

## Electrophysiological correlates of associative visual agnosia lesioned in the ventral pathway

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### Abstract

Visual agnosia has been well studied by anatomical, neuropsychological and neuroimaging studies. However, functional changes in the brain have been rarely assessed by electrophysiological methods. We carried out electrophysiological examinations on a 23-year-old man with associative visual agnosia, prosopagnosia and cerebral achromatopsia to evaluate the higher brain dysfunctions of visual recognition. Electrophysiological methods consisted of achromatic, chromatic and category-specific visual evoked potentials (CS-VEPs), and event-related potentials (ERPs) with color and motion discrimination tasks. Brain magnetic resonance imaging revealed large white matter lesions in the bilateral temporo-occipital lobes involving the lingual and fusiform gyri (V4) and inferior longitudinal fasciculi due to multiple sclerosis. Examinations including CS-VEPs demonstrated dysfunctions of face and object perception while sparing semantic word perception after primary visual cortex (V1) in the ventral pathway. ERPs showed abnormal color perception in the ventral pathway with normal motion perception in the dorsal pathway. These electrophysiological findings were consistent with lesions in the ventral pathway that were detected by clinical and neuroimaging findings. Therefore, CS-VEPs and ERPs with color and motion discrimination tasks are useful methods for assessing the functional changes of visual recognition such as visual agnosia.

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### 1. Introduction

Visual agnosia is a rare clinical disorder, and defined as an impairment in the visual recognition of objects, symbols, pictures, faces or colors with preserved language and intellectual functions [1]. The causative lesions of visual agnosia have been well investigated by anatomical and neuroimaging studies, but such methods are not capable of demonstrating the functional changes in the brain. In contrast, electrophysiological methods have excellent time resolution and are useful for assessing the functional changes in the brain. However, a few studies have been

carried out to clarify the functional causative lesions of various visual agnosia using electrophysiological methods because conventional visual evoked potentials (VEPs) have not been able to assess the visual function after primary visual cortex (V1) in spite of few reports of event-related potentials (ERPs) study in prosopagnosic patients [2–4].

There are two functionally and anatomically distinct visual streams: a parvocellular pathway (or a ventral stream) projecting to the inferior temporal cortex for object vision, and a magnocellular pathway (or a dorsal stream) connected to the parietal cortex for spatial vision [5,6]. Recently, we have developed VEPs with visual stimuli designed to preferentially stimulate the two parallel visual pathways such as parvocellular (color and form perception) and magnocellular (motion and depth) pathways [7,8], and ERPs with visual stimuli designed to separately investigate each

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pathway after V1 [9]. More recently, we have developed the category-specific VEPs (CS-VEPs) with visual stimuli designed to segregately investigate the responses of faces, objects or words stimuli within the ventral pathway. Therefore, not conventional VEPs but these VEPs and ERPs are capable of examining the higher brain dysfunctions of visual recognition in ventral or dorsal streams.

In the present study, we investigated a case of multiple sclerosis (MS) with associative visual agnosia, prosopagnosia and cerebral achromatopsia. Special attention was paid to visual perception using our techniques of VEPs and ERPs, and compared with clinical findings and neuroimaging examinations. We herein report the usefulness of VEPs and ERPs for the functional analysis of visual agnosia related to dysfunction of the ventral stream.

## 2. Materials and methods

### 2.1. Case report

The case is a 23-year-old right-handed man. Five years prior to the first admission, his eyesight became dim and this symptom lasted for 2–3 months. On the first admission, he complained of the reappearance of such symptom. At that time, he was alert, although right homonymous hemianopsia and mild muscle weakness in both lower limbs were seen. Lumbar puncture revealed an elevation of a protein level, myelin basic protein amounts (4.5 ng/ml; normal <4.0) and IgG index (0.74; normal <0.70). Magnetic resonance imaging (MRI) showed high signal intensity areas on T2-weighted and FLAIR images in the white matter of the frontal and occipital lobes bilaterally. He was diagnosed as

having MS. He was treated with corticosteroids and he got well. Three months after the first admission, he sometimes had seen red and blue flashes. It was also difficult for him to distinguish between different types of cars. Four months after the first admission, he developed tonic–clonic seizures after he saw red and blue flashes. He was readmitted to our hospital.

On neurologic examination, he was alert and fully oriented. His corrected visual acuity was 0.9/0.9 with a right homonymous upper quadrant anopsia. His optic fundi showed optic nerve atrophy bilaterally. Motor examination was normal except that coordination was slightly disturbed on the left side. Hyperreflexia of biceps brachii and bilateral quadriceps femoris on the left side were noted.

