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Pareidolia in Parkinson's disease without dementia: A positron emission tomography study

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ABSTRACT

Background: Pareidolia, which is a particular type of complex visual illusion, has been reported to be a phenomenon analogous to visual hallucinations in patients with dementia with Lewy bodies. However, whether pareidolia is observed in Parkinson's disease (PD) or whether there are common underlying mechanisms of these two types of visual misperceptions remains to be elucidated.
Methods: A test to evoke pareidolia, the Pareidolia test, was administered to 53 patients with PD without dementia and 24 healthy controls. The regional cerebral *metabolic rate* of glucose was measured using 18F-fluorodeoxyglucose positron emission tomography in the PD patients.
Results: PD patients without dementia produced a greater number of pareidolic illusions compared with the controls. Pareidolia was observed in all of the patients having visual hallucinations as well as a subset of those without visual hallucinations. The number of pareidolic illusions was correlated with hypometabolism in the bilateral temporal, parietal and occipital cortices. The index of visual hallucinations was correlated with hypometabolism in the left parietal cortex. A region associated with both pareidolia and visual hallucinations was found in the left parietal lobe.
Conclusions: Our study suggests that PD patients without dementia experience pareidolia more frequently than healthy controls and that posterior cortical dysfunction could be a common neural mechanism of pareidolia and visual hallucinations. Pareidolia could represent subclinical hallucinations or a predisposition to visual hallucinations in Lewy body disease.

1. Introduction

Visual misperceptions, i.e., visual hallucinations and illusions, are among the behavioral symptoms that distinguish Lewy body diseases (LBD) from other movement and cognitive disorders. Visual hallucinations have been reported to be present in approximately 80% of patients with dementia with Lewy bodies (DLB) [1,2], in more than 50% of patients with Parkinson's disease (PD) with dementia [1,3] and in 10% of patients with PD without dementia [1,3,4]. Visual illusions have been observed in 30–50% of patients with DLB [5], in 58% of patients with PD with dementia [3] and in 6–19% of patients with PD without dementia [3,4]. These two different types of visual misperceptions have been grouped under the term *PD-associated psychosis* [6], in which visual illusions have been categorized as minor hallucinations [7]. However, there have been few empirical studies addressing the common underlying mechanisms of visual illusions and visual hallucinations.

The earliest clinical observations documented the frequent comorbidity of visual hallucinations with sleep-wake disorders, leading to the hypothesis that endogenous imagery produced during dreaming is the source of hallucinatory images [8,9]. In addition, there is abundant clinical evidence supporting the hypothesis linking visual hallucinations with visual deficits, which were first described a hundred years ago [8,10]. More recently, neuropsychological studies demonstrated the contribution of attention deficit to the emergence of visual hallucinations [11,12]. These hypotheses have been integrated in recent neurobiological models of visual hallucinations in

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LBD, in which sleep disturbance/dream image intrusion is considered to arise from lesions in the brainstem and forebrain cholinergic and/or monoaminergic systems, whereas visual deficits are suggested to be associated with temporo-occipital cortical lesions [9]. Attention deficits have been attributed to disruptions of the cholinergic projections to the fronto-temporal cortices or the hypofunction of the dorsal attention network consisting of the dorsolateral prefrontal and posterior parietal cortices [11,12].

In our previous studies, we devised the Pareidolia test, a tool evoking pareidolia, which is a complex visual illusion involving ambiguous forms that are perceived as meaningful objects. We found that patients with DLB experienced pareidolia more frequently than patients with Alzheimer's disease (AD) or healthy controls [13,14]. Visual hallucinations and pareidolia in DLB were phenomenologically similar, with humans and animals being the most common themes. In addition, both conditions were improved by treatment with cholinesterase inhibitors [13–16]. These findings suggest that visual hallucinations and pareidolia share underlying mechanisms in DLB. Pareidolia was observed not only in patients with DLB who had visual hallucinations but also those who did not [13], suggesting that pareidolia might represent a subclinical hallucination or a predisposition to visual hallucinations. Based on these findings, we predicted that pareidolia would be observed in a subset of PD patients without dementia or frank psychosis and that both visual hallucinations and pareidolia would be associated with dysfunction in similar brain regions, specifically temporo-occipital or fronto-parietal cortices. In this study, we tested this hypothesis using the Pareidolia test and 18F-fluorodeoxyglucose positron emission tomography (FDG-PET).

2. Materials and methods

The study was approved by Tohoku University Hospital ethics committee. All subjects gave written informed consent.

2.1. Participants

We recruited 53 PD patients without dementia and their caregivers and 24 healthy controls matched for age, sex, education and visual acuity. The demographics and clinical profiles of the participants are shown in Table 1. The diagnosis of PD was made according to the UK Parkinson's Disease Society Brain Bank criteria [17]. The patients' motor symptoms were evaluated using Hoehn and Yahr (H&Y) staging and the Unified Parkinson's Disease Rating Scale (UPDRS) part III [18]. The UPDRS part III scores were recorded while the patients were in the 'ON' state. The inclusion criteria for the patients were the following: (1) age between 50 and 75 years; (2) age at onset greater than 40 years; (3) H&Y stage from 1 to 3; (4) best corrected visual acuity $\geq$ 20/70; and (5) a score of 24 or greater on the Mini-mental State Examination (MMSE). The exclusion criteria were as follows: (1) a history of other neurological, psychiatric or severe ocular diseases; (2) any magnetic resonance imaging (MRI) evidence of focal brain lesions and (3) the presence of dementia according to the *Diagnostic* and Statistical Manual of Mental Disorders, Third Edition Revised, supplemented by the Clinical Dementia Rating (1 or greater). Of the 53 patients with PD, 47 were taking levodopa and/or dopamine agonists. These drugs were stopped at least 5 h before PET scanning. None of the patients was taking anticholinergic drugs, cholinesterase inhibitors or antidepressants.

