

Noise Pareidolia Test in Parkinson's Disease and Atypical Parkinsonian Syndromes: A Retrospective Study

Review began 02/13/2024

Review ended 02/21/2024

Published 03/03/2024

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Abstract

Introduction: Pareidolias, or visual misperceptions, are a non-motor symptom of Parkinson's disease (PD) with unclear pathophysiology. The noise pareidolia test (NPT) is a tool for screening pareidolias. The usefulness of the NPT in differentiating PD from atypical parkinsonian syndromes (APS) is also unknown.

Methods: We retrospectively investigated 74 patients with PD and 18 patients with APS who took the NPT. Correlations between the number of pareidolic responses, gray matter volume, and cerebral blood flow were also examined in the patients with PD.

Results: The median number of pareidolic responses in patients with PD and patients with APS was 0 (interquartile range (IQR): 0-3) and 0 (IQR: 0-1), respectively, and tended to be higher in patients with PD than in those with APS ($p = 0.077$). It was significantly higher in patients with PD who had hallucinations (2; IQR: 0-9) ($p = 0.016$). The area under the receiver operating characteristic curve for the number of pareidolic responses in the NPT was 0.62 when used to differentiate PD and APS, and the optimal cutoff number of pareidolic responses was 2/3. Sensitivity and specificity were 25.7% and 100%, respectively. In the PD group, the number of pareidolic responses was correlated with age ($r = 0.27$; $p = 0.021$) and the Frontal Assessment Battery (FAB) score ($r = -0.34$; $p = 0.0099$). Magnetic resonance imaging showed no significant correlation between the number of pareidolic responses and the volume of focal gray matter. On cerebral hypoperfusion mapping, the left parietal lobe had a significant correlation with the number of pareidolic responses ($r = 0.35$; $p = 0.027$).

Conclusion: The number of pareidolic responses in NPT was suggested to be useful as a red flag to rule out APS in differentiating PD from APS. In PD without dementia, the number of pareidolic responses was associated with reduced blood flow in the left parietal lobe.

Categories: Neurology

Keywords: noise pareidolia test, pareidolia, visual misperception, visual hallucination, atypical parkinsonian syndrome, parkinson's disease

Introduction

Parkinson's disease (PD) is a common neurodegenerative disease in which patients suffer from motor symptoms and various non-motor ones [1]. Visual misperception is a non-motor symptom of PD, categorized as minor hallucinations [2], and has been reported to be present in 19%-25% of cases of PD without dementia [3], 58%-65% of cases of PD with dementia [3], and 32% of cases of dementia with Lewy bodies (DLB) [4]. Pareidolias are visual misperceptions in which ambiguous shapes are perceived as meaningful objects; they are considered to be a phenomenon similar to visual hallucinations [5]. Few tools are currently available for the assessment of pareidolias, or visual hallucinations. The scenery pareidolia test [6] is a useful tool to detect pareidolias in PD but is time-consuming and thus unsuitable for routine clinical use. A simplified version, the noise pareidolia test (NPT), was subsequently developed and is now widely used in Japan. In this test, patients with DLB reportedly have pareidolias more frequently than patients with Alzheimer's disease and more than healthy controls. Moreover, pareidolic responses in patients with DLB had a significant correlation with the severity of visual hallucinations, suggesting that NPT is a useful tool for the assessment of visual hallucinations in patients with DLB [7]. Patients with PD also reportedly have more pareidolic responses according to the NPT than those with multiple system atrophy (MSA) [8]. However, the influence of cognitive decline on pareidolic responses could not be excluded from that study because it included patients with dementia.

Furthermore, the pathophysiology remains unclear. Recent studies have suggested that pareidolias are associated with hypometabolism in the parietal, temporal, and occipital lobes [6], decreased cerebral blood flow in the bilateral frontal lobes, left cingulate cortex, and left angular and superior marginal gyri [9], decreased dopamine transporter uptake in the right striatum [10], altered frontotemporal connectivity [11],

How to cite this article

Matsumoto T, Koh J, Sakata M, et al. (March 03, 2024) Noise Pareidolia Test in Parkinson's Disease and Atypical Parkinsonian Syndromes: A Retrospective Study. Cureus 16(3): e55436. DOI 10.7759/cureus.55436

disturbed interactions between the dorsal and ventral attention networks [12], and increased normalized clustering coefficient and lower frontal degree centrality examined using electroencephalogram [13]. However, evidence of its pathophysiology is inadequate.