On neuropsychological examinations, Mini-Mental State Examination was 30/30. Wechsler Adult Intelligence Scale-Revised showed that the verbal IQ was 93 and the performance IQ was 57. Thus, total IQ was 75. His performance IQ was hard to determine exactly because of visual agnosia. In Wechsler Memory Scale-Revised, the general memory score was 90, attention/concentration was 97, verbal memory was 95, visual memory was 75, and delayed recall was 97, resulting in a low visual memory score.

His perception of real common objects was normal. In contrast, his ability to recognize or name objects in photographs and line drawings was severely impaired. In a presentation of 50 line drawings of the objects, he could recognize or name only 20 out of 50 (40 %) objects. He could match and copy line drawings correctly (Fig. 1), although he failed to name them. For example, when he copied a bird or airplane, he said, “I don’t know”. When he copied a fox, he said, “It is a dog”. When he was shown 45 dissimilar drawings of familiar objects (e.g., 15 drawings of

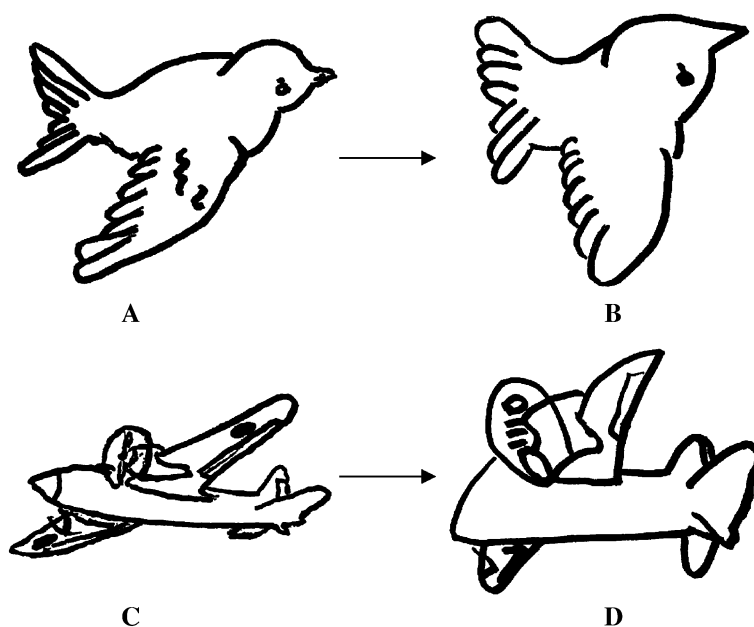


Fig. 1. Copying of line drawings (A, C: original, B, D: copy). The patient could make complete copies of a bird (A, B) and an airplane (C, D).

stationary items, 15 drawings of carpenter's tools and 15 drawings of decorations), he could not categorize them correctly in two trials. His ability to recognize objects through tactile and auditory modalities was normal.

Color vision was evaluated by the Ishihara color plates and Farnsworth Munsell (FM) 100-Hue Test. On Ishihara color plates, it was difficult for him to distinguish the numbers or lines from the background of the plates (12 out of 25). On the FM 100-Hue Test, he made severe errors (Fig. 2). The failure patterns of these tests differed from the pattern in congenital color blindness. When the 15 colored sheets were presented visually, he was able to name them correctly and point to the correct color when the name was given verbally. He could match color sheets correctly. When the ability of color imagery was tested on a 15-item test (e.g., color of a post), his answers were perfect. He was able to point to the correct color when the object name was given verbally and when the picture of an object was presented visually.

It was sometimes difficult for him to recognize or discriminate faces of members of his family, the medical staff, and patients in the same ward although he could recognize them by their voices, names or other particular characteristics such as their gait. When a photograph of his mother was presented, he mistook her for an aunt on his mother's side. When asked to identify 15 famous people (e.g. the Japanese Prime Minister, an entertainer), he was not able to identify any of them (0 out of 15, 0 %). He could discriminate gender of adults and children. He was able to recognize variability of emotional facial expressions (e.g., crying, laughing) in photographs and line drawings. He was able to discriminate and name each part of a face (e.g., a nose or mouth). He sometimes could not imagine faces of his family members and the medical staff. There was no agnosia of other modality such as tactile, auditory and spatial agnosia, aphasia and apraxia.

On laboratory examinations, blood examination was normal. Tests for autoantibodies were negative. A lumbar puncture revealed that cerebrospinal fluid was normal. He did not have HLA-B51.

