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Case Report

Cerebral Functional Magnetic Resonance Imaging and Multifocal Visual Evoked Potentials in a Patient with Unexplained Impairment of Visual Function: A Case Report

Olav H. Haugen[a, b] Sten Andréasson[c] Lars Ersland[d]
Alexander R. Craven[e] Kenneth Hugdahl[e, f]

[a]Department of Ophthalmology, Haukeland University Hospital, Bergen, Norway; [b]Department of Clinical Medicine, Faculty of Medicine and Dentistry, University of Bergen, Bergen, Norway; [c]Department of Ophthalmology, University of Lund, Lund, Sweden; [d]Department of Clinical Engineering, Haukeland University Hospital, Bergen, Norway; [e]Department of Biological and Medical Psychology, University of Bergen, Bergen, Norway; [f]Department of Radiology, Haukeland University Hospital, Bergen, Norway

Keywords
Migraine with visual aura · Functional magnetic resonance imaging · Multifocal visual evoked potentials · Unexplained visual loss

Abstract
We present a case of a young female with a slowly progressing visual impairment who was examined with multifocal visual evoked potentials and functional magnetic resonance imaging (fMRI) for underlying neuronal abnormality. The fMRI examination consisted of presenting black-and-white checkerboard stimuli, and her activation patterns were compared to the pat-

Olav H. Haugen
Department of Ophthalmology
Haukeland University Hospital
Bergen 5021 (Norway)
E-Mail olav.haugen@helse-bergen.no

terns from 4 normal-sighted subjects. The results showed clear differences in neuronal activation between the patient and the controls in the occipital and parietal lobes. Although we have shown neuronal correlates in a case of unexplained visual loss, it is still an open question as to whether this has an organic or functional cause, which should be the subject for future research.

Introduction

Functional magnetic resonance imaging (fMRI) is a noninvasive method for visualizing brain activity in connection with motor and sensory performance, including the visual system. So far, fMRI has mostly been used for research purposes, but there have been studies suggesting areas of clinical application, including visual disturbances and ophthalmological conditions such as amblyopia, optic neuritis, cerebral visual impairment, and glaucoma [1, 2]. We present the result of fMRI examination of a patient with a slowly progressing visual impairment. A search in the literature revealed only 1 previous study related to a similar clinical problem as the one reported in the current case study [3]. A functional neuroimaging (fMRI) approach can be instrumental in revealing neuronal correlates in cases with unexplained visual loss, as in the patient presented in this study.

Methods

Our patient, a female born in 1975, got migraine with visual aura in her early teens. At the same time, she also experienced a gradual decline in visual acuity. She has been followed at our department for more than 20 years, and clinical data have been extracted from her hospital record.

Results

The results of different clinical examinations are presented chronologically in Table 1. The results of the multifocal visual evoked potentials (mfVEP) and fMRI examinations will be presented in more detail.

Examination with mfVEPs

In 2011, the patient was examined with multifocal electroretinography (mfERG) and mfVEPs at the University Hospital in Lund, Sweden. mfERG, which reflects macular function, was normal. mfVEPs were recorded using the Visual Evoked Response Imaging System (VERIS 4.3; EDI, San Mateo, CA, USA), developed by Baseler et al. [4]. A cathode ray tube monitor with a refresh rate of 75 Hz was used for recording, and the stimuli had the appearance of a dartboard containing 60 segments. The monitor was part of a system with a refractor unit in combination with an infrared eye camera to monitor the position of the eye. The amplitudes of the

first component in a defined paracentral region (sector C) of the cortical response, as previously described by Bengtsson et al. [5], were measured and compared to normal controls. mfVEP revealed pathological changes with reduced amplitudes from the first component in sector C compared to normal (Fig. 1).

Shortly after the examination in Sweden, a visual acuity of 0.25 and 0.125 in the right and left eye, respectively, was measured. At the same time, the patient had to give up working due to increasing visual impairment. A year later, in 2012, her acuity had diminished to 0.05 and 0.01 in the right and left eye, respectively.

