Metabolic Alterations in Patients With Parkinson Disease and Visual Hallucinations

Henning Boecker, MD; Andres O. Ceballos-Baumann, MD; Dominik Volk; Bastian Conrad, MD; Hans Forstl, MD; Peter Haussermann, MD

Background: Visual hallucinations (VHs) occur frequently in advanced stages of Parkinson disease (PD). Which brain regions are affected in PD with VH is not well understood.

Objectives: To characterize the pattern of affected brain regions in PD with VH and to determine whether functional changes in PD with VH occur preferentially in visual association areas, as is suggested by the complex clinical symptomatology.

Design: Positron emission tomography measurements using fluorodeoxyglucose F 18. Between-group statistical analysis, accounting for the variance related to disease stage.

Setting: University hospital.

Patients: Eight patients with PD and VH and 11 patients with PD without VH were analyzed. The presence of VH during the month before positron emission tomography was rated using the Neuropsychiatric Inventory subscale for VH (PD and VH, 4.63; PD without VH, 0.00; P < .002).

Results: Parkinson disease with VH, compared with PD without VH, was characterized by reduction in the regional cerebral metabolic rate for glucose consumption (P < .05, corrected for false discovery rate) in occipitotemporoparietal regions, sparing the occipital pole. No significant increase in regional glucose metabolism was detected in patients with PD and VH.

Conclusions: The pattern of resting-state metabolic changes in regions of the dorsal and ventral visual streams, but not in primary visual cortex, in patients with PD and VH, is compatible with the functional roles of visual association areas in higher-order visual processing. These findings may help to further elucidate the functional mechanisms underlying VH in PD.

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phy (PET) with fluorodeoxyglucose F 18 ($^{18}$F-FDG) provides a measure of the regional cerebral metabolic rate of glucose consumption (rCMRGlc) and may serve to identify affected brain areas in PD with VH under resting conditions.

**METHODS**

**PATIENTS**

We evaluated 8 right-handed patients with PD and VH (mean ± SD, 72.88 ± 6.60) and 11 patients with PD without VH (mean ± SD, 70.56 ± 6.96; age-matched, $P = .47$). Diagnosis was made by consensus between experienced clinicians using the United Kingdom Parkinson Disease Society Tissue Bank criteria. $^{10}$ Severity of PD was rated with the Unified Parkinson Disease Rating Scale motor score and the Hoehn and Yahr Scale. Cognition was assessed using the Mini-Mental State Examination. None of the patients with PD fulfilled the clinical criteria for diffuse Lewy body disease. $^{11}$ Cognitive decline did not precede the classical motor parkinsonian symptoms in any patients. Patients with a history of stroke, cerebral tumor, traumatic brain injury, epilepsy, or psychiatric illness were excluded from this evaluation. Magnetic resonance imaging was performed in all but 2 patients who had pacemakers, for whom computed tomography was performed. Brain lesions or signs of regional or general brain atrophy were excluded on visual inspection by 2 independent experienced neuroradiologists. Demographic data and ratings are summarized in Table 1. Severity of VH was rated before PET using the Neuropsychiatric Inventory subscale for VH, $^{12}$ which assesses the occurrence and severity of VH within the past month. Other behavioral and psychological symptoms associated with PD (eg, delusions, agitation, anxiety, depression) were also evaluated using the Neuropsychiatric Inventory. $^{12}$

Written informed consent according to the Declaration of Helsinki was obtained from the patients after a full explanation of the procedures involved was given. Approval to examine patients with PD with $^{18}$F-FDG PET was given by the local ethics committee and the radiation protection authorities.