In this study, we investigated the usefulness of NPT in non-demented PD and atypical parkinsonian syndromes (APS), including MSA with predominant parkinsonism (MSA-P) and progressive supranuclear palsy (PSP). We also examined the relationship between the result of the NPT and cerebral blood flow assessed using ^{99m}Tc -ethyl cysteinate dimer (ECD)-single-photon emission computed tomography (SPECT).

Materials And Methods

Study design

The results of the NPT in non-demented patients with PD, MSA, and PSP were retrospectively examined to determine its characteristics and diagnostic ability. Additionally, we examined the association between NPT scores with brain MRI and cerebral perfusion SPECT in the group of patients with PD.

Setting

This study was conducted at a single institution, Wakayama Medical University, a university hospital in Wakayama, Japan. Data from the subjects were consecutively collected between January 2015 and December 2020. Inpatients with PD, MSA-P, and PSP who were admitted for diagnosis, drug adjustment, and consideration of indications for device therapy during the period of interest and who underwent the NPT were retrospectively identified from the database.

Subjects

The eligibility criteria were as follows: patients with PD, MSA-P, and PSP whose Mini-Mental State Examination (MMSE) scores were ≥ 24 . Clinical diagnoses were made according to the United Kingdom Parkinson's Disease Society Brain Bank criteria for PD [14], the criteria described in the second consensus statement by Gilman et al. for probable or possible MSA [15], and the Movement Disorder Society clinical diagnostic criteria for probable or possible PSP [16]. Excluded were patients with ophthalmologic diseases or visual field abnormalities and those with focal brain lesions or severe ischemic changes on imaging studies.

We collected patient characteristics, including age, sex, disease duration, levodopa equivalent daily dose (LEDD) [17], the Unified Parkinson's Disease Rating Scale (UPDRS) part III, MMSE, Frontal Assessment Battery (FAB), and the presence of clinical visual hallucinations or misperceptions. The UPDRS part III scores were assessed while the patients were in the on state, i.e., when their motor symptoms were sufficiently improved by medication.

Noise pareidolia test

The NPT, which was developed at Tohoku University in Japan, is a simple neuropsychologic test to evoke and measure visual misperceptions [7]. In this test, the subjects are gradually presented with 40 task images. Each image is presented within 30 seconds. The task images consist of black-and-white patterns, and eight of the 40 images are embedded with images of human faces; 32 are not. The subjects were instructed to answer whether a task image contained a human face. If faces were perceived, the subjects were requested to answer "yes" and to point to the area where they thought these faces were, and if not, they were requested to answer "no." They were instructed to answer "yes" only when faces were clearly seen after explanation and three training trials had been completed. Patient responses were categorized into three types: (1) 'correct responses', in which the subjects correctly identified the faces contained in the task images or correctly responded that there were no faces; (2) 'pareidolic responses', in which the subjects falsely identified faces that were not actually in the images; and (3) 'miss', in which the subjects failed to detect the faces embedded in the task images. Subjects received no feedback, regardless of whether or not the responses were correct.

Magnetic resonance imaging acquisition and analysis

A 3-Tesla MRI scanner (Siemens MAGNETOM Skyra, Siemens Medical Solutions USA, Inc., Malvern, PA) with a 32-channel head coil was used to scan each subject. The following parameters were used to acquire T1-weighted structural images (sagittal): repetition time = 580 ms, echo time = 11.0 ms, field of view = 220 mm, base resolution = 256, and slice thickness = 0.55 mm.

To perform voxel-based morphometry, we used Statistical Parametric Mapping Version 12 (SPM12, Functional Imaging Laboratory, UCL Queen Square Institute of Neurology, London, UK) in MATLAB (The MathWorks, Inc., Natick, MA). The T1-weighted structural images were segmented into gray matter, white matter, cerebrospinal fluid, and other non-brain parts. Spatial normalization was performed on gray matter probability maps using the diffeomorphic anatomical registration through the exponentiated Lie algebra algorithm. Normalized images were smoothed using an 8-mm full width at half maximum Gaussian kernel. Age was included as a covariate. The total brain volume was applied for global calculations. The masking

images were created using T1-weighted images of all subjects, and implicit and explicit masking were adapted. Multiple regression analysis was performed to evaluate the correlation between the number of pareidolic responses in the NPT and the volume of gray matter. Family-wise error-corrected p-values < 0.05 were considered significant, and uncorrected p-values < 0.001 were also analyzed for exploratory analysis.

