

Visual information processing in recently abstaining methamphetamine-dependent individuals: Evoked Potentials study

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Keywords

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Abstract

Objective: Methamphetamine (MAP) is an indirect dopamine agonist that can temporarily increase cognitive performance. However, its long-term abuse may cause dopamine depletion and consequent cognitive and attentional impairment. The worsening of visual functions in Parkinson's disease and their improvement after levodopa administration implicates the role of dopamine in the physiology of vision. This provides the rationale for the investigation of visual functions in abstaining MAP abusers.

Methods: We investigated changes in visually evoked potentials (VEPs) to pattern-reversal and motion-onset stimuli. Such changes serve as indices of visual information processing in the primary and associative areas in a group of recently abstaining MAP abusers (5 females, 18 males, MAP abuse 5.3 ± 2.8 years) and in 23 age- and gender-paired controls.

Results: We did not find differences between the groups in visual acuity. In the group of MAP abusers we observed an attenuation of the early responses around 80 ms and a prolongation of the P1 peak latency after the reversal of high spatial frequency checkerboards (10 and 20 arc min checks). Furthermore, an attenuation of the latter positive response (170 to 250 ms) was observed among all the stimuli in parieto-frontal derivations for the MAP abusers.

Conclusions: This is the first report suggesting a slowing and attenuation of VEP responses during visual processing in abstaining methamphetamine abusers.

Introduction

Methamphetamine (MAP) is a synthetically derived, amphetamine-based psycho-stimulant. Its relatively simple production has made it a widely abused illegal drug [1]. The MAP effect varies with dosage such that a low dose can evoke increased energy, attentiveness, decreased appetite, and increased libido in abuse-naïve users [2]. MAP's primary mechanism of action is increasing extracellular monoamine neurotransmitters (dopamine, norepinephrine and serotonin) by redistributing them from vesicular stores and by reverse transport induction [3]. However, chronic MAP use has been shown to decrease dopamine levels in several post-mortem and in vivo neuroimaging studies [1]. MAP neurotoxicity is related to the dysregulation of neurotransmitters and subsequent neuropsychological impairment of working memory, sustained attention, and suppression of irrelevant information [4].

Studies exploring MAP neurotoxicity have suggested frontal cortex and striatum impairment. Furthermore, detoxicated MAP users have been shown to have an accentuated metabolic brain activity in the parietal region. Positron emission tomography via injection of fluorodeoxyglucose was used to evaluate brain metabolism [5]. Similar results were seen using perfusion magnetic resonance imaging in the brains of 20 MAP users in another study. The study also revealed an increase in occipital and parietal activity in former MAP users compared to healthy controls [6]. However, some studies have shown normal metabolic function in the primary visual cortex of former MAP users [7, 8] by using proton magnetic resonance spectroscopy. These findings in MAP users provide the rationale for our study.

Interestingly, there are studies suggesting that low levels of dopamine can lead to the deterioration of visual function [9] or that administration of levodopa can improve visual functions [10]. Therefore, the MAP's neurotoxic effects on dopamine levels form another reason for this study.

An electrophysiological examination of the visual system such as visual evoked potentials (VEPs) can objectively evaluate the visual system in abstaining MAP abusers. To our knowledge, there are no prior studies that have evaluated VEPs in MAP abusers. The purpose of our study is to explore the functional state of the visual and associated cortex regions in subjects who are in treatment for substance dependence and who have recently abstained from MAP abuse.

We recorded VEPs after brain activation by pattern-reversal or motion-onset visual stimuli to assess neural processing between group of abstaining MAP subjects and controls.

Methods

Participants

We tested 23 subjects (19 to 34 years of age; 5 females) with a history of methamphetamine use (DSM-IV Code 304.40) who had been treated for three months at the Drug Dependence Treatment Unit of the Psychiatric Clinic during years 2005-2007. The average duration of methamphetamine abuse (intravenous in all cases) was 5.3 ± 2.8 years. The control group consisted of 23 healthy age- and gender-matched volunteers (19 to 36 years of age, 5 females). The control group had no prior history of using illegal drugs, including methamphetamine, and no prior ophthalmological or neurological abnormalities.

Informed consent was obtained from each subject. The study was approved by the Ethical Committee of the Faculty of Medicine in Hradec Králové, and experiments were conducted in accordance with the Declaration of Helsinki [11].

The patients had stopped taking MAP one to two months before they entered the study. Abstinence was required by the treatment programme, and dependence on any other substance apart from MAP was an exclusion criterion. During the program, visitors were not allowed to visit the subjects undergoing treatment.

Stimuli

The main positive peak P1 (P100) of the pattern-reversal visual evoked potentials (P-VEPs) originates in the primary visual area [12]. As a result, we used full-field (37x28 deg) 96% luminance contrast checkerboard (check sizes 10, 20 and 40 arc min: P-VEPs 10', P-VEPs 20' and P-VEPs 40') reversing at 2Hz to assess the function of the primary visual cortex.

We used motion-onset stimuli to activate secondary visual areas [13, 14] because the N2 peak of motion-onset visual evoked potentials (M-VEPs) is related to excitation of the parietal and medio-temporal areas [15]. We recorded three types of M-VEP responses to radial motion-onset of concentric circles. The stimuli subtended either 1) the 37x28 deg of the visual field – full display (M-VEPs FF), 2) the central 8 deg of the visual field (M-VEPs c8°), or 3) the intersection between the periphery outside of the central 20 deg and the full display (M-VEPs m20°). The stimuli randomly moved for 200 ms in a centripetal or centrifugal direction and were then stationary for 1000 ms. The detailed stimuli parameters for the radial motion are described elsewhere [16].

The stimuli were presented on a 21" computer monitor (Vision Master Pro 510, Iiyama Japan) subtending 37x28 deg of the visual field at a 0.6 meter viewing distance. The monitor was driven using the Visual Stimulus Generator 2/5 (CRS Ltd., UK) at a 105 Hz vertical refresh frequency. A mean luminance of 17 cd/m^2 was used for all projected stimuli.

