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Association between changes in visual evoked magnetic fields and non-motor features in Parkinson's disease

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ABSTRACT

Visual dysfunction can be caused by several abnormalities, including dysfunctions in the visual cortex and retina. Our aim was to investigate changes in visual evoked brain responses in the primary visual cortex associated with Parkinson's disease (PD). Sixteen healthy control subjects and ten patients with PD participated in this study. We assessed the visual evoked magnetic field (VEF) using magnetoencephalography (MEG). Checkerboard pattern reversal (CPR) and monotonous grating pattern (MGP) stimulations were used. Magnetic resonance imaging (MRI) was performed to analyze brain volume and generate a tractogram. Cognitive and olfactory function, and Unified Parkinson's Disease Rating Scale (UPDRS) scores were evaluated in patients with PD. Four components of the VEF (1M, 2M, 3M, 4M) were observed following stimulation. For both stimuli, results from the 1M and 2M components were significantly greater and the latency of the 1M component was increased markedly in the PD group compared with the healthy control group. In the PD group, 1M latency correlated with the UPDRS score of 1 for both stimuli, and a correlation was observed between olfactory function and the UPDRS score of 3 for the CPR stimulation alone. We suggest that the conduction delay observed following visual stimulation occurs peripherally rather than in the primary visual cortex. Degeneration of selective elements of the visual system in the retina, possibly midget cells, may be involved.

Key Words: Parkinson's Disease; Visual Evoked Response; Retina; Olfactory Function

INTRODUCTION

Parkinson's disease (PD), a common neurodegenerative disorder characterized by bradykinesia, rigidity, and rest tremor, was first described by James Parkinson in 1817. Recently, autonomic dysfunction, pain, sleep disturbances, and depression have been recognized as common factors that are important for diagnosing prodromal symptoms in PD. Hallucination is a non-motor symptom that is caused by impaired visual input and central visual processing,[1)] as well as impaired

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brainstem regulation of the sleep-wake cycle, with fluctuating vigilance, intrusion of rapid eye movement dream imagery into wakefulness, and the emergence of internally generated imagery. The occurrence of hallucination is accelerated by oxidative stress[2] and can be a side effect of medication.[1] Hallucinations are thought to be induced by abnormal cortical and subcortical brain structures in patients with PD with dementia. Watanabe and collegues reported significant cortical atrophy in the bilateral dorsolateral prefrontal cortex, left ventral section of the cingulate cortex, and bilateral visual cortex.[3] Patients with early-stage PD sometimes complain of visual defects before the appearance of hallucinations. Hallucinations are often associated with schizophrenia. However, in schizophrenia, hallucinations often take the form of an auditory command. In contrast, the hallucinations described in PD are usually simple visual hallucinations. Healthy people can sometimes develop Charles Bonnet syndrome (CBS) due to visual impairments, and patients with CBS sometimes develop PD.[4]

Intraneuronal aggregation and propagation of α-synuclein is the pathological hallmark of PD.[5] It has been suggested that α-synuclein pathology mediates PD progression. While degeneration of dopaminergic neurons in the substantia nigra are responsible for the main clinical features of PD, a variety of symptoms can precede the first occurrence of the classical motor features of PD. The initial α-synuclein pathology is localized in cardiac,[6] gut, nucleus dorsalis vagus, and olfactory bulb neurons.[5] Abnormal retinograms, foveal pit remodeling, and retinal thinning have been described in patients with PD. These observations imply that there is retinal involvement in PD, and that the distribution of α-synuclein is limited to the inner nuclear layer (INL) and inner plexiform layer (IPL).[7] These results are consistent with the physiological, clinical, and imaging manifestations of impaired vision in PD.

