) occur in several pathologic conditions; however, the neural mechanisms underlying these symptoms remain unclear. Although dopamine may have a role, indirect evidence indicates that serotonin may also contribute to the pathogenesis of complex VHs, probably via involvement of the serotonin 2 receptor.

Objective: To examine for the first time in vivo changes in serotonin 2A receptor neurotransmission among patients having Parkinson disease (PD) with VHs.

Design: Case-control study.

Setting: Academic research.

Patients: Seven patients having PD with VHs and 7 age-matched patients having PD without VHs were recruited.

Main Outcome Measures: We used the selective serotonin 2A receptor ligand setoperone F 18 during positron emission tomography among nondemented patients having PD with VHs.

Results: Patients having PD with VHs demonstrate increased serotonin 2A receptor binding in the ventral visual pathway (including the bilateral inferooccipital gyrus, right fusiform gyrus, and inferotemporal cortex) as well as the bilateral dorsolateral prefrontal cortex, medial orbitofrontal cortex, and insula.

Conclusions: This pilot study provides the first in vivo evidence suggesting a role for serotonin 2A receptors in mediating VHs via the ventral visual pathway in PD. Treatment studies should be performed using selective serotonin 2A receptor antagonists, which have important implications for the clinical management of VHs and psychosis in PD.

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VISUAL HALLUCINATIONS (VHs) are abnormal perceptions in the absence of an adequate visual stimulus. Complex well-formed VHs have been described in several pathologic conditions, including peduncular hallucinosis, schizophrenia, cortical Lewy body dementia, and Parkinson disease (PD). A potential common substrate for complex VHs in all of these conditions is suppression of normal inhibitory cortical inputs over the visual association cortex, leading to complex VHs as a “release phenomenon.” However, the neural mechanisms underlying VHs remain unclear. Although dopamine may have a role, indirect evidence indicates that serotonin may also contribute to the pathogenesis of complex VHs, probably via involvement of the serotonin 2 receptor. In fact, hallucinogenic lysergic acid diethylamide acts via serotonin 2A receptors, and atypical antipsychotics (e.g., clozapine and quetiapine fumarate) that effectively reduce VHs, as well as dopamine receptor antagonists, are serotonin 2A and 2C receptor antagonists. In PD, this antipsychotic effect on VHs occurs at low dosages (approximately 10-fold less than in schizophrenia); at such dosages, there is high occupancy of serotonin 2A receptors and low occupancy of dopamine receptors. Together, these observations suggest that serotonin 2A receptors may be involved in VHs in PD; however, the pathogenesis underlying these phenomena and the potential action site of serotonin 2A ligands in reducing such symptoms is unknown to date. Therefore, the specific objective of this pilot study was to measure for the first time in vivo changes in serotonin 2A receptor binding using the selective serotonin 2A receptor ligand setoperone F 18 during positron emission tomography (PET) among age-matched nondemented patients having PD with well-formed VHs vs patients having PD without VHs.
PATIENTS

Patients were recruited from the Movement Disorders Centre at Toronto Western Hospital who met the United Kingdom’s Parkinson’s Disease Society Brain Bank criteria for the diagnosis of idiopathic PD. Seven patients having PD with VHs and 7 age-matched patients having PD without VHs were recruited. Parkinsonian disability was assessed using the Hoehn and Yahr Rating Scale and the Unified Parkinson Disease Rating Scale (UPDRS) part III, motor score, while taking medication. Because of recall bias in defining the date at onset of PD, the duration of treatment with antiparkinsonian medication was used as the measure of disease duration. All PD medication use was stable for 2 months before the study.

Patients having PD with VHs were experiencing well-formed VHs, with no psychotic features and with full insight retained (ie, score of 2 on question 2 of the UPDRS part I). The severity of VHs was rated using the Neuropsychiatric Inventory VHs subscale, which assesses the occurrence and severity of VHs within the past month and other behavioral and psychological symptoms (eg, delusions, aggression, anxiety, and depression). Visual hallucinations had to be present for at least 2 months; the long duration was required to eliminate changes in the level of hallucinations because of acute changes in PD medication use and to ensure that all reversible causes of psychosis (eg, infection and metabolic derangement) had been excluded. All patients underwent psychiatric evaluation (using the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders [Fourth Edition]) to exclude DSM-IV Axis I psychiatric disorders. Depression and anxiety were evaluated by clinical diagnosis, and depression was measured using the Beck Depression Inventory. No patient was taking antipsychotic drugs. As much as possible, no serotonin binding drugs were allowed. However, because of the common association of depression and anxiety with PD, 2 patients in each group were taking an antidepressant. All concomitant medications were stable for at least 2 months before study enrollment. To reduce any possible confounding effects of cognitive changes, nondemented patients with PD (Montreal Cognitive Assessment cutoff score >26) were recruited. In addition, patients were excluded who had a history of stroke, cerebral tumor, traumatic brain injury, epilepsy, unstable psychiatric illness, current alcohol or other drug abuse or withdrawal, or any medical reason that precluded the patient from tolerating magnetic resonance imaging and PET. The study was approved by the Centre for Addiction and Mental Health Research Ethics Board and by the University Health Network Subjects Review Committee. For each patient, written informed consent was obtained.