Recordings

The acquisition was performed in a darkened, sound-attenuated, electromagnetically shielded room with a background luminance of 0.1 cd/m^2 . During the experiment, the subjects were seated in a comfortable chair and instructed to visually fixate on the marked centre of the

stimulus field without following the moving pattern. The correct fixation was monitored using a near-infrared camera. EEG sweeps of 440 ms duration were recorded from 6 unipolar derivations (O_L , O_Z , O_R , P_Z , C_Z , F_Z) using the right earlobe (A_2) as a reference (O_L , O_R electrodes were placed 5 cm to the left or right of the O_Z position). The recordings were taken binocularly. The ground electrode was connected to the reference electrode. All electrode impedances were kept below 5 k Ω . After amplification (20,000 times) in the frequency band of 0.3 - 100 Hz (amplifiers Contact Precision Instruments - PSYLAB, System 5), the signal was sampled at 500 Hz and off-line averaged and digitally smoothed by Savitzky-Golay filter (3rd polynomial order, 21 samples) on a personal computer. The recordings were synchronized with the monitor electron beam's backward trace immediately before the first motion or the structure reversal video frame.

Each subject underwent one recording session, which consisted of repeated binocular stimulations including three spatial frequencies of the pattern-reversal stimuli and three types of motion stimuli. Eighty single sweeps were averaged for all stimulus conditions. The order of stimuli presentation was identical in both groups to avoid habituation and/or fatigue bias [17].

Analysis

Statistical analysis of the recordings was based on the group differences in the VEPs waveforms. A technique using the Principal Component Analysis was adopted to avoid multiple statistical comparisons (PC1) [18]. The method extracts the first principal component of a waveform created as a difference between pairs of patients and controls. The component projections (weights) were tested among subjects using the Student's t test. The exact timing of the amplitude differences was determined by the pointwise paired t tests.

Because the full-wave comparison can be partially insensitive to small latency shifts, we also evaluated the following important clinical VEPs parameters: the interpeak amplitudes, the P1 peak time latency of the P-VEPs, and the N2 peak time of the M-VEPs.

A significance level of 5% ($p=0.05$) was used for all statistical tests.

Results

Even though the groups did not differ by sex or age (Willcoxon matched pair test $p=0.944$), we found significant differences in several tested parameters of the VEPs between the groups. All the evaluated VEP peaks were manually marked as a local maximum/minimum. In the case of a split peak, the mid-point of the wave was evaluated. *Amplitude* denotes a mean of interpeak amplitudes of local extremes closely preceding and following the evaluated peak. Because some data (the P1 peak *Amplitude* of P-VEP 10' in both groups and the N2 peak latency of M-VEP c8° in patient group) did not show normal distribution (tested by Shapiro-Wilk's W test), the Wilcoxon matched-pairs non-parametric test was used to assess the difference between the groups.

When the responses from the primary visual area were assessed by the P1 peak of P-VEPs, we found significantly smaller *Amplitudes* (29% and 34%) for stimulation by middle size (20 arc min) and fine (10 arc min) checkerboard pattern in the MAP group. The P1 latency of P-VEP 10' was significantly longer among patients. Although the intergroup median difference was small, the paired differences of latencies were statistically significant as depicted in Fig. 1. The detailed description of the P-VEP parameters is listed in Table 1.

Besides the evaluation of the aforementioned clinically used parameters, we also compared full VEP curves, which enabled us to search for group differences in full recording time. The overall assessment of VEPs differences by the PC1 method brought significant results in the all P-VEP, M-VEP-FF and M-VEPc8° as is depicted in Figure 2 and Figure 3. Therefore we use the pointwise comparisons to refer absolute amplitude changes in the following. We detected a strong amplitude reduction within all tested P-VEPs in the central and parietal derivations. This was also visible in other derivations (see the grand averages in Figs. 2a, 2b and 2c).

Figure 4 provides a comprehensive overview of the time and location of the intergroup's significant differences in the VEP amplitudes. The dominant reductions of P-VEPs in patients were around 80 ms (negative peak - N1) in parieto-occipital derivations and 200 ms (late positivity – P2 peak) in the fronto-parietal area. In addition to these amplitude reductions, we also found a few cases of the P-VEP amplitude enhancement (marked in gray in Fig. 4). This was apparent for P-VEP 40' in the left occipital derivation.

The N2 peak latency to radial motion onset was significantly delayed when the central and full field stimuli were used in the patient group (see Table 1). The N2 *Amplitude* did not differ between the groups (see Table 1). Similar to what was seen in the P1 latency, the M-VEP N2 peak latencies differed significantly in a paired comparison. Figures 1c and 1d effectively document this in scatter-plots. Whole curves analysis showed that M-VEPs amplitude was severely reduced in late positive peak within the central, parietal, and frontal derivations for all motion stimuli (see Fig. 3). We also observed a small amplitude enhancement of the M-VEPs in central occipital derivation O_Z once the periphery of the visual field was stimulated. Figure 4 displays other enhancements as gray regions preceding larger reductions (in black). These are caused by alternating VEPs polarity such that the faster changing activity is during the crossing of the zero line smaller than the slower activity (cf. P_Z derivation of M-VEPs FF in Fig. 3 and the fourth row in the P_Z subplot of Fig. 4d).

Discussion

Our study was partly motivated by reports of increased metabolic activity in the occipito-parietal region in abstaining MAP abusers [5, 6, 18]. Volkow et al. used positron emission tomography in 15 detoxified MAP abusers and found higher brain activity (up to 14%) in comparison to non-matched 21 healthy controls. They found an increase of [¹⁸F] fluorodeoxyglucose consumption in the occipito-parietal region. It is important to note that the subjects in this study had their eyes open during the examination and that they did not perform any particular tasks. The same authors also used perfusion MRI to study 20 MAP abusers [6].