On neuroimaging examinations, MRI showed low signal intensity lesions on T1-weighted images and high signal intensity lesions on FLAIR images in the white matter of bilateral frontal lobes and ventral parts of temporo-occipital lobes, particularly at lingual and fusiform gyri and inferior longitudinal fasciculi (Fig. 3A,B). Compared with the previous brain MRI (not shown), high signal intensity areas in the white matter of the right temporo-occipital lobe, particularly in the white matter below lingual and fusiform gyri and inferior longitudinal fasciculi were enlarged. Gadolinium enhancement was seen in the white matter lesion of the right temporo-occipital lobe. Single photon emission computed tomography (SPECT) showed a decrease of cerebral blood flow at the temporo-occipital lobe of the right side. Fluorodeoxyglucose positron emission tomography (FDG-PET) demonstrated a decrease of glucose metabolism at the bilateral frontal lobes and bilateral ventral parts of temporo-occipital lobes, which were more pronounced on the right side (Fig. 4).

## 2.2. Electrophysiological examinations

Conventional electroencephalogram (EEG) was recorded from Ag/AgCl disk electrodes placed at Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1 and O2 (International 10–20 System).

Pattern-reversal VEPs to a black–white checkerboard pattern and chromatic VEPs to isoluminant red–green sinusoidal gratings were recorded from Ag/AgCl electrodes applied to the scalp with collodion. Electrode impedance was below 5000  $\Omega$ . The VEPs was recorded from a mid-

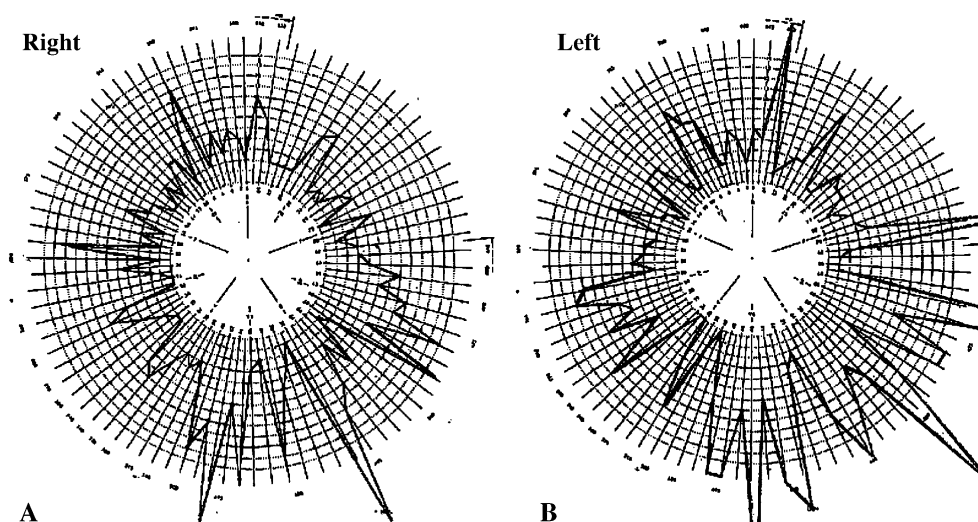


Fig. 2. Farnsworth Munsell 100-Hue test (A: Right eye. B: Left eye). The extent of radial displacement indicates the degree of disturbed hue discrimination.

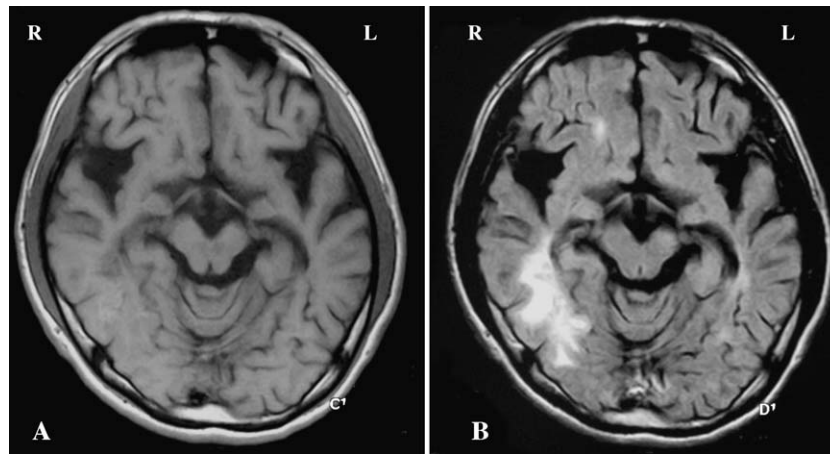


Fig. 3. Brain MRI on T1-weighted and FLAIR images (A: T1-weighted image. B: FLAIR image). Low signal intensity areas (A) and high signal intensity areas (B) are shown in the white matter of bilateral frontal lobes and ventral parts of temporo-occipital lobes, particularly at lingual and fusiform gyri and at inferior longitudinal fasciculi.