Acquisition of SPECT data and analysis

Images from ^{99m}Tc -ECD-SPECT were acquired using the Infinia Discovery NM630 (General Electric Co., Boston, MA), which was equipped with low-energy, high-resolution collimators. Before acquisition, the patients were placed in the supine position in a quiet room and were instructed to keep their eyes closed during imaging. The scan was started five minutes after an intravenous injection of 600 mBq of ^{99m}Tc -ECD. The SPECT images were continuously obtained using a 64×64 matrix of 4.42-mm pixel size over 360° in 4° steps for four rotations, with a zoom of 2.00. The total acquisition time was 18 minutes. The projection data were pre-filtered through a Butterworth filter (cutoff, 0.5 cycle/cm; power, 10) and reconstructed using a Ramp filter with the application of Chang's attenuation correction ($\mu = 0.11 \text{ cm}^{-1}$). Scatter correction was not performed.

Analysis of SPECT imaging was performed using SPM12, an easy Z-score imaging system (eZIS, Fujifilm RI Pharma, Tokyo, Japan), and voxel-based stereotactic extraction estimation (vbSEE, Fujifilm RI Pharma, Tokyo, Japan), as previously reported [18-20]. After anatomical normalization using SPM12, we used eZIS to investigate decreases in cerebral blood flow. The Z-scores were calculated for each patient according to the degree of decrease in regional ^{99m}Tc -ECD uptake compared with the normal database. The Z-score was defined as follows: $\{(\text{normal database mean}) - (\text{individual value})\} / (\text{control standard deviation})$. Subsequently, we used vbSEE to convert the Z-score map data into a Talairach brain coordinating space. Voxel-based stereotactic extraction estimation was used to calculate the percentage of voxels that showed an uptake reduction of > 2 standard deviations from the average of controls in a given volume of interest (VOI), designated as extent. Voxel-based stereotactic extraction estimation can change the VOI to hemisphere, lobe, and lobule levels; in this study, we selected the lobe and lobule levels. The extent of the target VOIs was used to examine the correlation between the number of pareidolic responses and decreases in ^{99m}Tc -ECD uptake in the target VOIs.

Statistical analysis

All statistical analyses, except for the structural MRI data analysis, were performed using JMP Pro, version 14.1.0 (SAS Institute, Cary, NC). Demographic data of the patients with PD and APS were compared using the chi-square test for sex and visual hallucination or misperception and the Mann-Whitney U test for age, disease duration, LEDD, UPDRS part III, MMSE, and FAB. Correlations between the number of pareidolic responses and the clinical data of patients with PD were evaluated using Pearson's correlation coefficient. Also, linear multiple regression analysis was performed using the stepwise method to identify the determinants of the number of pareidolic responses. To investigate the ability of the NPT to differentiate PD from APS, receiver operating characteristic curves were used, and the cutoff scores were defined using the Youden index [21]. Missing values were excluded from the statistical analyses. P-values < 0.05 were used to denote statistical significance.

Results

We collected data on 74 patients with PD and 18 patients with APS (Table 1). In patients with PD, UPDRS part III and FAB score data were not available for two and 17 patients, respectively. No statistically significant differences in sex, age, disease duration, LEDD, or MMSE were observed between the two groups. The APS group had significantly lower FAB scores than the PD group ($p = 0.026$).

| Group | PD (n = 74) | APS (n = 18) | P-values |
|--|-----------------|-----------------|--------------------|
| Sex, n (female/male) | 41/33 | 12/6 | 0.39 ^a |
| Age, year | 67.5 (58–74) | 65 (53–73.25) | 0.36 ^b |
| Disease duration, month | 31 (15.75–98.5) | 18.5 (13.5–75) | 0.19 ^b |
| Visual hallucination or misperception, n | 11 | 0 | 0.081 ^a |
| LEDD, mg/day | 214.8 (0–985.9) | 112.5 (0–828.4) | 0.40 ^b |
| UPDRS part III | 19 (13–28) | – | – |
| MMSE | 28 (26–30) | 28 (25.75–29) | 0.18 ^b |
| FAB | 15 (13–17) | 14 (10.75–16) | 0.027 ^b |

TABLE 1: Demographic and clinical profiles of patients with PD and APS

Data are shown as absolute numbers or medians (interquartile ranges).