Pattern reversal visual evoked potentials (VEPs) are useful for investigating the physiology and pathophysiology of the visual system, including the visual pathways and visual cortex.[8] A number of studies have reported that the major positive components (P1 or P100) of the pattern reversal visual evoked potentials (VEP) are delayed in PD,[9] but these changes were not significant for checkerboard patterns.[9] In some reports, VEP amplitude was not found to be attenuated in PD.[10] Thus, the results concerning VEPs are still controversial. VEPs contain at least three components, namely N75, P100, and N145.[11] These amplitudes influence each other, but it can be difficult to detect an amplitude of N75. It is not possible to measure exact inter-peak latency in some diseases.

But recently, magnetoencephalography (MEG) has emerged as a powerful tool to analyze evoked brain responses. Theoretically, MEG can be used for brain dipole localization and for detecting specific brain currents orientated tangential to the skull without interference from the skull. MEG can clearly detect N75, P100, and N145 components, as it has the benefit of detecting electrical interneuronal transmission.

The diffuse-light flash stimulus (fVEP) and checkerboard pattern VEP (pVEP) were used to detect the visual response in the occipital cortex. pVEP testing detects minor visual pathway abnormalities with much greater sensitivity and accuracy than fVEP testing. The precise origin of the VEP signal remains unclear, however, it provides an indication of the integrity of the afferent visual pathway. Thus, two types of VEP stimulate different types of retinal cells. MEG can therefore be applied to detect the two types of visual evoked magnetic fields (VEF).

The purpose of this study was to detect any slight abnormalities in visual pathways before the occurrence of hallucinations using VEF.

METHODS

Subjects: Ten patients (four male and six female individuals) with PD and 16 age-matched healthy control (HC) subjects (nine male and seven female individuals) participated in this study (Table 1). No patients with PD reported having hallucinations and visual impairments. All participants had near vision acuity of over 0.8, as measured using the Landolt ring. Healthy subjects had no evidence of diabetes, cerebrovascular disease, parkinsonism, or excess smoking or alcoholism, and were able to perform activities of daily living. Patients were recruited from the Nagoya University Hospital, Japan, and elderly subjects were volunteers. The study was approved by the Ethical Committee of Nagoya University and informed consent to participate was obtained from all participants prior to the study. The patient group fulfilled the diagnostic criteria for PD.[12] Motor performance was assessed using the Hoehn and Yahr (H&Y) scale, and motor and non-motor symptoms were assessed using the Unified Parkinson's Disease Rating Scale (UPDRS). The scores from the patients with PD are shown in Table 1.

VEFs were recorded using a 160-channel whole head MEG system (PQ-1160C, Yokogawa Electric Corporation, Japan). The detection coils of the system were arranged in a uniformly distributed array in concentric circles over a spherically concave surface. Thus, all of the sensor coils were equally sensitive to the weak magnetic signals in the brain. Participants were examined while in a supine position looking at a fixed point on the center of a screen (32° length × 40° width, visual angle) 30 cm in front of their face. The luminance of both stimulations was 100 cd/m^2. All stimulations were presented in the left hemi-visual field (29°×18°). To avoid time variability in the LCD projectors and computer-to-projector system, we used a photo sensor in the screen to obtain the correct stimulation triggers. Seventy-eight channels in the occipital areas were analyzed. Peak latencies were identified from the peaks of the root mean square (RMS),

Table 1 Characteristics of study subjects

	HC	PD
age	63.2 ± 7.5	66.6 ± 5.0
sex (F/M)	16 (7 / 9)	10 (6 /4)
MMSE	29.7 ± 0.7	29.1 ± 1.1
MoCA-J	27.3 ± 1.3	27.3 ± 1.6
FAB	16.8 ± 1.0	17.0 ± 1.2
OSIT-J (smell)	9.1 ± 2.0	4.4 ± 3.6 *
duration (years)	–	5.9 ± 3.1
H/Y	–	2.6 ± 0.8
UPDRS1	–	2.0 ± 1.5
UPDRS2	–	8.8 ± 4.8
UPDRS3	–	21.0 ± 8.4
UPDRS4	–	4.6 ± 3.7

** : Significant difference between HC and PD ($P < 0.05$)

HC, ealthy control subjects; PD, Parkinson's disease patients; MMSE, Mini Mental State Examination; MoCA-J, Montreal Cognitive Assessment-Japan; FAB, Frontal Assessment Battery; OSIT-J, Odor Stick Identification Test for Japanese; H&Y, Hoehn and Yahr scale; UPDRS, Unified Parkinson's Disease Rating Scale.

and then peak RMSs were estimated.