IMAGING PROCEDURE

In each patient, a setoperone F 18 PET image and a standard fast spin-echo T1-weighted magnetic resonance image were obtained for coregistration and exclusion of pathologic brain conditions. A 1.5-T imaging system was used (Signa; GE Medical Systems, Milwaukee, Wisconsin).

PET was performed using a whole-body camera system (Biograph HiRez XVI; Siemens Molecular Imaging, Knoxville, Tennessee) operating in 3-dimensional mode with an in-plane resolution of approximately 4.6-mm full width at half maximum. Patients were positioned supine on the PET bed. The head was maintained in a fixed position using a thermofomed mask. A catheter was then inserted into an antecubital vein for radiotracer administration. A scout view was obtained to determine accurate positioning of the patient, and a low-dose (2-4 Sv) computed tomography image was acquired to correct for attenuation. Dynamic PET began immediately with an intravenous bolus injection of setoperone F 18 (mean [SD] dose, 5.0 [0.2] mCi [185±6 [74±5] Bq]) and lasted for 90 minutes. Setoperone F 18 was prepared by fluorode F 18 displacement on the nitroderivative precursor of setoperone. This yielded setoperone F 18 of high radiochemical purity (>99%) and high specific activity (mean [SD], 1.02±11 [1±11] Bq/µmol at the time of injection). Emission data were acquired in list mode and were reconstructed by 2-dimensional filtered back-projection to yield dynamic images in 22 frames using the following sequence: five 1-minute frames and seven-teen 5-minute frames, resulting in 81 sections with a 236×296-pixel matrix (pixel size, 2 mm). Patients received their usual medication regimens for the duration of imaging.

IMAGE ANALYSIS

To obtain a measure of serotonin 2A binding potential, we used a voxel-by-voxel analysis with statistical parametric mapping to avoid subjectivity and to adopt the principle of data-driven analysis. Parametric binding potential images were generated by calculating setoperone F 18 binding potential for each voxel using a simplified reference tissue model (PMOD version 2.7; PMOD Technologies, Ltd, Zurich, Switzerland). Based on previous findings that cerebellar binding is not significantly displaced by serotonin 2A antagonists in nonhuman primates and in human subjects, the cerebellum (excluding the vermis) was used as the reference region. These images were then coregistered to the corresponding T1-weighted magnetic resonance image, spatially normalized into standardized stereotaxic space using an automated feature-matching algorithm, and spatially smoothed using a gaussian filter (8-mm full width at half maximum) using available software (SPM5 [http://www.fil.ion.ucl.ac.uk/spm/software/spm5]).

STATISTICAL ANALYSIS

Statistical analysis for differences in clinical characteristics between patients having PD with VHs vs those with PD without VHs was performed using appropriate parametric (unpaired) or nonparametric (Mann-Whitney) t test. On normalized smoothed images, analysis of covariance was performed in which age, PD treatment duration, and disease severity (UPDRS part III score) were treated as regressors of no interest. Maps of t statistics were constructed representing results of voxel-by-voxel t test of change in setoperone F 18 binding potential between the 2 patient groups, with a threshold of P<.001 uncorrected at the voxel level and an extent threshold of 20 voxels. Regions were considered significant at P<.05 corrected at the cluster level. All P values reported herein are at the corrected cluster level. All coordinates reported herein are based on the Talairach atlas (http://imaging.mrc-cbu.cam.ac.uk/imaging/MniTalairach). P<.05 represents statistical significance.

RESULTS

CLINICAL FEATURES

The demographics and clinical features of the 2 patient groups are given in Table 1. The groups were matched for age and cognition (Montreal Cognitive Assessment score). Parkinson disease disability, as assessed using the Hoehn and Yahr Rating Scale, was also matched. Although patients were carefully recruited to ensure matching clinical features, the PD treatment duration was longer...
and the disease severity (UPDRS part III score) higher in patients with VHs. There is a known association of VHs in patients having PD of longer disease duration. Patients having PD of shorter disease duration with VHs may be more likely to have cortical Lewy body disease with early dementia; however, the presence of cognitive impairment was evaluated using the Montreal Cognitive Assessment, and no difference was observed between the 2 patient groups. Nevertheless, clinical variables might correlate with the presence of VHs or with differences in binding potential. Accordingly, these clinical factors were included in statistical parametric mapping as regressors of no interest. No significant differences were noted in the mean total daily doses of levodopa, amantadine hydrochloride, or pramipexole (no patient was taking any other dopamine agonist) between the 2 patient groups; there was also no significant difference in the use of monoamine oxidase inhibitors (Table 1).