^a Chi-square test; ^b Mann–Whitney U test

PD: Parkinson’s disease; APS: atypical parkinsonian syndrome; LEDD: levodopa equivalent daily dose; UPDRS: Unified Parkinson’s Disease Rating Scale; MMSE: Mini-Mental State Examination; FAB: Frontal Assessment Battery

Regarding the pareidolic responses assessed using the NPT in PD and APS, the median number of pareidolic responses was 0 (interquartile range (IQR): 0-3) and 0 (IQR: 0-1), respectively; the mean number of pareidolic responses was 2.5 ± 4.4 (95% confidence intervals (95% CI), 1.5-3.5) and 0.4 ± 0.7 (95% CI, 0.0-0.7), respectively; the maximum number of pareidolic responses was 20 and two, respectively (Figure 1). The pareidolic responses tended to be higher in PD than in APS ($p = 0.077$). In 11 patients with PD who had experienced hallucinations, the number of pareidolic responses was two (IQR: 0-9), which was significantly higher than that in patients with APS ($p = 0.016$); conversely, this number was not significantly different from that in patients with PD without hallucinations (median: 0; IQR: 0-2) ($p = 0.15$). The area under the curve for the pareidolic responses assessed using the NPT was 0.62 when used to differentiate patients with PD from those with APS. When the optimal cutoff for the pareidolic responses was 2/3, the sensitivity and specificity were 25.7% and 100%, respectively. In the group of patients with PD, patients with pareidolic responses (the number of pareidolic responses was ≥ 1) were significantly older and had lower FAB scores than those without pareidolic responses (Table 2). The pareidolic responses correlated with age ($r = 0.27$; $p = 0.021$) and FAB score ($r = -0.34$; $p = 0.0099$) (Figure 2) but did not correlate with disease duration ($r = 0.14$; $p = 0.24$), LEDD ($r = 0.15$; $p = 0.19$), UPDRS part 3 ($r = 0.094$; $p = 0.43$), or MMSE ($r = -0.15$; $p = 0.19$).

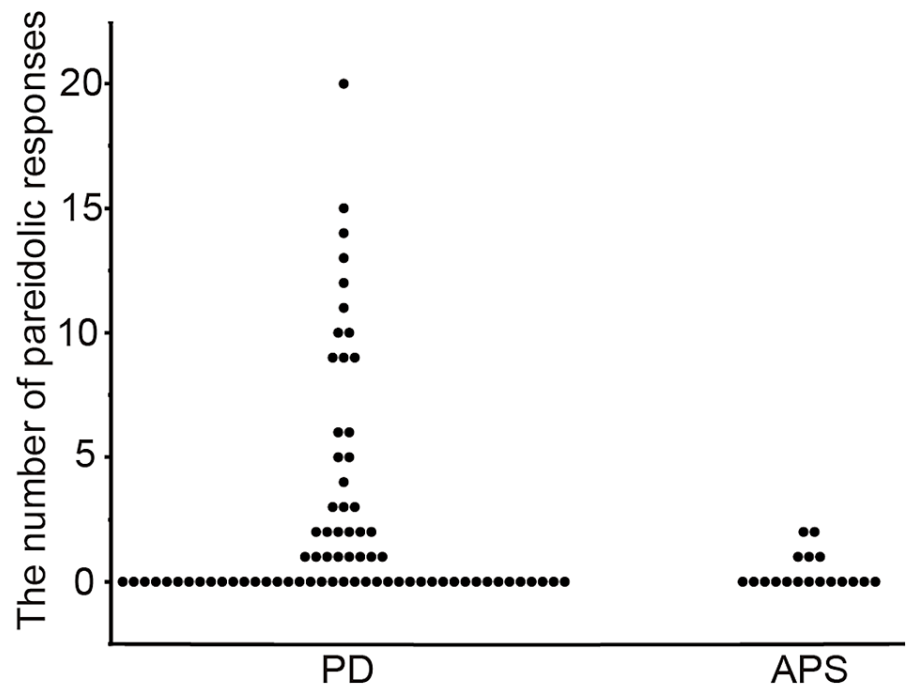


FIGURE 1: Number of pareidolic responses on the noise pareidolia test in patients with PD and APS

The number of pareidolic responses tended to be higher ($p = 0.077$) and had a larger variance in PD than in APS.