occipital electrode (2.5 cm above theinion) with a mid-frontal reference 12 cm above the nasion), except for pattern appearance VEPs where the linked earlobes served as a reference. The ground electrode was at the vertex. A total of 100 responses were summated with an analysis time of 300 ms. The checkerboard pattern consisted of 30' checks of high contrast (90 %) that were phase-reversed at a rate of 1 Hz. The mean luminance was 180 cd/m<sup>2</sup>. Isoluminant chromatic sinusoidal gratings (red–green) at 2 cycles/deg (cpd) appeared for 200 ms and were replaced by a yellowish background for 800 ms in recording chromatic pattern appearance VEPs. The mean luminance was 16 cd/m<sup>2</sup> [10]. The VEPs was judged abnormal if the peak latencies of major components exceeded the mean + 3 S.D. or if no reproducible responses were obtained.

CS-VEPs were recorded from Ag/AgCl disk electrodes placed at Cz, T5, T6 and Oz (International 10–20 System). The linked earlobes served as a reference. Electrode imped-

ance was below 5000  $\Omega$ . Sixty responses were averaged. We used the stimuli such as pictures of faces (famous people), objects (bicycle), and words (Chinese characters and Japanese syllabary). In normal subjects, positive potentials at 190 ms (P190) recorded from Cz, negative potentials at 170 ms (N170) recorded from T6 and T5 (larger at T6) and negative–positive complex (N80/P120) recorded from Oz were evoked [11].

ERPs were recorded from Fp1, Fp2, F7, Fz, F8, C3, C4, T5, T6, Pz, O1 and O2 using color and motion discrimination tasks [9]. In a color task, 128 dots of 5 mm diameter (8.6 mm in radius) were presented in a random spatial pattern on a uniform blue background. The mode of presentation was onset–offset; dots were presented for 500 ms and the display was covered with a uniform blue background for 2000 ms. Red dots (CIE coordinates,  $x=0.610$ ,  $y=0.345$ ) were used as frequent stimuli (non-target) and rare stimuli (target) were green (CIE coordinates,

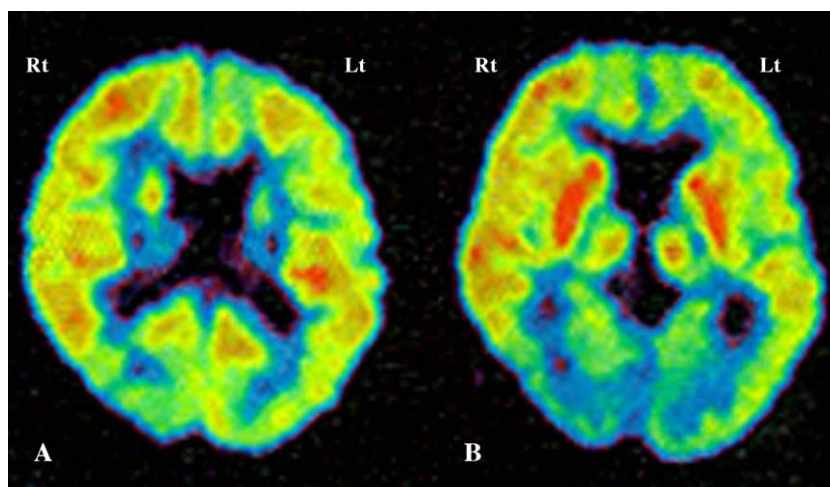


Fig. 4. FDG-PET (A: 80 mm, B: 50 mm from orbitomeatal line). Decrease of glucose metabolism, which is more pronounced on the right side, is shown in the frontal lobes and ventral parts of temporo-occipital lobes.