**PET IMAGING**

Each patient had fasted for at least 6 hours and dopaminergic medication was discontinued for at least 12 hours before PET. Scanning was performed in 3-dimensional mode using a high-resolution PET scanner (ECAT EXACT HR+; CTI PET Systems Inc, Knoxville, Tennessee) after injection of 185 MBq (to convert megabecquerels to microcuries, divide by 0.037) of $^{18}$F-FDG. PET imaging was performed while the patient was under resting conditions (ie, eyes closed, with dimmed ambient light). We used a 20-minute static acquisition protocol beginning 30 minutes after injection of $^{18}$F-FDG. Transmission scans were obtained for attenuation-correction purposes using a rotating germanium 68–gallium 68 source. After correction for random counts, dead time, and scatter, images were reconstructed with filtered back-projection (Hamm filter; cutoff frequency, 0.5 cycles/projection element), resulting in 47 sections in a 128×128 matrix (pixel size, 2.0 mm) and interplane separation of 3.447 mm.

**IMAGE ANALYSIS**

For stereotactic normalization, a fully automated analysis (NEUROSTAT; University of Michigan, Ann Arbor) was performed. $^{13}$ Linear scaling and nonlinear warping of the data set adjusted the individual brains to the proportional grid system proposed by Talairach and Tournoux. $^{14}$ This resulted in a standardized image set with a uniform voxel size of 2.25-mm interpolation to 60 sections. The image sets were smoothed with an isotropic gaussian filter (12-mm FWHM [full width at half maximum]) and individual global counts were normalized to a mean value of 30 mg/100 mL/min. The statistical analysis was performed with Statistical Parametric Mapping software (SPM2, Wellcome Department of Imaging Neuroscience, London, England) under MATLAB 5.3 (The Mathworks Inc, Natick, Massachusetts) using the Compare populations: 1 scan per subject routine with analysis of covariance. Because the patients with PD and VH had advanced disease (Table 1), the individual Unified Parkinson Disease Rating Scale motor scores were treated as regressors of no interest. All resulting SPM $t$ values were transformed into SPM $z$ values and thresholded at $P < .05$, false discovery rate (FDR)–corrected.

The 2 patient groups differed significantly only in 2 clinical measures, namely, disease stage and the occurrence of VH within the past month (Table 1). There were no statistically significant differences between the 2 groups for all other Neuropsychiatric Inventory scores and the levodopa equivalent dose. The between-group statistical comparison (accounting for the variance related to disease stage) revealed significant ($P < .05$, FDR-corrected) rCMGlc reductions in the PD and VH group in occipitotemporoparietal regions (left side more than right side), sparing the occipital pole. The topography of metabolic reductions in PD with VH overlaps with dorsal stream regions (bilateral inferior and superior parietal lobe regions, left middle temporal gyrus, and right posterior cingulate) and ventral stream regions (left parahippocampal gyrus, left lingual gyrus, left V5/MT) (Figure and Table 2).

<table>
<thead>
<tr>
<th>Variable</th>
<th>PD + VH ($n = 8$)</th>
<th>PD − VH ($n = 13$)</th>
<th>$P$ Value $^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>8</td>
<td>11</td>
<td>...</td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>5/3</td>
<td>8/3</td>
<td>...</td>
</tr>
<tr>
<td>Age, y</td>
<td>72.88 ± 6.60</td>
<td>70.56 ± 6.96</td>
<td>.47</td>
</tr>
<tr>
<td>Duration of disease, y</td>
<td>11.00 ± 6.46</td>
<td>8.05 ± 5.85</td>
<td>.31</td>
</tr>
<tr>
<td>Severity of disease (UPDRS III-motor function)</td>
<td>46.25 ± 15.98</td>
<td>32.73 ± 9.00</td>
<td>.03</td>
</tr>
<tr>
<td>Severity of disease (H&amp;Y scale)</td>
<td>3.31 ± 0.59</td>
<td>2.68 ± 1.54</td>
<td>.01</td>
</tr>
<tr>
<td>Hallucinations (NPI subscore) $^c$</td>
<td>4.63 ± 4.34</td>
<td>0.00 ± 0.00</td>
<td>.002</td>
</tr>
<tr>
<td>MMSE score</td>
<td>25.75 ± 1.67</td>
<td>26.82 ± 1.54</td>
<td>.17</td>
</tr>
<tr>
<td>Levodopa equivalent dose, mg</td>
<td>667 ± 430</td>
<td>617 ± 430</td>
<td>.80</td>
</tr>
</tbody>
</table>

Table 1. Patient Demographic Data and Ratings $^a$

Abbreviations: H&Y, Hoehn and Yahr score (stadium 0-5); MMSE, Mini-Mental State Examination (0-30 points); NPI, Neuropsychiatric inventory; PD + VH and PD − VH, Parkinson disease with and without visual hallucinations, respectively; UPDRS, Unified Parkinson Disease Rating Scale (0-108 points); ellipses, not applicable.