Examination with fMRI

The fMRI examinations were done twice with about 1.5 years in between the MR scan sessions. The patient scans were compared with those of 4 normal-sighted female control subjects of about the same age. There was a scanner upgrade between the first and second sessions for the patient; therefore, the scan of the fourth control subject was also made after the upgrade, confirming that there were no major effects due to the upgrade. In order to examine the functional status of the visual cortex, a classic black-and-white checkerboard stimulus [6, 7] was used, inverting with a frequency of 2 Hz. The checkerboards were shown through LCD-goggles (NordicNeurolab, Inc., http://www.nordicneurolab.com/) mounted to the MR head-coil. The task was simply to watch the checkerboards whenever they were presented. The stimulus was an 8 × 8 black-and-white checkerboard that occupied most of the visual field, and with easily resolved elements, ensuring that the reduced visual acuity did not limit the ability to perceive the stimuli. In order to examine eventual cognitive impairments, we added fMRI runs within a session where a square in 1 of the quadrants, or in the center, was suddenly either replaced with a triangle, or changed its color to red. In this task, the subjects reported the position of the targets (triangle or red square) appearing in the goggles: upper/mid/lower or left/mid/right. By these alterations, we introduced an attention and visual search component to the perceptual checkerboard design [8, 9]. By presenting the target stimuli in distinct regions, any asymmetries of visual search accuracy could be detected [10]. Each run consisted of four 30-s task blocks (ON-blocks) and 4 blocks without stimulus (OFF-blocks) in a classic fMRI block design [11]. Each ON block contained 10 target stimuli, presented for 1 s each during a continuously alternating checkerboard.

MRI Acquisition: fMRI Data Analysis and Visualization

MRI was performed with a 3.0 T GE Signa HDx scanner. Functional data were collected with an EPI sequence (TR 3.0 s, matrix 64 × 64 in-plane pixels, and with 35 axial slices, 3 mm in thickness, 1-mm gap, FA 90) and processed with the SPM12 software package (http://www.fil.ion.ucl.ac.uk/spm). First-level statistical analysis for the relevant ON-OFF contrasts (presentation vs. no presentation) were evaluated with *t* tests, the threshold for significance was set at $p < 0.05$ using the FWE-correction for multiple comparisons, and with $k > 100$ voxels for the first-level analyses, and with $p < 0.05$, false-discovery rate (FDR) corrected, with $k > 100$ voxels for the second-level group analysis when comparing the controls versus the patient images, and with $p = 0.001$, uncorrected, 10 voxels for the reversed contrast, since there were no supra-threshold voxels at the FDR-correction level. The results of the statistical analyses were visualized by using the "montage" visualization tool in the SPM software package. We have chosen to visualize these activations as individual cases for direct comparison of

the 2 patient sessions with each of the 4 control subjects. Additionally, group average data (both patient sessions vs. all control subjects) and data aggregated across stimulus conditions are presented. Finally, we calculated the errors made by the subjects for the target-stimulus conditions.

Behavioral Data: Response Errors

The control subjects made no errors (100% correct) for detection of the triangles and red square targets. The patient made 40.6% errors (average of the 2 sessions) with respect to the target stimuli in the upper left and 37.5% errors in the upper right quadrant; the corresponding error% for the lower 2 quadrants was 9.3 and 6.2%.

MRI Activations: Case Comparisons

The upper panel of Figure 2 shows significant activations from the first-level analysis for each of the 4 control subjects, and the lower panel shows the corresponding activations from the 2 patient scan sessions. The data are visualized as coronal slices with 1-mm increments from –75 to –66 mm posterior to the vertical midline through the anterior commissure (0 mm), thus covering the primary visual cortex and the calcarine sulcus (BA 17) in the occipital lobe. The upper panel of Figure 2 shows distinct activation of the calcarine sulcus with the typical "butterfly wing" spreading in each hemisphere. This pattern of activation was in clear contrast to the activation seen in the patient in the lower panel, and in particular for the left hemisphere "wing" of the calcarine sulcus where the patient lacked activation.