No patient had evidence of any major psychiatric disorder. Mood disturbances included generalized anxiety disorder in one patient with VHs and in another patient without VHs, as well as a history of anxiety in 2 patients without VHs, one of whom had current dysthymia. No significant difference was noted in the Beck Depression Inventory scores between the 2 patient groups. The Neuropsychiatric Inventory hallucinations subscore was significantly higher in the VHs group. As already noted, no patient was taking an antipsychotic drug. One patient was taking citalopram hydrobromide, and another patient was taking sertraline hydrochloride; they were in different patient groups. No other potentially serotonin binding drugs were used by patients in the cohort.

Patients having PD with VHs had stable nonpsychotic symptoms predominantly in the evening or at night. The phenomenology of the VHs consisted of the following: insects on a rug, dead leaves in a hallway, print lifting off the page, animals (eg, a raccoon), persons in a bedroom or living room, persons in the distance having a party, and human faces turning into the faces of dogs. One patient had additional auditory hallucinations of music. Two patients with VHs had clinical features of rapid-eye movement sleep behavior disorder. Subjective sleep disturbance (insomnia or hypersomnolence) as assessed using the UPDRS part IV was reported by all patients with VHs and by 5 of 7 patients without VHs (no formal sleep studies were performed).

**EFFECT OF VHs ON SEROTONIN 2A BINDING POTENTIAL**

Using setoperone F 18, the patient group with VHs demonstrated increased serotonin 2A receptor binding in cortical regions. The between-group statistical comparison (controlling for age, PD treatment duration, and disease severity [UPDRS part III score]) revealed significant serotonin 2A binding potential increases among the patients with VHs in the following regions: bilateral inferooccipital cortex, bilateral inferotemporal gyrus (Brodmann area [BA] 19, P < .002), bilateral dorso-lateral prefrontal cortex (BAs 9, 10, and 46, P < .001), medial orbitofrontal cortex (BA 11, P < .001), and posterior cingulate cortex (BA 31, P < .003). At the subcortical level, significant serotonin 2A binding potential increases were found in the

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**Table 1. Demographic and Clinical Characteristics of Patients With Parkinson Disease (PD)**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients Without VHs</th>
<th>Patients With VHs</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, No.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>6</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>66.7 (8.3)</td>
<td>69.2 (7.2)</td>
<td>.95</td>
</tr>
<tr>
<td>Montreal Cognitive Assessment score, median (range)b</td>
<td>28 (27-30)</td>
<td>27 (27-30)</td>
<td>.33</td>
</tr>
<tr>
<td>Hoehn and Yahr Rating Scale score on medication, median (range)c</td>
<td>3 (3-3)</td>
<td>3 (2-3)</td>
<td>.38</td>
</tr>
<tr>
<td>Unified Parkinson Disease Rating Scale part III score on medication, median (range)d</td>
<td>24 (19-39)</td>
<td>15 (14-20)</td>
<td>.03</td>
</tr>
<tr>
<td>PD treatment duration, mean (SD), y</td>
<td>10.3 (5.6)</td>
<td>4.1 (1.8)</td>
<td>.02</td>
</tr>
<tr>
<td>Total levodopa dose, mean (SD), mg/d</td>
<td>778.6 (343.8)</td>
<td>464.3 (235.8)</td>
<td>.07</td>
</tr>
<tr>
<td>Pramipexole dose, mean (SD), mg/d</td>
<td>0.93 (0.89)</td>
<td>0.60 (0.98)</td>
<td>.31</td>
</tr>
<tr>
<td>Neuropsychiatric Inventory hallucinations subscore, median (range)e</td>
<td>3 (1-8)</td>
<td>0 (0-0)</td>
<td>.002</td>
</tr>
<tr>
<td>Beck Depression Inventory, median (range)f</td>
<td>11 (3-24)</td>
<td>7 (2-20)</td>
<td>.22</td>
</tr>
<tr>
<td>Other PD drugs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selegiline hydrochloride</td>
<td>(n=1), amantadine (n=4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rasagiline mesylate (n=1), amantadine hydrochloride</td>
<td>(n=2)</td>
<td></td>
<td>.61</td>
</tr>
</tbody>
</table>
| Sertraline hydrochloride, 50 mg (n=1); citalopram, 20 mg (n=1) | | | . .
| Potential serotonin binding drugs | | | |

Abbreviations: Ellipses, not applicable; VHs, visual hallucinations.

*Significant differences (P < .05) are given in boldface type.