$^a$Patient clinical and demographic data are included in the statistical analysis. Data are given as mean ± SD unless otherwise indicated.

$^b$Significant between-group differences are given in boldface type.

$^c$The NPI score is calculated as follows: scale 1 to 12 equals frequency (1-4 points) multiplied by severity (1-3 points).
The pathophysiological mechanisms of VH in PD are not well understood. Abnormal processing of extrastriate visual associative regions has been hypothesized, and our data indicate that the metabolic abnormalities are clustered in regions of the dorsal and ventral visual streams (Figure and Table 2). While the occipital pole is affected in PD without dementia, PD with dementia, and diffuse Lewy body disease, our data do not suggest that the primary visual cortex is more severely affected in PD with VH. The metabolic reductions in nonprimary visual areas match well with the clinical phenomenology of complex, nonstationary scenarios, similar to hallucinations reported in patients with temporo-occipital and parieto-occipital lesions.

The 2 principal visual processing routes seem to be affected in PD with VH: the ventral stream for object and form vision and the dorsal stream for spatial location and motion vision. The precuneus, an integrative region involved in the processing of spatial aspects of movement and spatial location, was affected bilaterally. Imaging studies have shown that spatial navigation and tracking of moving objects are associated with precuneus activation. The inferior parietal cortex was also affected bilaterally. Imaging has supported its fundamental role for praxis and imitative behavior. The patient cohort with PD and VH was also characterized by hypometabolism of the left parahippocampal gyrus. In patients with diffuse Lewy body disease, Harding et al described an association between the distribution of temporal lobe Lewy bodies and well-formed VH. Recent imaging data indicate that the parahippocampal place area in the inferior temporal cortex exhibits category-specific responses during perception of visual scenes. Considering the nonstationary character of VH, it is interesting that the cluster of affected regions encroached onto the left temporo-occipital junction (Figure) with area MT/V5, the brain site for visual motion processing.

Our findings extend previous and partly contradictory single-photon emission computed tomography and PET data published hitherto in this disease condition: one single-photon emission computed tomography study revealed decreased regional cerebral blood flow (rCBF) in left temporal regions in PD with VH, and another study reported temporal rCBF increases and reduced rCBF in the right fusiform gyrus. Although there are indications that the dynamic coupling between blood flow and glucose metabolism is not always maintained in neurological and psychiatric diseases, it is unlikely that the discrepancies between PET and single-photon emission imaging and PET studies can be explained by PET signal artifacts. Our data rather suggest direct metabolic changes in the left temporo-occipital cortex and in the inferior parietal lobule.