They reported an increase in regional blood flow in the left temporo-parietal white matter (13%), left occipital (10%), and right posterior parietal (24%) regions and a decrease in blood flow in the right parietal region (11%) in comparison to sex and age-matched controls. However, they do not mention the tasks that subjects may have undertaken during the study. Other studies have used proton magnetic resonance spectroscopy in MAP-dependent individuals and reported a normally functioning primary visual cortex [7, 8].

In our study, we rarely observed increased VEP amplitudes (refer to the gray regions in Fig. 4). On the contrary, the reduction of VEPs in the MAP group was the most frequent change observed (expressed as the black regions in Fig. 4). This seems to contradict prior studies that have suggested an enhancement or normal activity in the occipito-parietal region. We believe that these discrepancies can be attributed to the different visual tasks performed during recordings (as discussed in the paragraph above). Though there are various reports describing the relation between metabolic and electrophysiology techniques (e.g., [19]), we have to emphasise that our results have been accumulated differently in comparison to these prior studies. The VEP recordings represent a correlate of transient neural activity, while the metabolic studies record sustained activity throughout the metabolic processes.

The most dominant early differences of the VEPs between groups we observed in the full wave comparison 80 ms after the stimulus onset (see Fig.4) and in P1 peak (see Table 1). Because we recorded only six derivations in this study, we rely on previous VEPs source studies to determine particular visual areas of reduced VEPs activity among MAP subjects. It was described that early peaks (N75 – N1 and P100 – P1) of the pattern-reversal VEPs are generated in the primary visual area (V1/V2) of the occipital lobe [12]. Though a recent study by Barnikol et al. suggests that it is also generated in the medio-temporal area (motion processing V5), which is activated in parallel [20], the stimuli for the V5 activation should have a low spatial frequency [21]. However, we observed the differences for the smallest checks. As a result, we conclude that the early visual cortical processing of former MAP users is altered in the primary visual area (V1/V2).

Another explanation for VEP changes might be due to dopamine modulation of the center-surround antagonism of the receptive visual fields in the retina. Electroretinogram findings have been reduced or prolonged in Parkinson's disease (e.g. [9]). Another study reported MAP toxicity in rats' retina [22]. The retinal changes may possibly induce a decrease in visual acuity and subsequently reduce the amplitude in pattern-reversal VEPs [23].

There was no statistically significant difference in visual acuity between groups in our study. Furthermore, the changes in late VEPs components were not preceded by an impairment of the early responses in some derivations (e.g., the VEPs to pattern reversal of 40 arc min checks in occipital derivations; see Fig. 4). In consequence, we can suggest that the reduction of amplitudes and selective slowing of the cortical activity is the result of altered brain processing. This has also been proposed for Parkinson's disease [24]. However, we cannot reject a possible parallel impairment to the retina.

Interestingly, the P1 changes are largely expressed in the P_z derivation. Evaluation of Fig. 2 shows that the P-VEP is almost flat in the P_z derivation, and polarity reversal is present in the C_z derivation for MAP users. This implies that the VEP's electrical source is approximately "under" the P_z electrode. In the control group, the VEP responses in the C_z derivation are close to zero. This observation suggests that there is a shift or a change in orientation of electrical sources (dipoles) toward the O_z derivation within the abstaining MAP users. However, a multichannel experiment should to be performed in order to fully support this observation.

The major intergroup VEPs differences were observed for both pattern-reversal and motion-onset in the fronto-parietal derivations within 170 to 250 ms time frame. The abstaining MAP abusers' late positive peak (P2) displayed significantly smaller amplitude. Similar clinical results were observed in a group of 80 alcoholics such that the P2 peak of pattern-reversal VEPs was prolonged. The authors did not find correlation to other toxic effects of alcohol. [25]

Our analogous results for the P2 peak in P-VEPs and M-VEPs are in agreement with other studies. Similar independent components of pattern-reversal and motion-onset responses suggest that the P2 peak is generated by common neural processes [26]. Another study has found that the P2 peak of the motion-onset VEPs can be adapted by the preceding pattern-reversal [27]. As a result, amplitude reduction of P2 peak within the MAP group could correspond to faster or stronger adaptation.

We found only one study localising the P2 peak of M-VEP neural sources.[28]. These authors showed at P2 peak time activation of several sources, including the occipital, posterior-parietal, and temporal areas. We observed the strongest drop of amplitude in parieto-central derivations. It seems that the posterior-parietal cortex is among the hypofunctional regions of MAP abusers. The parietal area is involved in visual spatial attention [29] and closely cooperates with the frontal cortex such as gaze control[30]. Therefore, frontal area hypofunction in MAP abusers (i.e., decreased activity of the attention network node) can be related to an understimulation of the parietal node and subsequent lower P2 peak amplitudes. MAP abusers have been shown to do worse than control subjects in tasks that require the suppression of a distractor [31] what supports attention impairment. However, the behavioural correlates and role of attention were not addressed in our VEP study.

In our experiments, we selectively assessed the processing of information in the primary and associative visual areas by VEPs recording. We report that long-term abuse of MAP exhibits changes in visual information processing. Our findings displayed slowing, attenuation, and reorganisation of VEPs to pattern-reversal and motion-onset stimuli among abstaining MAP abusers in comparison to age and sex-matched control group.