PD: Parkinson's disease; APS: atypical parkinsonian syndrome

| Group | PD with pareidolic responses (n = 33) | PD without pareidolic responses (n = 41) | P-values |
|--|---------------------------------------|--|----------------------|
| Sex, n (female/male) | 15/18 | 26/15 | 0.12 ^a |
| Age, year | 72 (66–77.5) | 61 (55.5–70.5) | < 0.001 ^b |
| Disease duration, month | 37 (16.5–126) | 29 (15.5–96.5) | 0.61 ^b |
| Visual hallucination or misperception, n | 7 | 4 | 0.17 ^a |
| LEDD, mg/day | 300 (0–1067) | 0 (0–933) | 0.17 ^b |
| UPDRS part III | 21 (13–28) | 18 (12–26.5) | 0.46 ^b |
| MMSE | 28 (27–29) | 29 (26–30) | 0.17 ^b |
| FAB | 14 (12–16) | 16 (15–17) | 0.0009 ^b |

TABLE 2: Demographic and clinical profiles of PD patients with and without pareidolic responses

Data are shown as absolute numbers or medians (interquartile ranges).

^a Chi-square test; ^b Mann–Whitney U test

PD: Parkinson's disease; APS: atypical parkinsonian syndrome; LEDD: levodopa equivalent daily dose; UPDRS: Unified Parkinson's Disease Rating Scale; MMSE: Mini-Mental State Examination; FAB: Frontal Assessment Battery

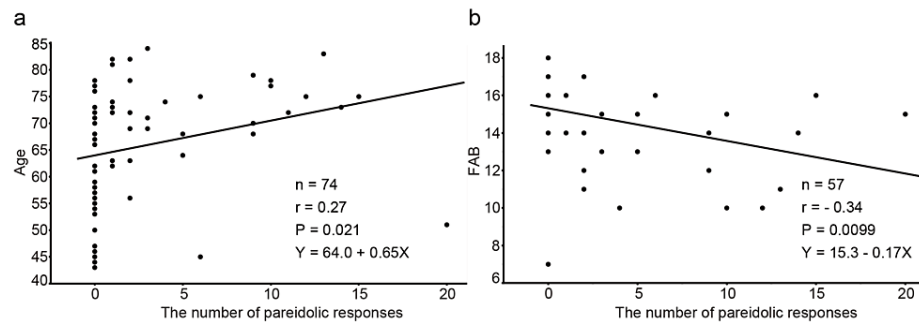


FIGURE 2: Correlation of age and FAB score with pareidolia in patients with PD

The pareidolic responses correlated with (a) age ($r = 0.27$; $p = 0.021$) and (b) FAB score ($r = -0.34$; $p = 0.0099$).

FAB: Frontal Assessment Battery; PD: Parkinson's disease

Structural MRI data were available for all 74 patients with PD. The multiple regression analysis on MRI images showed no significant correlations between the number of pareidolic responses and regional gray matter volume. However, the number of pareidolic responses had a weak correlation with the bilateral angular and postcentral gyri, left frontal lobe (frontal eye field), and right frontal lobe (inferior frontal gyrus) (uncorrected, $p < 0.001$).

The data of ^{99m}Tc -ECD SPECT were available for 40 patients with PD, whose demographics were not statistically different from those of all 74 patients with PD. On cerebral hypoperfusion mapping, the left parietal lobe had a significant correlation with the number of pareidolic responses ($r = 0.35$; $p = 0.027$) (Table 3 and Figure 3). Based on the aforementioned results, we applied a multiple regression model to the number of pareidolic responses as the dependent variable and with the following factors as independent variables: age, LEDD, FAB, disease duration, and extent of decreased cerebral blood flow in the left parietal lobe. Only the left parietal blood flow was identified as a significant independent variable ($\beta = 0.17$; $p = 0.027$).