A second difference in the activations between the controls and the patient was the presence of parietal activations in the patient, as seen in the lower panel of Figure 2, which was absent in the controls (upper panel of Fig. 2). This most likely reflects a difference in the recruitment of cognitive resources when identifying the target stimuli, which was a very easy task for the controls but cognitively highly demanding and fatiguing for the patient, as reported in the interview after the sessions.

fMRI Activations: Group Analysis

Results of the group analysis are presented in Figure 3. As seen in the left-hand panels, contrasting the average activation for the 4 control subjects with the average activation from the 2 patient scan sessions showed significant surviving activations in the occipital lobe, and particularly in the left calcarine sulcus in the controls. The peak voxel x-, y-, and z-coordinates for the left calcarine (BA 17) were –28, –80, –22 mm, respectively, and 26, –76, –10 mm, respectively, for the right calcarine. The reversed contrast, i.e., the average of the patient scans minus the average of the controls (right-hand panels of Fig. 3), showed no surviving voxels at the FDR-corrected level of significance. Lowering the significance threshold to $p < 0.001$, uncorrected and with a minimum of 10 voxels to define a cluster, showed small significant clusters in the parietal lobule (BA in the patient, not seen in the controls). The corresponding peak x-, y-, and z-voxel activations were –44, –70, –36 mm, respectively, in the left hemisphere, and 50, –32, –24 mm, respectively, in the right hemisphere (not seen in Fig. 3).

Discussion

The fMRI examinations showed significant differences between the patient and the controls. In all controls, a uniform "butterfly wing"-shaped activation of the primary visual cortex was seen in the calcarine sulcus, while there was virtually no activation in the parietal region (Fig. 3). This reflects that the visual stimulation of the test situation primarily activates the visual cortex in the occipital lobe. Because the task is easy for the control subjects, little cognitive effort is needed, corresponding to the sparse activation of the parietal lobes [12].

In contrast to this, the fMRI scans of our patient showed an odd-looking activation pattern of the primary visual cortex, indeed very different from the expected normal activation seen in the controls. This difference was especially pronounced on the left side. Furthermore, her scans showed a strong activation of the parietal lobes, reflecting that she tried hard to solve the task presented to her, with significant cognitive effort needed. The fMRI results matched the performance data, with dramatically more errors in detecting the triangle and red square target stimuli for the patient. However, the errors were about equal for left- and right-sided target presentations, a finding which did not match the more pronounced left-sided failure of activation. In order to further investigate the functional integrity of the patient's occipital cortex, MR perfusion and diffusion tensor imaging (DTI) examinations were done. These ruled out any major abnormality in blood perfusion to the occipital cortex and also that the fMRI findings could be explained as caused by perfusion artefacts. There was a slight reduction in the white matter density in the occipital lobe, as seen in the DTI analysis, and this may warrant further examinations with DTI, using high-resolution techniques.

Color perception of the patient gave different results with different examination methods. As the macula looked perfectly normal both on the fundus photograph and OCT and with normal electroretinography (ERG), a real color perception defect is unlikely.

Comparing the fMRI findings in our patient with those in the study by Werring et al. [3], there are some methodological differences. These authors used fMRI to study the underlying neuronal mechanisms in 5 cases with an established conversion disorder diagnosis and unexplained visual loss. They used monocular photic stimuli while scanning the patients, whereas our study applied checkerboard pattern reversal stimuli viewed through goggles. Their study showed reduced neuronal activation in the visual cortex and increased activation in brain areas related to cognition, somewhat similar to the present case. However, it should be noted that in the study by Werring et al. [3], all patients had a DSM-IV diagnosis of conversion disorder, which was not the case for the patient in the current study.