$x=0.302$ ,  $y=0.576$ ). Luminance of random dots and the background were equally calibrated at  $7.8 \text{ cd/m}^2$ . Rare stimuli were presented randomly between frequent stimuli. The frequent/rare stimulus ratio was 80:20. In a motion task, the 3-D structured coherent and unstructured incoherent motion stimuli were constructed from the parallel projection of 128 white random dots with 5-mm diameter and  $0.01 \text{ cd/m}^2$  of luminance. These dots covered the surface of a black virtual cylinder of 17.8-cm diameter and 16-cm height [12], which was imaged on a black background. In the 3-D structured stimulation, the cylinder revolved clockwise at a fixed angular velocity of  $60^\circ/\text{s}$ . The dots on both the front and the back of the virtual cylinder were projected onto a monitor plane perpendicular to the subject's line of sight. In unstructured incoherent motion stimuli, randomly moving dots were also presented on the monitor. Each dot moved for 500 ms, and was then stationary for 2000 ms so that the recording of the ERPs could be synchronized with the onset of motion of the dots. The 3-D structured stimuli were used as frequent stimuli, and the unstructured stimuli were used as rare stimuli. Rare stimuli were presented randomly between frequent stimuli. The frequent/rare stimulus ratio was 80:20.

### 3. Results

A conventional EEG revealed slow dominant rhythm with irregular slow activities at the occipital and parietal regions. Epileptiform discharges were not recorded.

Pattern-reversal VEPs to a black–white checkerboard pattern showed a mild prolonged P100 latency bilaterally (right 126.6 ms, left 133.2 ms; normal  $102.1 \pm 5.1 \text{ ms}$ , mean  $\pm$  S.D.). Chromatic VEPs to isoluminant red–green sinusoidal gratings demonstrated normal latency of N120 bilaterally (right 125.4 ms, left 115.5 ms; normal  $118.0 \pm 7.6 \text{ ms}$ ).

On CS-VEPs to face and object stimuli, P190 at Cz was not evoked (face stimuli: normal  $185.7 \pm 20.3 \text{ ms}$ , object stimuli: normal  $197.3 \pm 26.0 \text{ ms}$ ), and N170 at T6 was normal latency with low amplitude (face stimuli: latency 165.0 ms; normal  $165.7 \pm 12.9 \text{ ms}$ , object stimuli: latency 152.0 ms; normal latency  $166.2 \pm 13.8 \text{ ms}$ ) (Fig. 5). With Chinese characters stimuli, P190 was evoked (latency 235.5 ms; normal  $203.9 \pm 22.3 \text{ ms}$ ) with low amplitude. With Japanese syllabary stimuli, P190 was evoked with prolonged latency (latency 268.5 ms; normal latency  $205.3 \pm 18.1 \text{ ms}$ ) and low amplitude. To both stimuli, N170 at T6 was