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VEPs			median	min	max	25%	75%	p
P-VEP 40'	Latency [ms]	Patients	110.0	102.0	120.0	108.0	114.0	0.126
		Controls	109.0	102.0	121.0	106.0	112.0	
	Amplitude [μ V]	Patients	11.8	6.2	23.2	9.3	14.7	0.692
		Controls	13.0	5.2	26.8	10.3	16.4	
P-VEP 20'	Latency [ms]	Patients	112.0	104.0	118.0	108.0	115.0	0.389
		Controls	110.0	98.0	120.0	105.0	116.0	
	Amplitude [μ V]	Patients	8.8	4.1	20.0	6.1	14.8	0.048
		Controls	11.6	5.8	24.7	10.4	15.8	
P-VEP 10'	Latency [ms]	Patients	122.0	112.0	147.0	116.0	127.0	0.021
		Controls	119.0	107.0	128.0	112.0	122.0	
	Amplitude [μ V]	Patients	9.0	4.6	22.3	5.8	13.3	0.001
		Controls	14.5	5.8	44.3	10.9	18.0	
M-VEP FF	Latency [ms]	Patients	164.0	130.0	185.0	159.0	172.0	0.004
		Controls	156.0	133.0	178.0	145.0	161.0	
	Amplitude [μ V]	Patients	9.2	3.6	15.4	6.4	10.7	0.487
		Controls	9.7	4.5	18.8	6.4	11.4	
M-VEP c8°	Latency [ms]	Patients	159.0	145.0	203.0	154.0	170.0	0.001
		Controls	157.0	139.0	186.0	147.0	161.0	
	Amplitude [μ V]	Patients	8.3	2.7	12.9	5.5	10.8	1.000
		Controls	8.4	3.3	15.8	4.8	10.7	
M-VEP m20°	Latency [ms]	Patients	158.0	135.0	175.0	153.0	165.0	0.465
		Controls	154.0	137.0	180.0	150.0	160.0	
	Amplitude [μ V]	Patients	7.7	2.3	15.0	6.1	11.9	0.323
		Controls	10.0	3.8	20.5	7.4	12.3	

Table 1

The parameters of VEPs recordings are described by median, minimum, maximum, lower (25%) and upper (75%) quartiles. The “p” denotes probability for Wilcoxon matched pair test between patients and controls. The significant differences are emphasized in bold. The *P-VEP40'*, *P-VEP20'* and *P-VEP10'* specify P1 peak latency and inter-peak. *Amplitude* for three different stimuli check sizes as they were read in central occipital derivation - O_z . The *M-VEP FF*, *M-VEP c8°* and *M-VEP m20°* indicates N2 peak parameters in one of the O_L , O_Z , O_R or P_Z derivations with the highest *Amplitude*.

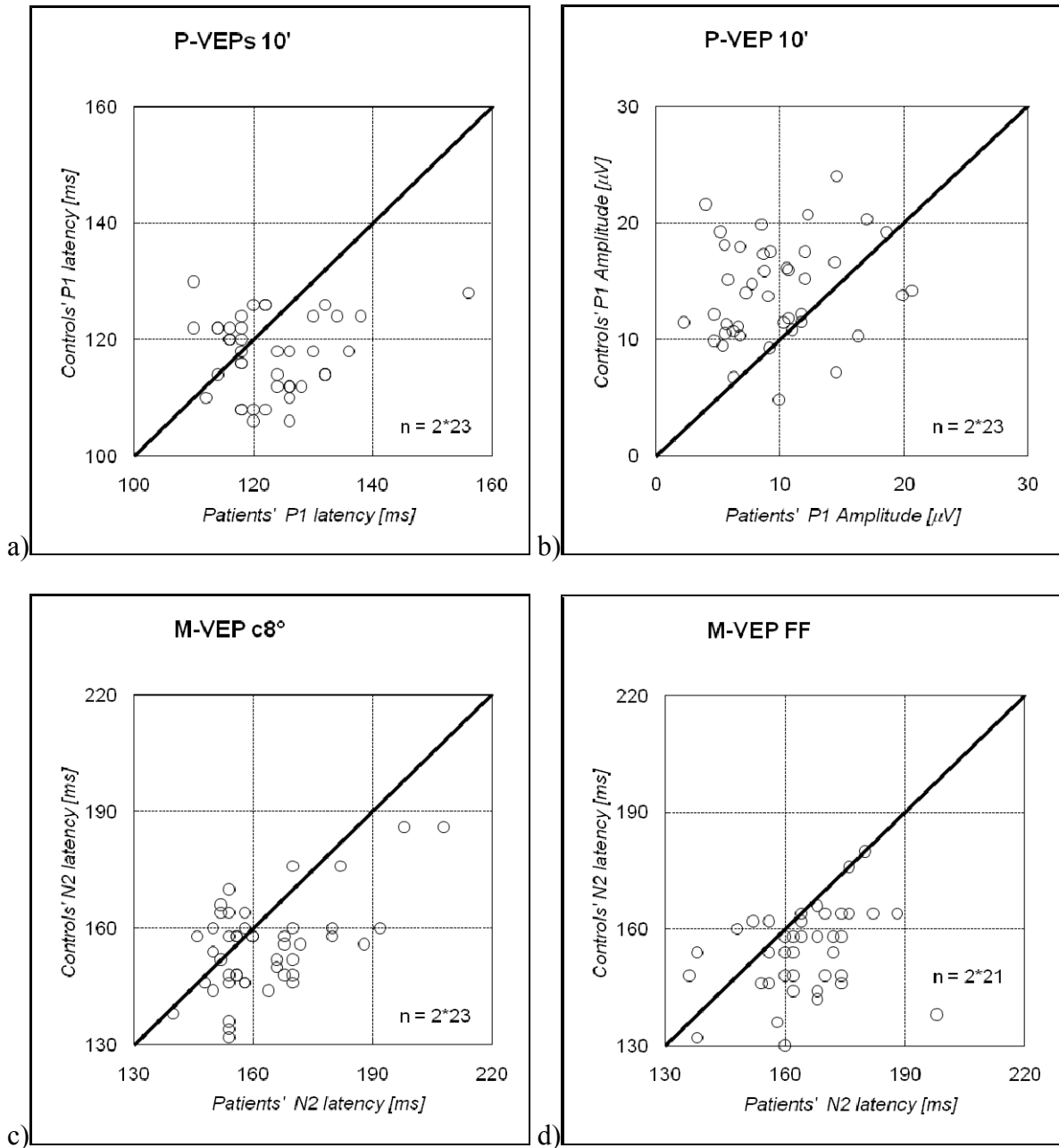
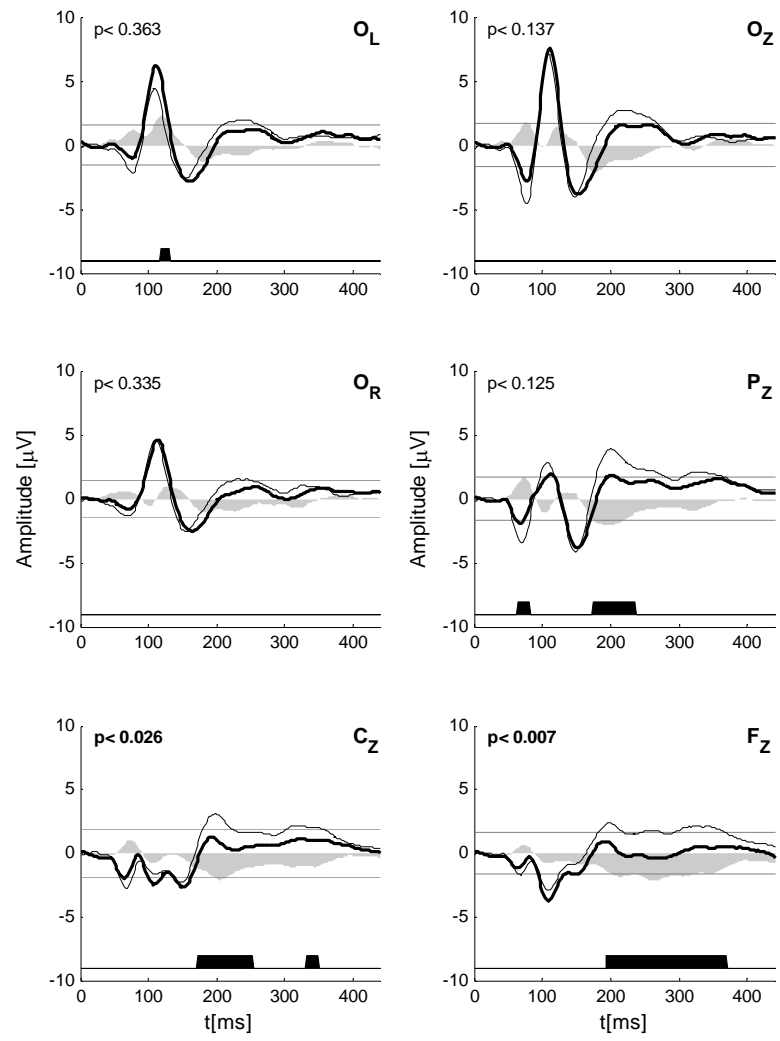