We used checkerboard pattern reversal (CPR) stimulation and monotonous grating pattern (MGP) stimulation. The CPR stimulation used a black and white reversal checkerboard pattern (checker size 0.7 degree). This stimulus was alternately presented for 700 ms with an interstimulus interval of 500 ms. MGP stimuli used a monotonous gray pattern for 700 ms with an interstimulus interval of 500 ms. A black background with a fixation point was presented during the interstimulus interval. The session lasted approximately 20 min, with an average of 200 stimulus presentations.

Magnetic responses were filtered using a 5–100 Hz bandpass filter and digitized at a sampling rate of 1000 Hz. Data from the 50 ms before and 400 ms after the application of each stimulus were analyzed. The DC offset of magnetic signals was achieved using the pre-stimulus period as the baseline. Trials in which the MEG deflection exceeded 2 fT were excluded from the averaging.

T1-weighted images (slice thickness 1.0 mm, TE [repetition time] 2.5 ms, TR [echo time] 2500 ms, 192 slices) and diffusion tensor images (slice thickness 2.0 mm, TE 92 ms, TR 13600 ms, 65 directions × 80 slices) were obtained using a 3T magnetic resonance (MR) imager (Siemens, 3 Tesla System).

Source analysis was based on a single equivalent current dipole (ECD) model in a spherical model fitted to the digitized head shape of each subject.[13] The dipole location was then overlaid on the magnetic resonance image (MRI) for each subject. T1-weighted sagittal sections were transformed using the 3-dimensional Fourier transformation method, and coronal and axial images were then reconstructed. To coordinate head location, as determined by a sensor position indicator, five Vitamin E capsules (5 mm in diameter) were individually attached to the central, right and left forehead, and both pre-auricular (PA) points, thereby allowing each digitized head point to be overlaid accurately on the MRI.

The cognitive status of subjects was evaluated in detail using the Mini Mental State Examination (MMSE) before participation in the study, and only individuals with normal mental function were enrolled. We also utilized the Montreal Cognitive Assessment-Japan (MoCA-J), a new cognitive screening instrument that was designed to address some of the limitations of the MMSE. In addition, we used the Frontal Assessment Battery (FAB). Hyposmia is one of the cardinal early symptoms of PD, therefore, we examined olfactory function using the Odor Stick Identification Test for the Japanese (OSIT-J, Daiichi Yakuhin, Co., Ltd., Tokyo, Japan), which consists of 12 odorants familiar to the Japanese population. This test has been successfully applied for the assessment of odor identification ability in Japanese patients with PD.[14]

The MEG signals were collected and stored on a magneto-optical disk for later processing and analysis using an off-line system. The epochs of each stimulus condition were collected and averaged separately. The peak latency of the first four components (maximum) of VEF, and the RMS value at the peak of the components, was calculated from the 88-channel waveform (occipital lobe). JMP software version 9.0.0 (SAS Institute Inc.) was used for statistical analyses. Significant differences between groups were defined as a P-value < 0.05. Categorical variables were analyzed using the Chi-square test. For comparisons between more than two groups, an analysis of variance (ANOVA) was used. If ANOVA results were significant, a Bonferroni post-hoc test was applied.

For comparisons between individuals with PD and HC, gray matter brain volume and tissue concentration differences were examined using Voxel-Based Morphometry (VBM) and SPM12. To examine changes in white matter, tract-based spatial statistics (TBSS) were implemented using FSL software. Surface-based statistical analyses were performed using Freesurfer software.