| | | r | P-values |
|--------------------------|-------|--------|----------|
| Frontal lobe | Left | −0.042 | 0.80 |
| | Right | −0.091 | 0.58 |
| Parietal lobe | Left | 0.35 | 0.027* |
| | Right | 0.21 | 0.18 |
| Postcentral gyrus | Left | 0.38 | 0.017* |
| | Right | 0.23 | 0.16 |
| Superior parietal lobule | Left | 0.33 | 0.040* |
| | Right | 0.21 | 0.20 |
| Inferior parietal lobule | Left | 0.38 | 0.016* |
| | Right | 0.24 | 0.13 |
| Precuneus | Left | 0.16 | 0.32 |
| | Right | 0.06 | 0.71 |
| Temporal lobe | Left | −0.056 | 0.73 |
| | Right | −0.029 | 0.86 |
| Occipital lobe | Left | 0.077 | 0.64 |
| | Right | 0.10 | 0.54 |

TABLE 3: Correlations between pareidolia and the extent of decreased cerebral blood flow

*p-values < 0.05

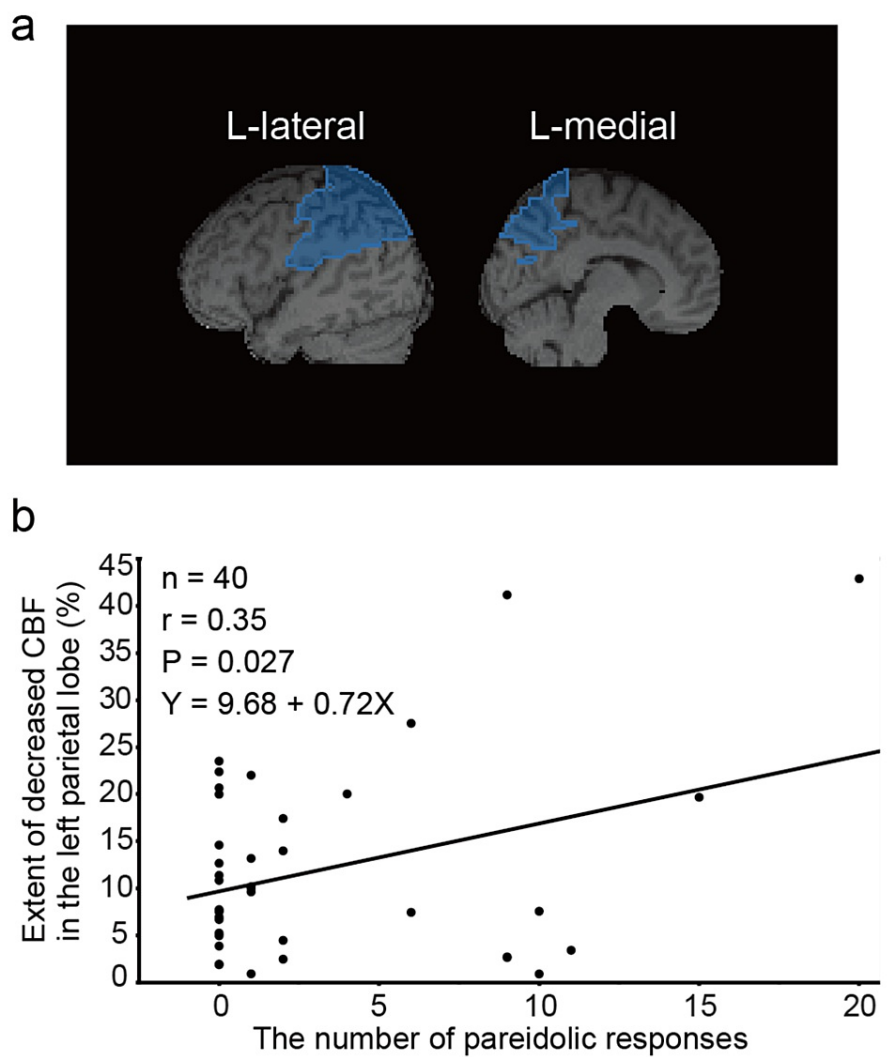


FIGURE 3: Correlation between pareidolia and left parietal lobe cerebral blood flow in patients with PD

a: Brain surface image on vbSEE; the left parietal lobe is highlighted according to Talairach's classification; b: The scatter plots show the extent of decrease in cerebral blood flow in the left parietal lobe and the number of pareidolic responses.

PD: Parkinson's disease; vbSEE: voxel-based stereotactic extraction estimation; L: left

Discussion

We investigated the usefulness of the NPT in differentiating PD from APS. The number of pareidolic responses tended to be higher in PD than in APS and had a large variance in the PD group, which reflected the heterogeneity in PD. Conversely, almost no pareidolic responses were observed in non-demented patients with APS. Pareidolic responses are thus suggested to be a specific symptom of Lewy body disease. Furthermore, the number of pareidolic responses was significantly higher in PD with visual hallucinations, suggesting that there are certain pathophysiological commonalities between visual hallucinations and pareidolic responses.