Figure 1

The scatter plots compare P1 peak latency (1a) and VEPs Amplitude (1b) to 10' checks' pattern reversal between MAP subjects and controls. The following subplots depict the N2 peak latency of radial motion onset VEPs for stimulation in full field (1c) and central 8° variant (1d). Each age and sex matched pair of a control and a MAP subject is represented by two points - repeated measurement ($n=2 \times 23$, only in 1c is the $n=2 \times 21$ because two patients were not recorded with this stimulation). Some points overlap in plot. Points located below the diagonal indicate longer latency (Figure 1a, 1c and 1d) or higher amplitude (Figure 1b) for patients in the pair. All comparisons were statistically significant (see Table 1).

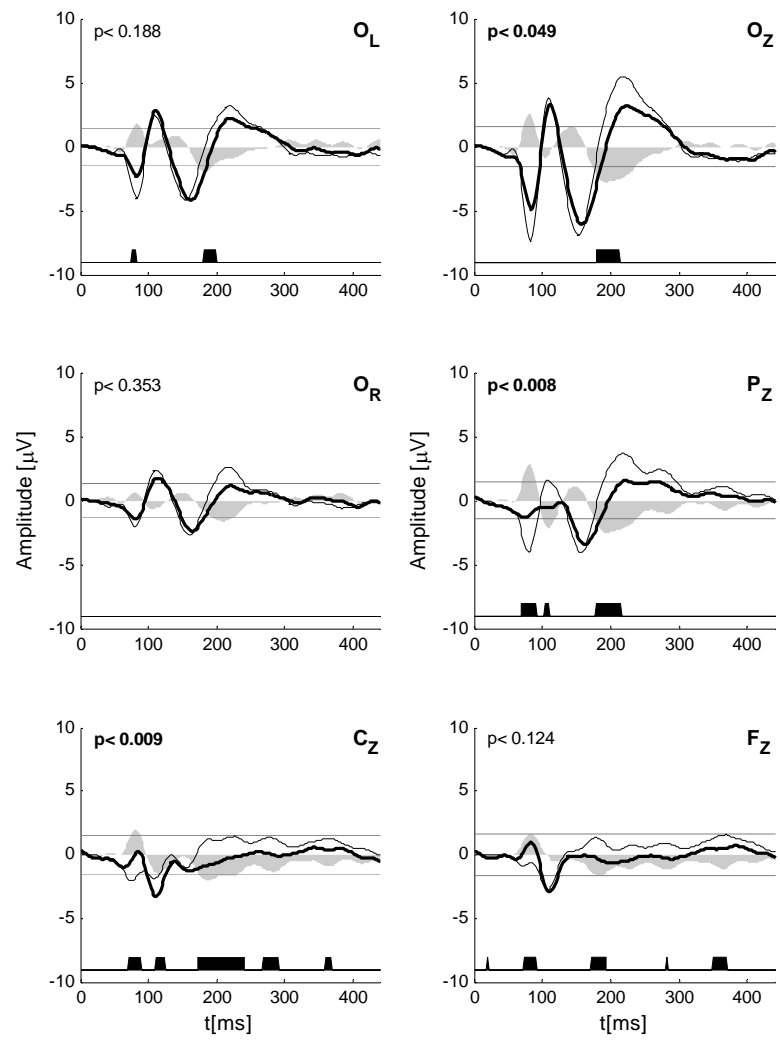
2a)