RESULTS

The initial (1M), second (2M), third (3M) and fourth (4M) components following stimulation were identified in almost subjects after a single stimulation. These were considered to be visual evoked brain responses in the primary visual cortex. No differences were found in VEF between male and female.

During CPR stimulation, the RMS for the 1M and 2M components showed significant differences between the PD and HC groups. The 1M peak latency was increased in the PD group compared to the HC group ($P < 0.01$). The interval between 1M and 2M was also significantly prolonged ($P < 0.05$).

Using MGP stimuli, the RMSs for the 1M and 2M components were larger in the PD than the HC group. The 1M peak latency was greater in the PD compared with the HC group ($P < 0.05$) (Table 2-2).

We recorded results from cognitive tests and the OSIT-J for the PD and HC groups, and UPDRS for the PD group (Table 1). OSIT-J scores were significantly lower in the PD group than the HC group. There were no significant differences between groups in the cognitive test scores.

The 1M peak latency of both stimuli correlated with the score in the UPDRS 1 (CPR stimuli: $R = 0.744$, $P = 0.034$; MGP stimuli: $R = 0.730$, $P = 0.026$) in the PD group. In addition, the 1M peak latency following CPR stimulation correlated significantly with the OSIT-J score ($R = –0.850$, $P = 0.004$) and UPDRS 3 ($R = 0.807$, $P = 0.015$), but no correlations were found in MGP with OSIT-J and UPDRS3 (Fig.1). There was no association between VEF components and cognitive tests.

We examined the effects of PD on the brain. There were no significant differences in gray matter brain volume between the groups, as measured by VBM.

Using TBSS, no differences were found in the white matter between the PD and HC groups. The 1M peak latency of VEF did not correlate with the FA value of the white matter in the

Table 2-1 The estimated root mean square and latency for the checkerboard pattern reversal stimuli

	HC	PD
1M Peak (fT)	11.2 ± 4.2	20.8 ± 5.8 *
2M Peak (fT)	41.7 ± 16.5	62.4 ± 27.5 *
3M Peak (fT)	45.7 ± 14.7	54.0 ± 23.5
1M Latency (ms)	68.1 ± 13.4	89.4 ± 8.1 *
2M Latency (ms)	110.8 ± 7.3	111.3 ± 11.2
3M Latency (ms)	140.4 ± 10.7	143.1 ± 10.8
4M Latency (ms)	175.2 ± 18.3	185.8 ± 17.3
Latency 2M-1M (ms)	41.6 ± 12.3	24.9 ± 6.0 *
Latency 3M-2M (ms)	29.6 ± 6.4	31.8 ± 4.0
Latency 4M-3M (ms)	35.6 ± 10.3	42.7 ± 11.9

JMP software version 9.0.0 (SAS Institute Inc.) was used for statistical analyses.
All values are represented as mean ± SD.
* Significant difference between HC and PD ($P < 0.05$)
** Significant difference between HC and PD ($P < 0.01$)
HC, healthy control subjects; PD, Parkinson's disease patients

Table 2-2 The estimated root mean square and latency for monotonous grating pattern stimulation

	HC	PD
1M Peak (fT)	12.2 ± 3.8	23.5 ± 6.7 *
2M Peak (fT)	33.6 ± 10.0	51.5 ± 23.8 *
3M Peak (fT)	33.9 ± 12.3	33.8 ± 10.1
1M Latency (ms)	76.9 ± 10.8	93.0 ± 7.6 *
2M Latency (ms)	120.2 ± 11.0	121.7 ± 9.2
3M Latency (ms)	152.8 ± 11.4	155.1 ± 14.2
4M Latency (ms)	181.5 ± 9.6	184.4 ± 9.5
Latency 2M-1M (ms)	44.8 ± 12.1	28.7 ± 9.3 *
Latency 3M-2M (ms)	33.6 ± 10.1	33.4 ± 9.8
Latency 4M-3M (ms)	29.6 ± 10.7	33.1 ± 11.1