We hypothesize that our patient has a deficit in the occipital/primary visual cortex that causes her visual difficulties, although we were unable to see any anatomical pathology on MRI. Anamnestically, she has a migraine diagnosis from her teenage years. It is of interest that she often perceived only part of the objects that she was looking at and that the visual picture often "pulsated." Today, the pathophysiology of migraine with aura is still incompletely understood, and there is ongoing debate whether neuronal or vascular mechanisms play the major role [13]. One may speculate that the changes seen on the fMRI screens in Figures 2 and 3 may reflect changes in the primary visual cortex caused by migraine-related events. Although our data support the view that her visual loss is related to abnormal changes in neuronal metabolism in the visual cortex, we cannot completely rule out the possibility that her problems may have a nonorganic origin and that the anomalous activations are the result of a functional,

rather than an organic deficit. What we have shown is that this kind of unexplained visual loss has neuronal correlates, but we leave it an open question as to the causal nature of the deficit, which should be the topic for future research.

Statement of Ethics

This study followed the tenets of the Declaration of Helsinki. Informed consent was obtained from the patient involved.

Disclosure Statement

The authors have no conflict of interest to disclose.

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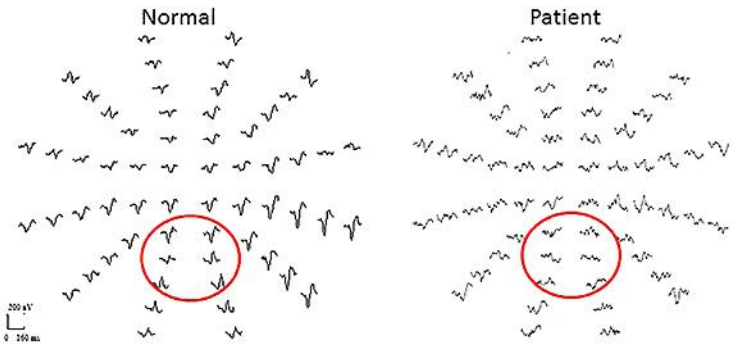

Fig. 1. Multifocal visual evoked potentials (mfVEPs) recordings displayed for the patient (left) and for a typical, normal subject (right), demonstrating the corresponding cortical responses to the central visual field. The red ring represents sector C, the region in the mfVEPs where the highest amplitudes are measured.