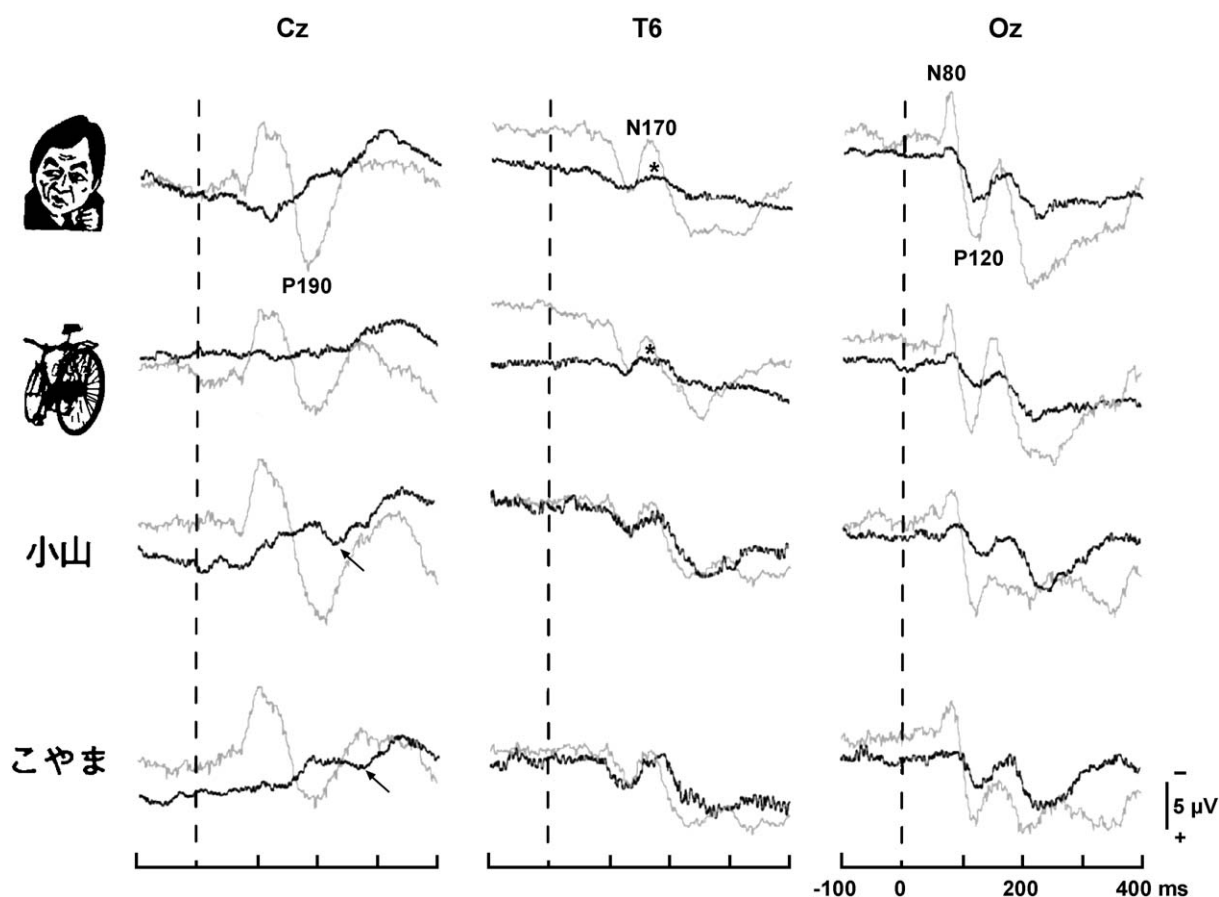


Fig. 5. CS-VEPs in response to realistic drawing of a face (former prime minister Hosokawa), object (bicycle), and words (Chinese characters and Japanese syllabary). Thick traces indicate the patient's data while thin traces represent average data of normal subjects ( $n=15$ ). With face and object stimuli, P190 at Cz was not obtained and the amplitude of N170 at T6 was low (asterisks). With word stimuli, P190 at Cz was evoked with low amplitude (arrows) while N170 at T6 appeared normally. For all stimuli, primary responses at Oz (N80/P120) were evoked normally with low amplitude.