JMP software version 9.0.0 (SAS Institute Inc.) was used for statistical analyses.
All values are represented as mean ± SD
* Significant difference between HC and PD ($P < 0.05$)
HC, elderly healthy control subjects; PD, Parkinson's disease patients

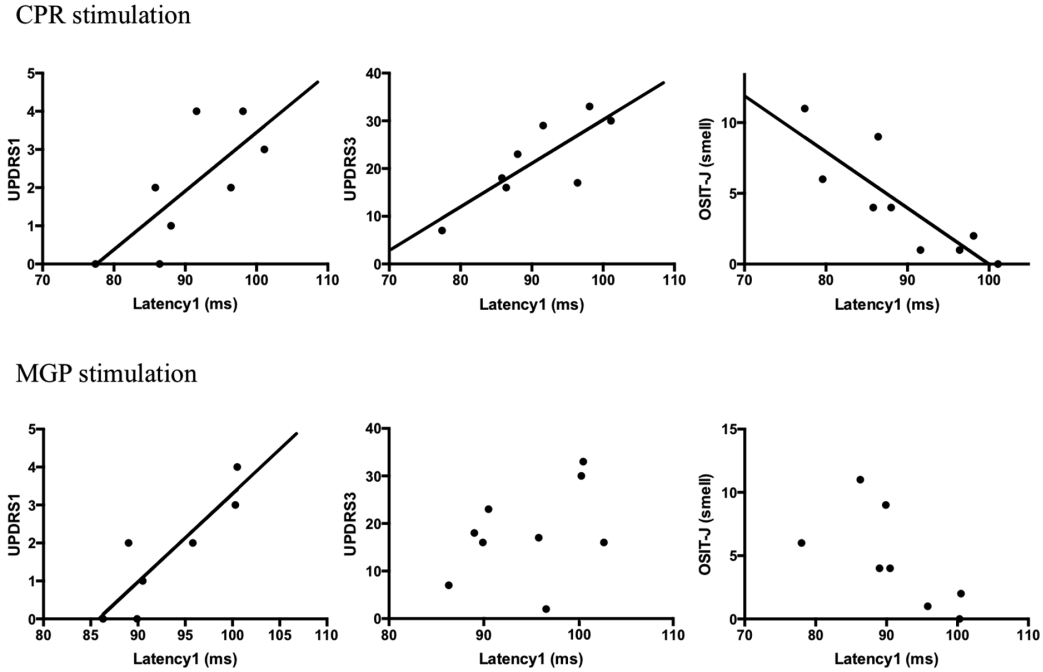

Fig. 1 Relationship between 1M latency and UPDRS 1 and 3 and OSIT-J score in PD group
The 1M peak latency for both stimuli correlated with the score in the UPDRS1 (CPR: R = 0.744, P = 0.034, MGP: R = 0.730, P = 0.026) in PD group. 1M peak latency in CPR correlated significantly with OSIT-J (R = –0.850, P = 0.004) and UPDRS3 (R = 0.807, P = 0.015), but no correlations were found in MGP with OSIT-J and UPDRS3. 1M peak was not detected in two PD patients. So the number of the patients plotted was eight.

optic radiation.

There was no significant difference or association between the thickness of the cortex and VEF components between the groups following surface-based statistical analyses.

DISCUSSION

While most reports show that the latency of the N75 and P100 in VEP increase with age, reports regarding patients with PD are still controversial. Theoretically, MEG can be used for brain dipole localization and detecting specific brain currents orientated tangential to the skull without interference from the skull. In some cases, the N75 peak could not be detected accurately using VEP. Therefore, we used MEG to assess functional differences in VEF components in age-matched controls and patients with PD. This is the first report to analyze the effects of the pathophysiology of PD on pattern reversal stimulation-induced VEF.