2.2. Neuropsychology

The word recall task from the Alzheimer's Disease Assessment Scale (ADAS) was used to assess memory and the Object Naming subtest from the Western Aphasia Battery for language. Visuoperceptual and visuospatial functions were assessed using the Shape Detection Screening and Position Discrimination subtests of the Visual Object and Space Perception battery [19], the Object Decision subtest of the Birmingham Object Recognition Battery [20], the Face Recognition subtests of the Visual Perception Test for Agnosia [21] and the overlapping figure identification test [22]. Attention was assessed by the digit span and the spatial span subtests from the Wechsler Memory Scale-Revised. Executive function was assessed by the Trail-making Test (the required time difference between parts A and B), phonetic and categorical verbal fluency tasks and the Frontal Assessment Battery (FAB).

2.3. Behavioral assessment

The Neuropsychiatric Inventory (NPI) [23] was administered to the caregivers of the patients. We made some modifications to the original NPI in accordance with previous studies [13]. First, the 'delusion' domain was separated into two different categories: persecutory delusions and delusional misidentifications. Second, we employed an additional domain for fluctuations in cognition. These modifications have been described elsewhere [13]. We also recorded the presence or absence of rapid eye movement sleep behavior disorder (RBD). Each patient and informant (bed partner) was asked questions such as "Has he/she ever seemed to act out his/her dreams, thrashed his/her arms and legs or talked or shouted in his/her sleep?"

2.4. The Pareidolia test

The methods have been described previously [13]. Briefly, the Pareidolia test (PT) is a simple neuropsychological test to evoke pareidolic illusions. The subjects were instructed to point to and describe in as much detail as possible the objects shown in each of 25 colored pictures containing animals, plants and objects (esupp Fig. 1). The subjects' responses were classified into three types: (1) correct responses, in which the subjects correctly identified the objects in the pictures; (2) illusory responses, in which the subjects identified objects that were not in the pictures; and (3) other responses, in which the subjects provided no response or said 'I don't know'. When the subjects responded with comments such as 'It looks like X' but did not believe that it was real, we did not count these as illusory responses. We calculated the sum of the correct responses and illusory responses for the 25 images for each subject. The content of the illusory responses was classified into four categories: people, animals, objects and other. To assess the locations of the illusory responses in each picture, we categorized the objects in the pictures into the 'gist' (i.e., major photographic subject that is important for the meaning of the image) and the 'detail/background' (i.e., information that is of little importance to the meaning of the image). As the items in the detail/background outnumbered those in the gist, the number of illusory responses in the detail/background was inevitably larger than that for the gist. Therefore, we used weighted numbers for illusory responses between the location categories (gist and detail/background), which were calculated as follows: the number of illusory responses in each location category was divided by the total number of items contained in each location category.

2.5. Statistical analyses

A paired t-test was used for between-group comparisons of the neuropsychological tests. The Mann–Whitney U test was used for between-group comparisons of the PT results. Relationships between performance on the PT and other neuropsychological and behavioral variables were assessed using Pearson's correlation coefficient or Spearman's rank correlation coefficient.

2.6. Positron emission tomography

The regional cerebral *metabolic rate* of glucose (CMRglc) was measured using FDG-PET. Each subject fasted for at least 5 h before the scan. The scans were performed using a Siemens Biograph Duo PET/computed tomography scanner. A 185–218 MBq injection of 18F-FDG was administered intravenously under resting conditions with the patient wearing an eye mask. We used a 10-min static acquisition protocol beginning 60 min after the injection of 18F-FDG. The in-plane and axial resolutions of the scanner were 3.38 mm full width at half maximum (FWHM).

The PET data were analyzed with SPM8 (Wellcome Department of Imaging Neuroscience, London, UK). All the PET images were normalized to the FDG template, based on the MNI reference brain (re-sampled voxel size $2 \times 2 \times 2$ mm^3). Then, all the images were smoothed using an isotropic Gaussian kernel of 10 mm FWHM. To reduce between-subject variation in the global metabolic rate, the count of each voxel was normalized to the total count of the brain using proportional scaling.

We performed a correlation analysis among CMRglc at rest, the number of illusory responses on the PT and the NPI hallucination domain total score to identify those brain regions showing decreased metabolism associated with pareidolic illusions and visual hallucinations. These analyses were conducted exclusively in the patients with PD. Age and sex were included as variables of no interest in all analyses. For comparison, we also created models including the levodopa equivalent dose (LED), UPDRS part III and MMSE as variables of no interest. The threshold of significance was set at uncorrected $P < 0.001$ at the voxel level and $k > 20$ voxels for the spatial extent. The PET data obtained from 53 patients were contrasted with those obtained from 14 healthy people which were available from the normal control PET database. The resulting map, with a liberal statistical threshold of uncorrected $P < 0.05$, was used as an inclusive mask to confine our correlation analyses to brain regions showing hypometabolism in the PD patients.

3. Results

3.1. Neuropsychology and behavior

The results are summarized in Table 1. The PD patients performed significantly worse than the controls on the ADAS word recall test, shape detection test, overlapping figure test, digit and spatial span tests, categorical verbal fluency test and Trail-making test. Based on the results of neuropsychological tests, none of our