P-VEPs 40'



2b)

P-VEPs 20'



2c)

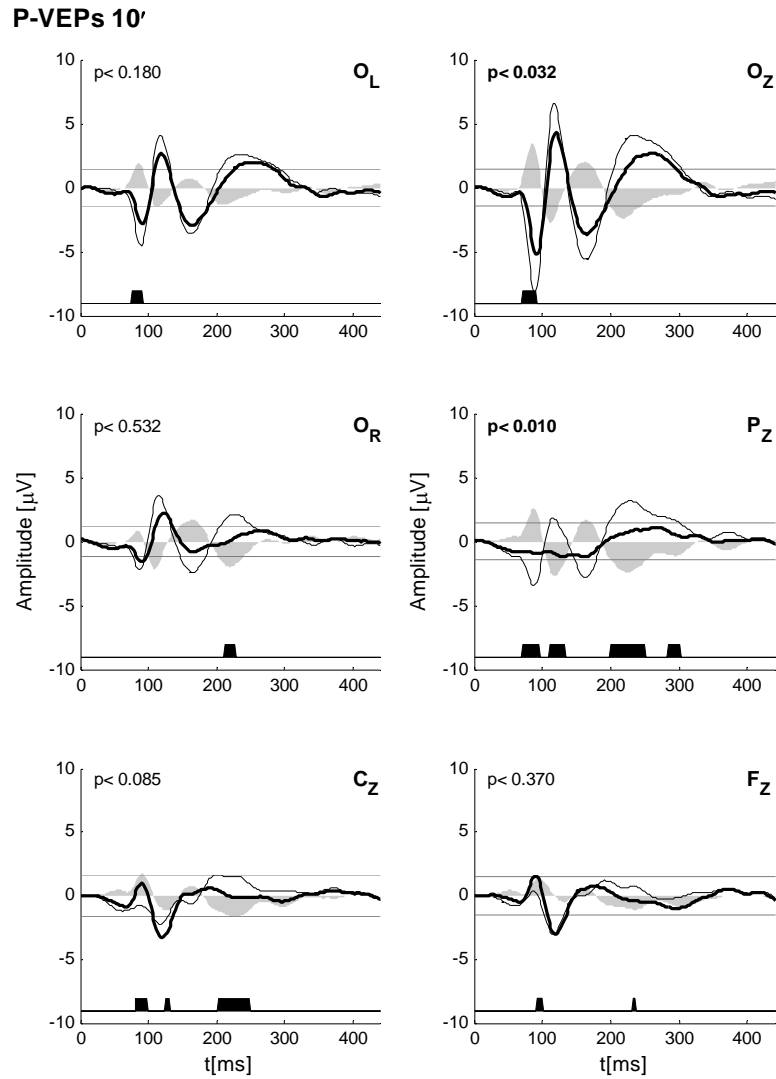
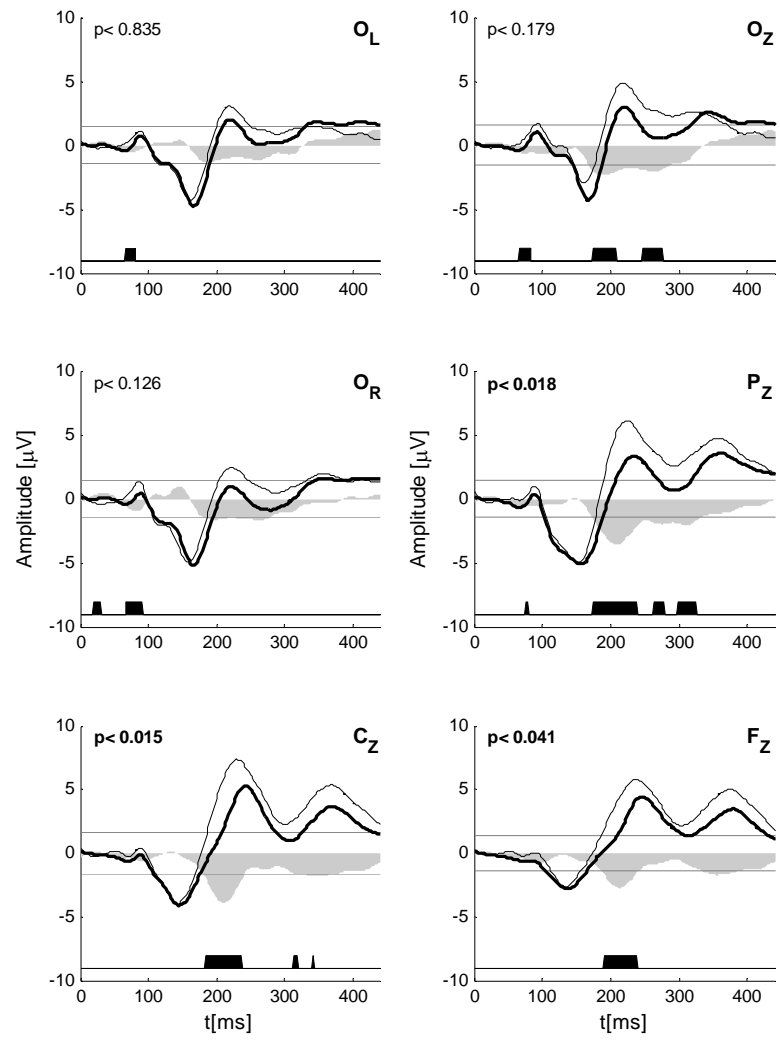