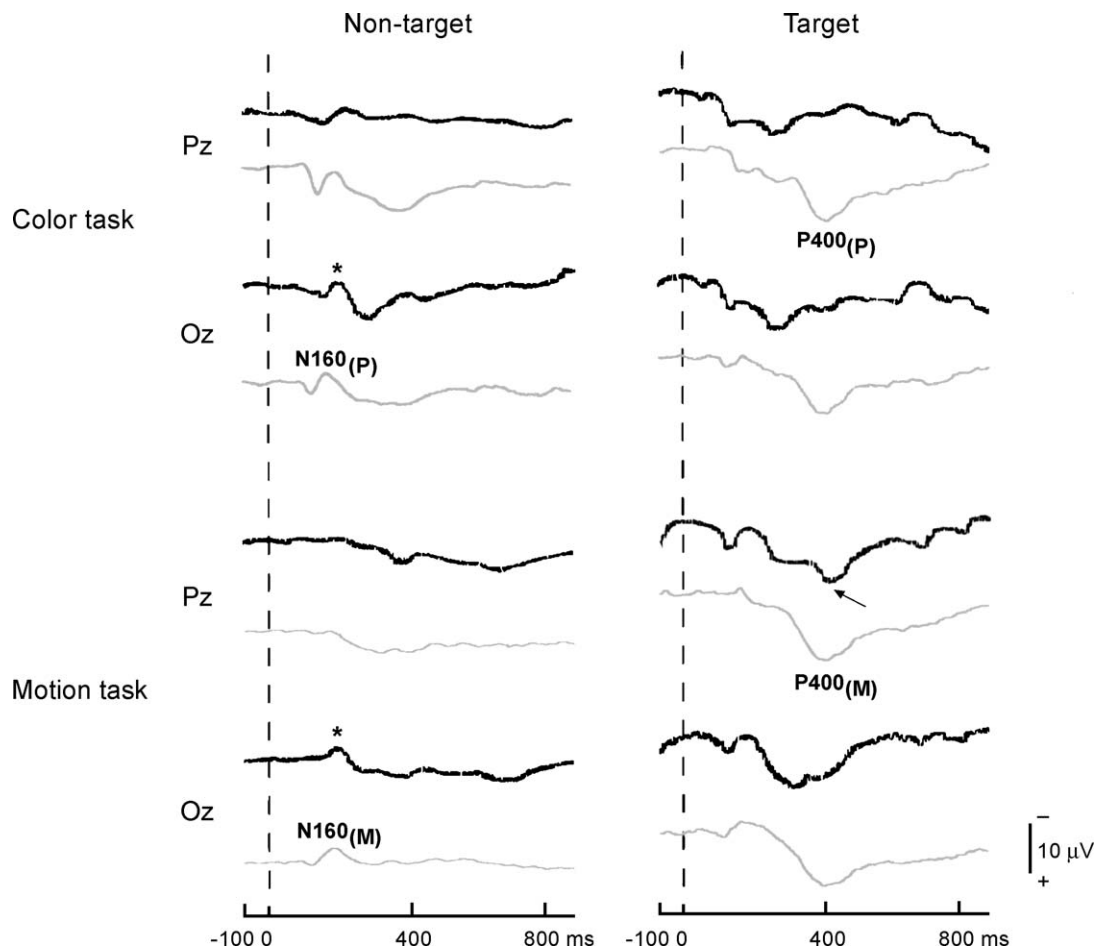


Fig. 6. Visual ERPs using color and motion discrimination tasks. Thick traces indicate the patient's data while thin traces represent average data of normal subjects ( $n=11$ ). In the color task, P400 (P) at Pz was not evoked while N160 (P) at Oz was normal. In the motion task, P400 (M) at Pz (arrow) and N160 (M) at Oz were normal.

normally evoked (Chinese characters stimuli: latency 178.5 ms; normal  $174.5.9 \pm 14.0$  ms, Japanese syllabary stimuli: latency 181.5 ms; normal  $167.4 \pm 10.2$  ms). To all stimuli, primary responses at Oz (N80/P120) were evoked normally.

On ERPs using color and motion discrimination tasks, P400 (P) was not evoked in the color discrimination task (normal  $408.8 \pm 35.3$  ms), but P400 (M) was evoked normally in the motion discrimination task (latency 414.0 ms; normal  $407.1 \pm 34.4$  ms). In both tasks, N160 was almost normally evoked (color discrimination task: latency 182.0 ms; normal  $160.5 \pm 20.3$  ms, motion discrimination task: latency 180.0 ms; normal  $163.9 \pm 14.5$  ms) (Fig. 6).

#### 4. Discussion

We report the case of a man with MS, who developed the higher brain dysfunction of the visual system such as associative visual agnosia, prosopagnosia and cerebral achromatopsia. These visual dysfunction were not able to be explained by his optic nerve atrophy, since his corrected

visual acuity was sufficiently preserved. Brain MRI and FDG-PET showed bilateral lesions in ventral parts of temporo-occipital lobes (ventral stream). CS-VEPs demonstrated the dysfunctions of object and face perception while sparing semantic word perception after V1. ERPs also showed abnormal color perception with preserved motion perception (dorsal stream). Therefore, the present case was considered to have the higher brain dysfunction of the ventral visual pathway in view of clinical, neuroimaging and electrophysiological findings.

Our patient's ability to recognize or name objects in the photographs and line drawings was severely impaired, although he could match samples and copy accurately. He was also not able to perform the categorization test correctly. His recognition of objects through tactile and auditory modalities was preserved. These findings suggested that he was considered to have associative visual agnosia [13]. Most cases of associative visual agnosia had bilateral hemispheric lesions [14–17], while there were some cases with left hemispheric lesions [18–20]. There are two major anatomical loci hypothesized of causative lesion of associative visual agnosia caused by bilateral hemispheric lesions:

(1) the primary visual pathways of the dominant hemisphere, the splenium of the corpus callosum, and the inferior longitudinal fasciculus of the non-dominant hemisphere [15] and (2) the bilateral inferior longitudinal fasciculi [17].

In the face recognition test, our patient, despite the preservation of visual acuity, showed a severe inability to recognize familiar persons on sight. Furthermore, he was easily able to recognize people by their voices, names or other particular characteristics. These findings suggested that he had prosopagnosia [21]. Recent studies have demonstrated that prosopagnosia is prevalent following lesions in the inferior occipito-temporal region [22,23]. Although bilateral damage was frequently observed [22,24], there are several lines of evidence that prosopagnosia might occur following unilateral damage to the right but not the left cerebral hemisphere [25–27]. Sergent et al. [28] compared two active face tasks (face identification and gender discrimination) and found significant differential activity bilaterally in the medial anterior temporal gyri, fusiform gyri, and temporal pole by FDG-PET. Again, activation was somewhat larger on the right side. Recent studies using functional MRI have also shown the activation of the fusiform gyri in response to unfamiliar faces [29,30].