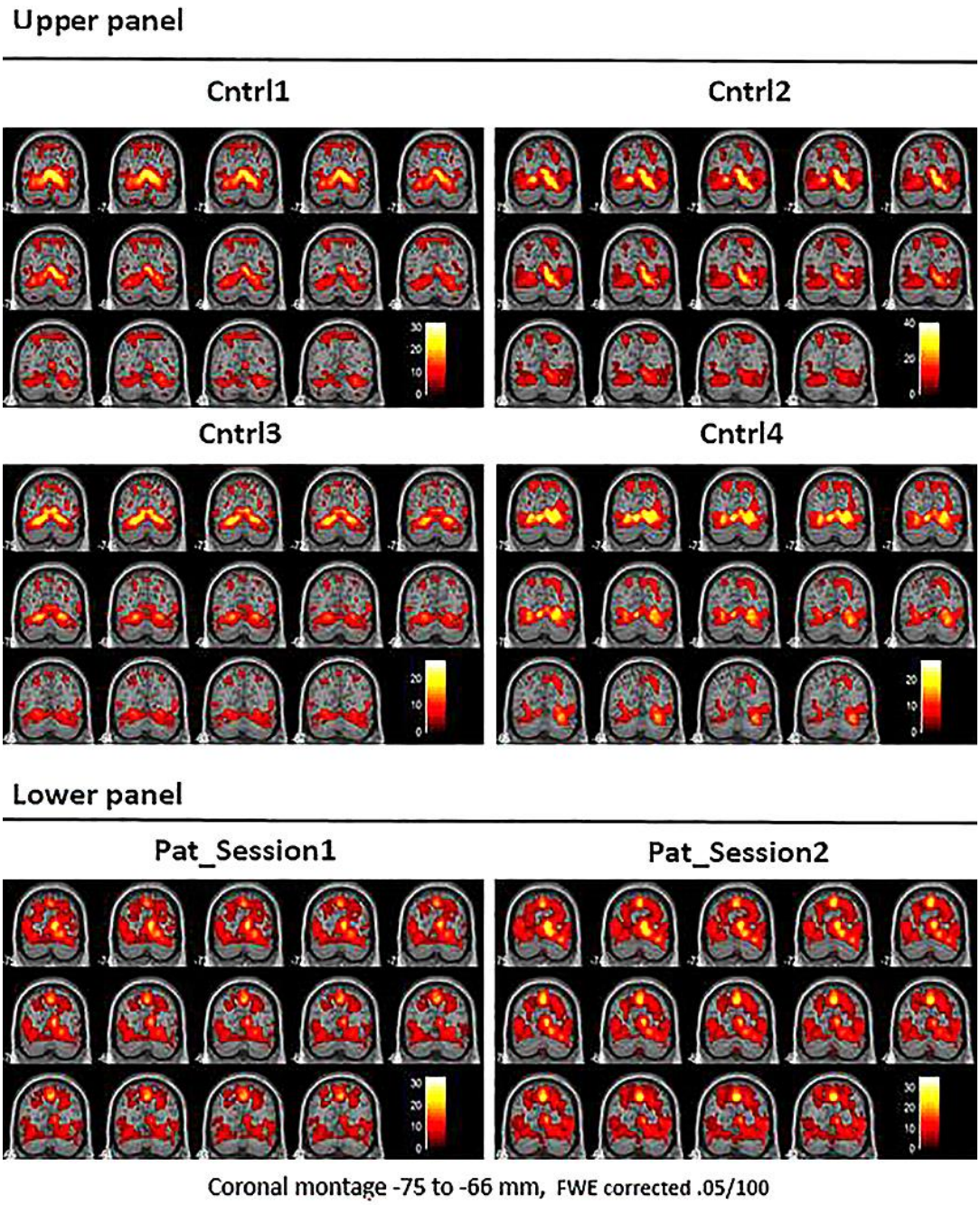

Fig. 2. Coronal slices showing fMRI activations in the occipital cortex for the 4 control subjects (upper panel) and the 2 patient scanning sessions (lower panel).

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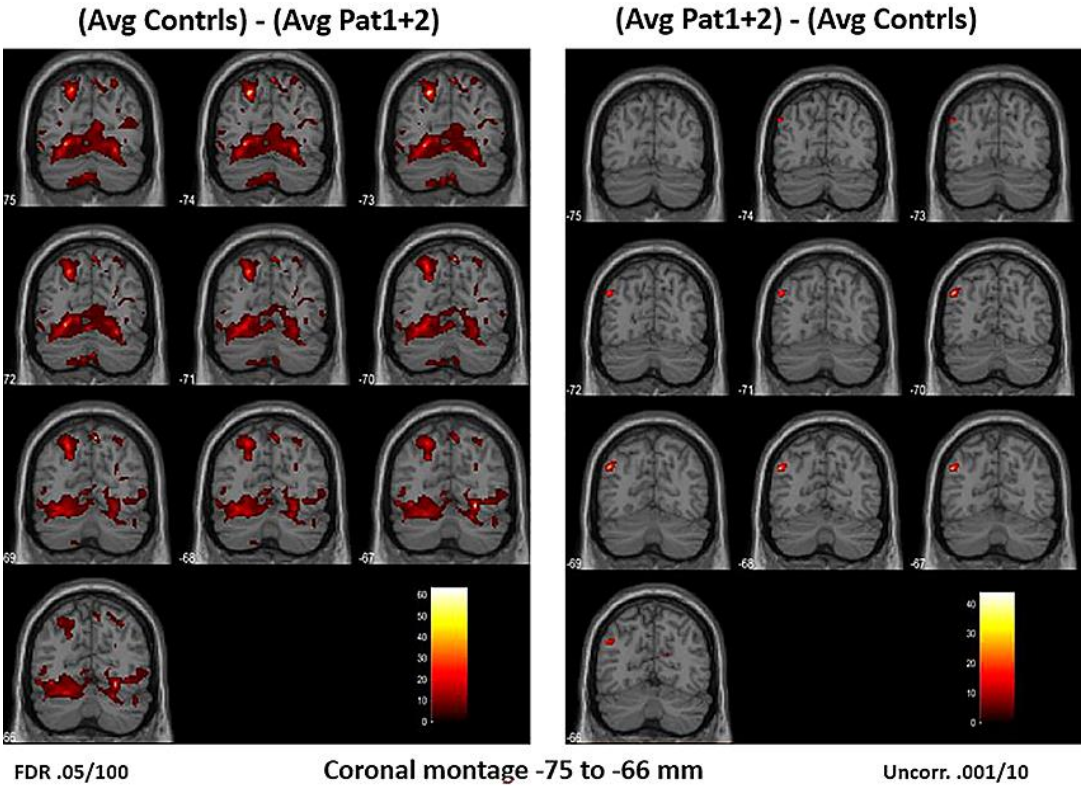