Figure 2

This figure depicts the grand averages of VEP responses to pattern-reversal (40', 20' and 10' check size in figures 2a, 2b and 2c, respectively). The thick lines represent grand averages of 23 patients. The thin solid curves were recorded from 23 matched controls. The gray filled area highlights the difference between the control and patient responses. The derivation is indicated in the upper right corner of each appropriate plot. The statistical difference of point-wise paired t-test is depicted in the bottom part of each plot as a black area. The gray area exceeding the variability of the signal is illustrated by two lines around the zero amplitude. This gives similar information. The variability was determined as 2.5 times the standard deviation within the first 60 ms of difference signal between patient-control VEPs. The overall difference of curves is assessed by PC1 method (see the *Analysis*), which is noted in the left upper corner of the plot. The responses show a statistically significant drop of activity in early processing (around 80 and 120 ms) but also a drop in the later positive wave (around 200 ms) within the MAP subjects.

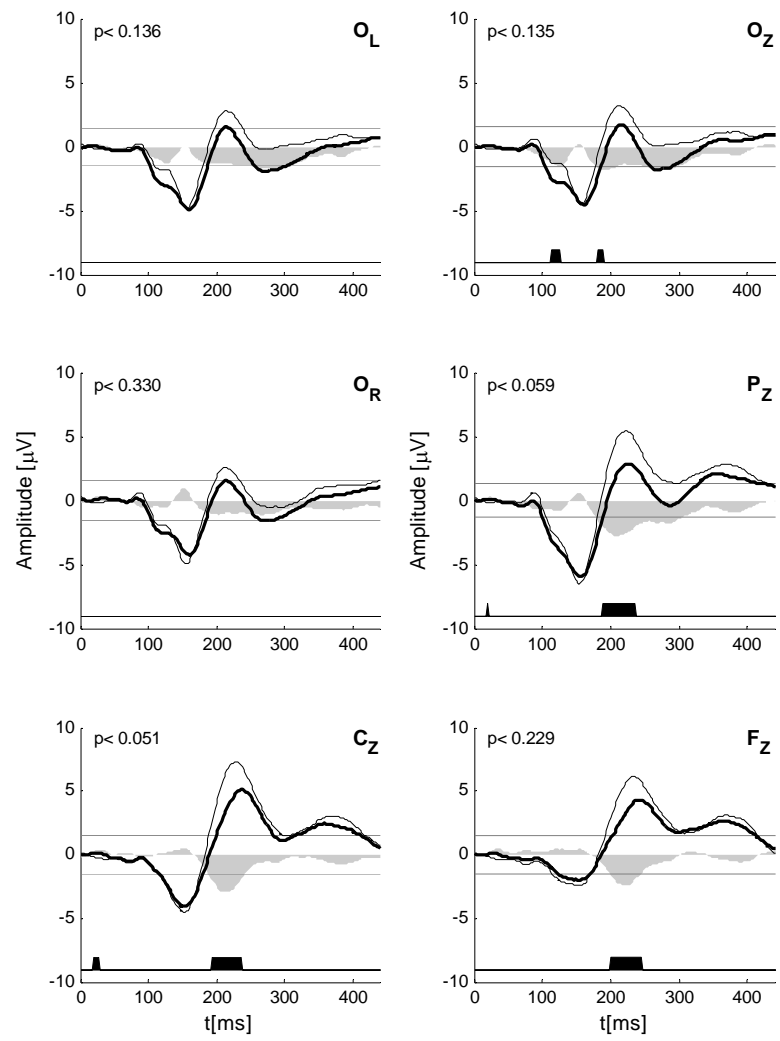
3a)

M-VEPs FF



3b)

M-VEPs m20°



3c)