Table 2. Categorical Analysis: Decreased Metabolism in PD + VH

<table>
<thead>
<tr>
<th>Region</th>
<th>P Value, FDR-Corrected</th>
<th>t Score</th>
<th>z Score</th>
<th>Talairach Coordinates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dorsal stream regions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left inferior parietal lobule, BA40</td>
<td>.046</td>
<td>6.05</td>
<td>4.24</td>
<td>−45, −55, 42</td>
</tr>
<tr>
<td>Left supramarginal gyrus, BA40</td>
<td>.046</td>
<td>5.73</td>
<td>4.11</td>
<td>−60, −47, 31</td>
</tr>
<tr>
<td>Right precuneus, BA7</td>
<td>.046</td>
<td>5.3</td>
<td>3.92</td>
<td>20, −63, 49</td>
</tr>
<tr>
<td>Right inferior parietal lobule, BA40</td>
<td>.046</td>
<td>4.95</td>
<td>3.75</td>
<td>40, −48, 48</td>
</tr>
<tr>
<td>Right cingulate gyrus, BA31</td>
<td>.046</td>
<td>5.07</td>
<td>3.81</td>
<td>2, −29, 41</td>
</tr>
<tr>
<td>Left precuneus, BA7</td>
<td>.048</td>
<td>4.28</td>
<td>3.41</td>
<td>−4, −57, 42</td>
</tr>
<tr>
<td>Left middle frontal gyrus, BA6</td>
<td>.046</td>
<td>4.82</td>
<td>3.69</td>
<td>−31, 7, 54</td>
</tr>
<tr>
<td>Left middle temporal gyrus, BA39</td>
<td>.049</td>
<td>3.90</td>
<td>3.19</td>
<td>51, −58, 22</td>
</tr>
<tr>
<td>Ventral stream regions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left parahippocampal gyrus</td>
<td>.047</td>
<td>4.49</td>
<td>3.52</td>
<td>−4, −37, 8</td>
</tr>
<tr>
<td>Left lingual gyrus, BA18</td>
<td>.049</td>
<td>3.91</td>
<td>3.19</td>
<td>−22, −54, 3</td>
</tr>
</tbody>
</table>

Abbreviations: BA, Brodmann area; FDR, false discovery rate; PD + VH and PD − VH, Parkinson disease with and without visual hallucinations, respectively.

aSignificant results in the statistical analysis comparing PD + VH with PD − VH (P < .05, FDR-corrected).
computed tomography data are attributable to local uncoupling of cerebral metabolism and blood flow in PD with VH. Rather, differences in patient characteristics and methods (eg, regions of interest vs parametric analyses) should be considered herein. A recent 18F-FDG PET study comparing 8 nondemented patients with PD and VH and 11 patients with PD without VH matched for age and Hoehn and Yahr scale and Mini-Mental State Examination scores reported relative increases in the regional cerebral metabolic rate for glucose consumption in frontal cortical areas in the PD with VH cohort.31 We also observed a relative frontal hypermetabolism in our PD with VH population, but at trend levels only (P < .001, uncorrected). Thus, the relevance of this finding remains unclear. Another observation in our patient cohort is that the metabolic changes were more pronounced in the left hemisphere. Because of the small sample size, this issue will have to be examined more closely in future studies with larger patient samples.

Regarding the basic mechanisms of VH, Lance19 hypothesized that the occurrence of VH after parieto-occipital (and, invariably, temporal) brain damage is linked to spontaneous discharges of neurons in the visual association cortices. An input deficiency mechanism is unlikely to account for our findings because the metabolic changes were not clustered in the primary visual cortex. Rather, local extrastriate neuronal degeneration or complex transmitter abnormalities should be considered: there is a known dopaminergic deficiency affecting the retina, lateral geniculate body, and visual cortex in PD.32 Furthermore, the parkinsonian brainstem pathology also affects ascending serotonergic pathways33 and there is cell loss in the basal nucleus of Meynert in PD,34 an important source of cholinergic input to visual association areas.35 Cholinesterase inhibitors ameliorate VH in PD, which underlines the putative role of cholinergic deafferentation for VH.36 In the future, the underlying molecular mechanisms should be addressed specifically with means of ligand PET, focusing on extrastriate visual areas.

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Author Contributions: Dr Boecker had full access to all of 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: Boecker, Ceballos-Baumann, Volk, Conrad, Forstl, and Haussermann. Acquisition of data: Boecker, Volk, and Haussermann. Analysis and interpretation of data: Boecker, Volk, Forstl, and Haussermann. Drafting of the manuscript: Boecker, Volk, Forstl, and Haussermann. Critical revision of the manuscript for important intellectual content: Boecker, Ceballos-Baumann, Volk, Conrad, Forstl, and Haussermann. Statistical analysis: Boecker, Volk, and Forstl. Obtained funding: Ceballos-Baumann, Volk, and Haussermann. Administrative, technical, and material support: Ceballos-Baumann, Volk, and Haussermann. Study supervision: Boecker, Ceballos-Baumann, Conrad, Forstl, and Haussermann.

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