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To our knowledge, this pilot study provides the first in vivo evidence that abnormalities in serotonin 2A receptor neurotransmission may be involved in the neural mechanisms underlying VHs in a well-categorized group of patients with PD. The findings indicate that serotonin 2A alterations are clustered mainly in the ventral visual pathway, including the bilateral inferooccipital gyrus (BA 19), right fusiform gyrus (BAs 20 and 37), and inferotemporal cortex (BA 20). This pathway is involved in the phenomenology of complex nonstationary scenarios, and several areas of the pathway have an important role in objective and subjective perception and recognition, all typical features of VHs in PD.

Findings in primates revealed that the inferotemporal cortex is part of a neural circuit involving the thalamus and ventral striatum that is responsible for visual processing and possibly VHs. Results of postmortem tissue examination from patients with PD suggest changes in subtypes of serotonin receptor binding in this circuitry, with increased serotonin 2C receptor binding in the substantia nigra pars reticulata and increased serotonin 1A and 2A receptor binding in orbitofrontal and temporal cortex, however, none of these studies specifically addressed the role of serotonin receptors in VHs. Therefore, the present study represents the first in vivo evidence suggesting that abnormalities in serotonin 2A receptor neurotransmission along this circuitry may be involved in the neural mechanisms underlying VHs associated with PD. Other evidence for involvement of the ventral visual pathway in mediating VHs comes from an activation study showing decreased regional cerebral blood flow in the right fusiform gyrus in PD with VHs.

Beyond visual cortical areas, our findings extend previous activation studies showing abnormalities in frontocortical areas in patients having PD with VHs, leading to the hypothesis that dysfunctional top-down cognitive processing directly affects the bottom-up processing of visual events. The importance of frontotemporal interactions in the hallucinatory experience of patients with schizophrenia has been recognized previously. In addition, according to a recent neurocogni-
Dysfunc-
tive model, aberrant connectivity between associative perceptual areas and frontal regions may be central to the pathogenesis of hallucinations. Dysfunction in the top-down network (ie, orbitofrontal and dorsolateral prefrontal cortex) could account for the emotional content, sense of externality, and nonvolition that accompany the experience, while dysfunction in the bottom-up network through overactivation in secondary sensory cortices may lead to the experience of vivid perceptions in the absence of sensory stimuli. In keeping with this model, the present study demonstrates in vivo change in serotonin 2A receptors in all these structures among patients having PD who are experiencing VHs.

Figure 2. Increased serotonin 2A binding potential (corrected \( P < .05 \) at the cluster level) is observed in the bilateral dorsolateral prefrontal cortex (DLPFC), medial orbitofrontal cortex, bilateral insula, posterior cingulate cortex, and ventral visual pathway (including the bilateral inferooccipital gyrus [IOG], right fusiform gyrus, and inferotemporal cortex). L indicates left; R, right; and VHs, visual hallucinations.

Figure 3. Serotonin 2A binding potential in the orbitofrontal cortex (Talairach coordinates, 5, 39, −18) relative to the total daily dose of levodopa. Although patients with visual hallucinations (VHs) showed increased serotonin 2A binding potential in this region and were taking more levodopa than patients without VHs, there was no significant correlation (−0.02) between those 2 factors. This was observed for all regions listed in Table 2. F indicates female; M, male; and y, years.
Overall, our findings suggest that abnormalities in serotonin 2A receptor neurotransmission may be involved in the neural mechanisms underlying VHs associated with PD. Further studies are needed to confirm these findings, as our pilot study comprised few patients and longer disease duration (although included in the analysis) in subjects with VHs. Despite these limitations, this imaging study provides a rational basis for treatment studies using selective serotonin 2A receptor antagonists, which have important implications not only for the clinical management of VHs and psychosis in PD but also for the role of various neurotransmitters in the pathogenesis of such disturbing symptoms.

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Author Contributions: Dr Strafella had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Ballanger, Strafella, van Eimeren, Zuworski, Rusjan, Houle, and Fox. Acquisition of data: Ballanger, Strafella, van Eimeren, Zuworski, Rusjan, Houle, and Fox. Analysis and interpretation of data: Ballanger, Strafella, van Eimeren, Zuworski, Rusjan, Houle, and Fox. Drafting of the manuscript: Ballanger, Strafella, van Eimeren, Zuworski, Rusjan, Houle, and Fox. Critical revision of the manuscript for important intellectual content: Ballanger, Strafella, van Eimeren, Zuworski, Rusjan, Houle, and Fox. Obtained funding: Strafella and Fox. Administrative, technical, and material support: Ballanger, Strafella, van Eimeren, Zuworski, Rusjan, Houle, and Fox. Study supervision: Ballanger, Strafella, van Eimeren, Zuworski, Rusjan, Houle, and Fox.

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Additional Contributions: The staff of the Movement Disorders Centre referred patients for this study, and the staff of the Vivian M. Rakoff PET Centre and Centre for Addiction and Mental Health assisted with the investigations.

REFERENCES