In the color perception test, it was difficult for him to perform Ishihara color plates and FM 100-Hue Test. The failure pattern of such test differed from the failure pattern in congenital color blindness. He was also able to perform verbal–verbal tasks. These results suggested that he had cerebral achromatopsia [31]. Cerebral achromatopsia can occur in case with bilateral inferior occipital lesion, particularly bilateral lingual gyri [32] and bilateral fusiform gyri [33].

As a whole, the patient in the present case was considered to have associative visual agnosia, prosopagnosia and cerebral achromatopsia from neuropsychological findings. In clinical aspects, the most considerable causative lesions, which cause these higher brain dysfunctions at the same time were bilateral ventral temporo-occipital lobes including lingual and fusiform gyri and inferior longitudinal fasciculi on the basis of several previous lesion studies. However, the possibility of additional injury to V1 of the dominant hemisphere and the splenium of the corpus callosum (hypothesis of Benson et al. [15]) cannot be excluded on the basis of neuropsychological examinations.

Brain MRI in this case showed large white matter lesions in the bilateral frontal and ventral temporo-occipital lobes, particularly lingual and fusiform gyri and inferior longitudinal fasciculi, without any lesions of the splenium of corpus callosum. FDG-PET showed a decrease of glucose metabolism in the bilateral frontal lobes and ventral parts of temporo-occipital lobes. Thus, considerable causative lesions of associative visual agnosia, prosopagnosia and cerebral achromatopsia in neuroimaging aspects were almost consistent with clinical considerable causative lesions. However, damage to the V1 could not be excluded because glucose metabolism, measured by FDG-PET, seemed to

decrease in white matter of ventral parts of temporo-occipital lobes and also in the cortex, including V1.

On electrophysiological examinations, the presence of N120 of the chromatic VEPs is considered to reflect normal color perception in V1 within the ventral pathway [8]. In the present case, despite the finding that glucose metabolism, measured by FDG-PET, seemed to decrease in white matter of ventral parts of temporo-occipital lobes and also in the cortex including V1, these areas were apparently not functionally damaged because N120 was normally evoked. Thus, we could demonstrate that the causative lesion of associative visual agnosia in the present case was the bilateral inferior longitudinal fasciculi in the ventral pathway rather than V1 by electrophysiological results.

Moreover, it is likely that color perception processing in the ventral pathway before and within V1 was not damaged in this case because of normal chromatic VEPs [8]. In our technique of visual ERPs with color and motion discrimination tasks, the absence of P400 (P) in the color discrimination task may reflect dysfunction of color perception processing after V1 in the ventral pathway while absence of P400 (M) in the motion discrimination task may reflect dysfunction in motion perception processing after V1 in the dorsal pathway [9]. In the present case, color perception processing in the ventral pathway was damaged but not motion perception processing in the dorsal pathway, because P400 (P) in the color task was not evoked with normal P400 (M) in the motion task. Thus, damage of color perception processing after V1 in the ventral pathway was suggested in the present case.

In CS-VEPs, P190 and N170 are predominantly considered to relate to face perception processing in the ventral pathway, and N170 at T6 may be originated from occipito-temporal region close to fusiform gyrus [11]. In the present case, P190 was not evoked and N170 was low in its amplitude to face and object stimuli. On the other hand, P190 was evoked with low amplitude, and N170 was evoked normally by Chinese characters and Japanese syllabary stimuli. These findings suggest that face and object perception processing were much more damaged than written character processing within the ventral pathway in the present case. It was also demonstrated that there was a damage of the fusiform gyri in the ventral pathway, because N170 at T6 was not evoked easily by face and object stimuli. Based on the findings of chromatic VEPs, CS-VEPs and visual ERPs, color and face perception processing after V1 in the ventral pathway was damaged in the present case. These electrophysiological findings agreed with lesions considered by clinical and neuroimaging findings. In previous case reports, Hécaen et al. [34] reported the case of associative visual agnosia without prosopagnosia. Albert et al. [16] also described the case of associative visual agnosia without alexia. Hence, these cases have suggested that recognition of faces, words, and objects can be damaged separately. Recently, it has been shown that discrete regions of inferior extrastriate

visual cortex are specialized for the recognition of faces, words and colors, varying in location for each module [35,36]. Our results support the concept that there are several visual information processing streams in the fusiform gyri within the ventral visual pathway.

## 5. Conclusion

Electrophysiological findings agreed well with lesions considered by clinical and neuroimaging findings, and suggested that each visual category may be processed in parallel as a module in the visual association cortex (V4). Therefore, electrophysiological methods applied to this study are useful in assessing the higher brain dysfunctions of visual recognition such as visual agnosia.

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