The NPT is considered unsuitable as a diagnostic marker of PD because of its low sensitivity. However, a high number of pareidolic responses can exclude APS because it has high specificity. Our data suggested a cutoff value of 2/3, although the data were not robust because of the small sample size. Indeed, in one report, some patients with MSA showed more than three pareidolic responses [8]. However, patients with cognitive impairment were not excluded from this study, which could have influenced the results of the NPT. Nevertheless, the number of pareidolic responses in MSA never exceeded four. Pareidolias might, therefore, be a red flag for PD.

The number of pareidolic responses had a weak correlation with age and the FAB score. A previous study on the scenery pareidolia test in non-demented patients with PD also suggested a correlation between the number of pareidolic responses and both age and FAB scores [6]. Pareidolias may, therefore, be associated with age and the FAB score, regardless of the testing method. Conversely, the APS group with fewer pareidolic responses had lower FAB scores. Pareidolia is, therefore, not thought to be caused by the frontal dysfunction itself but by the neuropsychiatric dysfunction associated with PD pathology in common with a decrease in the FAB.

We suggested that pareidolic responses were correlated with left parietal lobe hypoperfusion, but were not associated with frontal or occipital lobe hypoperfusion. This result was also reproduced in the multivariate analysis, but pareidolic responses tended to be correlated with frontal and parietal atrophy. A report also showed that hypometabolism in the left parietal lobe was associated with scenery pareidolias and visual hallucinations [6]. Furthermore, in a study on DLB, NPT scores were weakly correlated with decreased regional cerebral blood flow in the bilateral frontal lobes, left cingulate cortex, and left angular and superior marginal gyri [9]. The mechanism of visual hallucinations in Lewy body disease remains under debate; one hypothesis attributes this symptom to dysfunction of the attentional control networks. This model suggests that visual misperceptions and hallucinations are caused by dysfunction of the dorsal attention network, which consists of the frontal eye field, the dorsolateral prefrontal cortex, and the superior posterior parietal cortex [12]. Pareidolias may therefore be associated with abnormal attentional control networks involving the parietal and frontal lobes.

This study has some limitations. First, the patients were tested while continuing their usual medications, so the influence of dopaminergic therapy cannot be ignored. The pareidolic responses addressed in this study were to be deemed a mixture of drug-induced effects and PD pathology itself. Indeed, LEDDs were slightly higher in PD with pareidolia than in PD without pareidolia, but without statistical significance. Pareidolia in drug-naïve PD was, however, shown in one previous study [10]. Moreover, pareidolias were shown in multivariate analysis to be associated with left parietal hypoperfusion, but not LEDDs. We therefore speculated that pareidolias were more related to the pathophysiology of PD itself than to anti-parkinsonian drugs. A second limitation of this study is the possibility that the number of patients in the APS group was too small for the detection of differences from the PD group. Third, this was a retrospective study, and data on motor and non-motor symptoms were not fully available. Although the relationship between pareidolias and motor symptoms remains controversial [10,13], this study showed no correlation between pareidolias and UPDRS part III scores.

Conclusions

The number of pareidolic responses assessed using the NPT showed high variance in PD; however, this number was significantly higher in PD with visual hallucinations than in APS. In APS, the number of pareidolic responses was ≤ 2 and this may be used as a red flag to rule out APS in differentiating PD from APS. Furthermore, pareidolias in PD without dementia were suggested to be associated with reduced blood flow in the left parietal lobe.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Disclosures

Human subjects: Consent was obtained or waived by all participants in this study. Wakayama Medical University Ethics Committee issued approval 2890. This study was conducted according to the principles of the Declaration of Helsinki. **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** This work was supported by the Japan Society for the

Promotion of Science (JSPS) KAKENHI (grant number: JP21K13708). The funding source was not involved in the study design. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

Acknowledgements

The authors are grateful to Kenta Kotani, Kazuhiro Murotani, Takaki Sakamoto, and Yoshitaka Kumayama for their assistance in exporting the image data. We also acknowledge proofreading and editing by Benjamin Phillis at the Clinical Study Support Center at Wakayama Medical University.

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