As shown in Table 2-1 and Table 2-2, 1M latency was greatly increased in the PD group. Therefore, the origin of the conduction delay may be peripheral rather than cortical because 1M is the primary response.

The peak RMS of the 1M and 2M components following both stimulations were larger in the PD group than the HC group. These results suggest that the greater the damage, the larger the peak amplitudes. We suspect that retinal damage induces these changes because of cortical supersensitivity in order to compensate for the peripheral visual system.

Olfactory dysfunction is a useful marker for the early diagnosis of PD. Olfactory dysfunction in patients with early-stage PD correlates with various non-motor symptoms.[15) 16)] Since 1M latency following CPR stimulation correlated with the results in the OSIT-J and UPDRS tests, the underlying pathology of PD might develop in parallel with visual dysfunction in the early stages of PD.

Using CPR stimulation, 1M latency was found to be significantly different between the PD and HC groups, and 1M latency correlated with OSIT-J and UPDRS scores. The CPR stimulation is sensitive to changes in the visual system affecting the visual evoked response. The increase in 1M latency may indicate that degeneration occurs in more peripheral areas, since no significant white matter difference was found between the PD and HC groups using TBSS. The CPR stimulation included borderline/edge stimulation in the checkerboard matrix. It is possible that midget cells in the ganglion cell layer (GCL) of the retina, which have a central-outskirts antagonism type receptive field,[17)] could be significantly affected in the HC and PD groups.

It has been reported that dopamine neurons in the retina, labeled by tyrosine hydroxylase immunoreactivity, show innervation of the central retina in PD.[18)] It was also shown that retinal dopamine concentrations are decreased in PD, in addition to the nigrostriatal pathway.[19)]

Intracellular α-synuclein aggregates at the border of the INL and IPL appear to occur in neurons that are found in the typical position, frequency, and distribution pattern of dopaminergic amacrine cells. In addition, the GCL and intracellular globular α-synuclein inclusion in ganglion cells (GCs) have been observed in samples from patients with PD.[7)] Using optical coherence tomography (OCT), several studies failed to find any significant difference between patients with PD and healthy subjects.[20)] However, other studies have shown that patients with PD have reduced thickness and volume, for example, in the retinal nerve fiber layer (RNFL), inner retinal layer (IRL), macula, etc., compared to healthy controls.[21)] While the physiological differences between CPR stimulation and MGP stimulation are unclear, our study suggests that changes in the retinal system are responsible for the different results.

Abnormalities in the pattern electroretinogram (PERG) have also been reported,[22)] indicating

a retinal component for achromatic visual dysfunction. The PERG reflects the activity primarily from the rod system in primates.[23] The PERG contains an a-wave (initial negative deflection) followed by a b-wave (positive deflection). The leading edge of the a-wave is produced by the photoreceptors, while a mixture of cells, including photoreceptors, produces the remainder of the other waves. It has been reported that PERG amplitude is significantly reduced in patients with PD.[24, 25] With regard to PERG latency, some studies failed to find a significant difference between patients with PD and healthy subjects,[24, 25] while other studies have shown significant differences using blue-yellow gratings stimuli.[26] Sartucci's ERG method is a specialized technique. Thus, we did not analyze this specialist ERG in parallel. Further studies are needed to perform detailed VEF analyses of visual dysfunction in PD.

Our results suggest that the VEP pattern had a different reaction to the CPR and MGP stimuli. The alteration of the VEP in PD implies a dysfunction of retinal ganglion cells themselves or of the circuitry impinging on them, such as that involving dopaminergic amacrine cells.[27]

In conclusion, our results suggest that retinal degeneration occurs in PD prior to the presentation of hallucinations. We have demonstrated that the VEF and non-motor symptoms, e.g., olfactory function, are similarly impaired in the early stages of PD. Our report suggests that visual disorders might develop from a peripheral lesion, similar to other non-motor features in PD.

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CONFLICTS OF INTEREST

The authors have no conflict of interest to report.

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