Fig. 3. Coronal slices showing fMRI activations in the occipital cortex when comparing the average of the 4 control subjects (Avg Contrls) with the average of the 2 fMRI sessions of the patient (Avg Pat1 + 2) in the group analysis.

Table 1. Result of the different clinical examinations of our patient

Date	Examination performed	Clinical findings
1981	First examination by an ophthalmologist due to asthenopia	Normal findings, including visual acuity
1987	Examination by a general practitioner due to headache and visual disturbances	Diagnosis: migraine with visual aura, often as hemianopsia
1987	Examination by an ophthalmologist due to a feeling of "pulsation" of the visual field; only seeing part of the objects she looked at	Myopia –2.0 D bilaterally; probably normal corrected visual acuity (not recorded explicitly)
1991	Examination by a pediatric neurologist, EEG, cerebral CT	Normal findings
1995	Hospitalized at the Department of Ophthalmology due to reduced visual acuity Fundus examination Perimetry Full-field ERG Cerebral CT Examination by neurologist	 RE: 0.17 LE: 0.25 Normal fundus bilaterally High number of relative defects Normal Normal Normal clinical findings
1996	Control examination by an ophthalmologist	RE: 0.3 LE: 0.3
2001	Hospitalized at the Department of Cardiology due to episodes of near syncope Measure of blood pressure Echocardiography 24-h ECG registration	 Orthostatic hypotension Normal Physiological Wenckebach
2006	Hospitalized at the Department of Ophthalmology due to experience of further impairment of visual function Visual acuity Perimetry Color vision (Ishihara; Farnsworth D-15) ERG, VEP Cerebral CT and MRI	 RE: 0.3-0.5 LE: 0.3-0.5 Some relative and absolute defects, no specific pattern Varying responses Normal Normal
2006	Neurological work-up due to a family history (niece) with possible swallow reflex disorder Laboratory test battery (including Ach-receptor antibodies, neuron antibodies, thyroid function, celiac disease antibodies, levels of vitamins A, D, E)	 Normal results
2010	Ophthalmological control examination Visual acuity Fluorescein angiography OCT	 RE: 0.25 LE: 0.25 Normal Normal
2011	Referral to the University Hospital in Lund, Sweden Multifocal ERG Tested for mutations in the *OPA-1* gene Multifocal VEP Visual acuity	Normal No mutations Abnormal: reduced amplitude from the first component in sector C compared to normal (Fig. 1) RE: 0.25 LE: 0.125
2012 and 2013	Visual acuity Examination fMRI	RE: 0.05 LE: 0.025 Abnormal activation pattern compared to normal controls (see more details in the text)

EEG, electroencephalography; CT, computed tomography; ERG, electroretinography; RE, right eye; LE, left eye; ECG, electrocardiography; VEP, visual evoked potentials; fMRI, functional magnetic resonance imaging; OCT, optical coherence tomography.