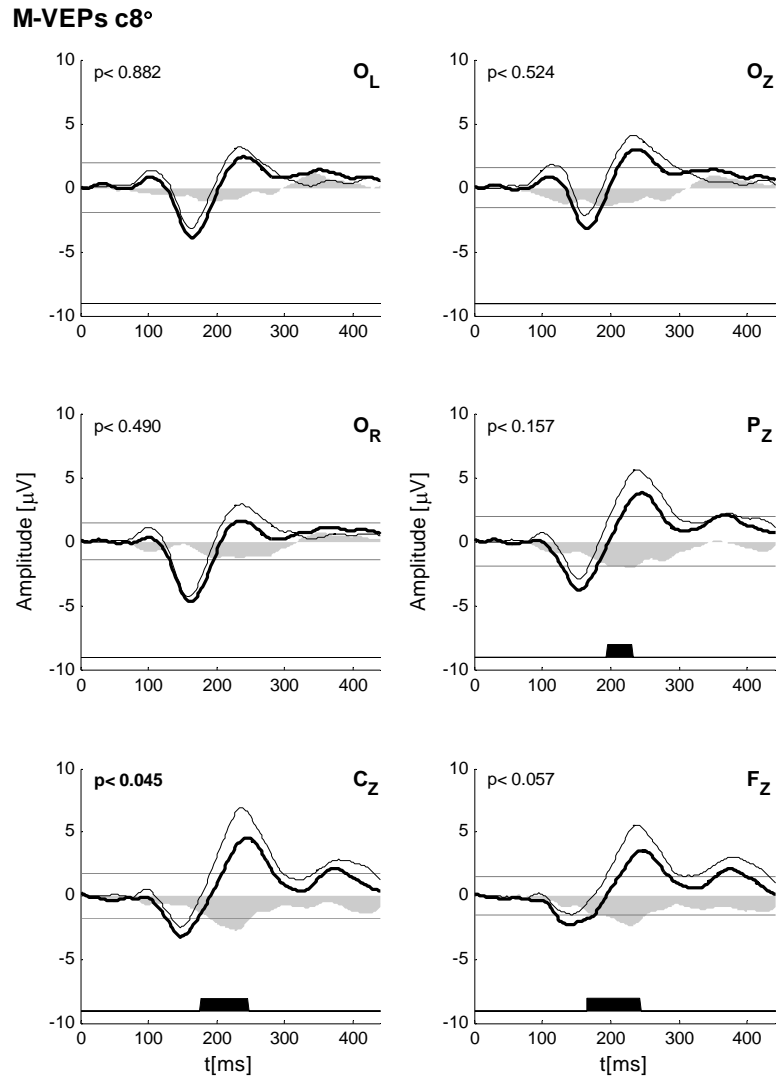


Figure 3

This figure depicts the grand average of M-VEP responses to the radial motion-onset (full-field, periphery out of central 20° and central 8° in figures 3a, 3b and 3c, respectively). The thick lines represent average responses from 23 MAP subjects. The thin solid curves were recorded from 23 matched controls. Refer to Fig. 2 for further description of the figure arrangements. We observed a statistically significant drop in a slow positive wave for MAP subjects.

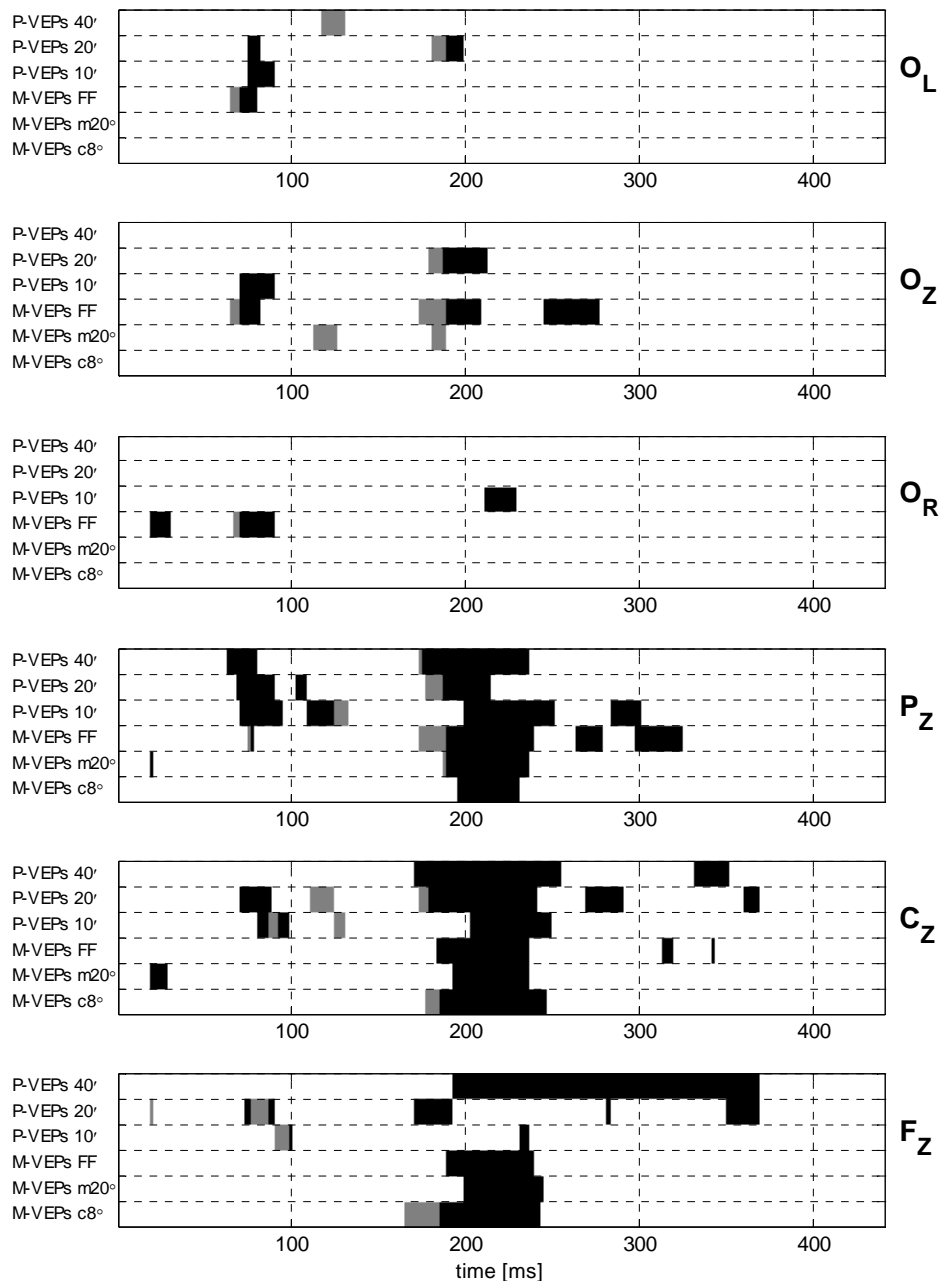


Figure 4

This figure summarizes the significant changes between MAP subjects and controls in VEPs results. The abscissa represents the time, and each plot represents one derivation. Stimuli are organized in rows. P-VEPs 40', P-VEPs 20', and P-VEPs 10' correspond to VEPs evoked by pattern-reversal of 40, 20, and 10 arc min checks. M-VEPs FF, M-VEPs m20°, and M-VEPs c8° indicate VEPs to radial motion-onset in full stimulus field, periphery out of central 20°, and central 8° of the visual field respectively. The significant drop in absolute amplitude within the MAP subjects is depicted in black, while the significant increase in amplitude is depicted in gray. The most systematic change is seen in the drop in amplitude around 200 ms within the frontal, parietal, and central derivations. Such systematic changes are also seen in the radial motion-onset VEPs. Each row corresponds to statistically significant differences of VEPs expressed as the bottom line of subplots in Fig. 2 and Fig. 3.