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Dipole Source Localization of Flash Visual Evoked Potentials to Cone Specific Stimuli

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Abstract–**This study aimed to analyze the neuronal sources of the visual evoked potentials (VEP) to flash stimuli of the blue- (S-cone) and the red-green (L- and M-cones) color channel of the human visual system. For 11 healthy volunteers a 64 channel electroencephalogram (EEG) was recorded during selective central excitation of S-cones and M- and L-cones. Individual and grand average data were first analyzed topographically. Source localization was then carried out with the help of a realistically shaped three compartment boundary element model and a mirrored moving dipole model restricted to occipital cortex. Two main components, N1 and P1, of blue- and red-green color channel were clearly distinguishable in all subjects. We found a significant latency difference between both stimulation channels for N1 and P1. Results showed no visible differences in the topography and no significant differences in dipole localization between both channels. Talairach coordinates of grand averages indicated activation in area 18. Comparison of results of separately stimulated eyes showed no differences. Our findings revealed that neural processing occurs in the same areas of the visual cortex for stimuli with identical conditions but different spectral properties. The signals of blue- and red-green color channels are transmitted in distinct pathways to the visual cortex, thus the latency differences might be caused by different anatomical and functional properties of these pathways.**

I. Introduction

Globally, glaucoma is a major cause of blindness. If diagnosed at an early stage, appropriate therapies can be initiated to prevent further progression of this medical condition. Electrophysiological examinations with stimuli activating the blue color channel can potentially reveal disorders in color perception for both glaucomatous patients and patients with suspicion of glaucoma [1-3]. Based on specific stimulation of the S-cones these methods have the potential of earlier diagnosing glaucoma compared to conventional procedures. To accomplish this, a selective color stimulation of the blue channel is required. Consequently, we utilized different color models, the physiological properties of the human eye and the silent substitution technique (SST) [4], [5] to generate stimulation sequences that allow a selective excitation of the S-cones and L-and M-cones.

Studies using visual stimuli with different color compositions revealed activities in areas V1, V2 and V4, whereby V4 was assumed to be the major area responsible for color processing [6]. Concerning responses to flash visual evoked potentials (VEP) it is strongly assumed that early components arise from activities in striate cortex (V1, area 17) and secondary components (circa 100–200 ms) from activities in extrastriate cortex (area 18 and 19) [7]. Overall, no detailed statements have been made in present studies about the exact temporal and spatial properties of VEP particularly under application of selective color stimulation.

In our study we aimed to reconstruct the neuronal sources of the VEP under selective stimulation of the blue- and red-green-cones and therefore to examine possible differences of the source parameters.

II. Materials and Methods

A. Subjects

In this study 11 healthy volunteers: 4 females and 7 males (mean age ± standard deviation, 25.8 ± 5.3) were examined. All subjects were free of eye diseases and correct color vision was checked with ishihara-plats. Vision of three probands was corrected (maximal ± 2 dpt). None of the volunteers had a history of neurological or psychological disorders and furthermore, none were taking any medication or drugs (except birth control pills).

B. Stimulation

We analyzed several stimulators for their spectral and dynamical properties [8] and decided to use the LCD-display "MYRICA V30" (Fujitsu Siemens), that proved to be the best choice for an effective, selective stimulation that is required for our studies. The silent substitution technique (SST) is described in [4] and [5]. Based on the stimulation principle of the SST a maximal activation of one cone type can be achieved while the activation level of the other cone types is kept constant. We generated two flash stimulation sequences which each consist of two states in order to excite the blue- and the red-green-channel. Throughout blue channel stimulation, for instance, a maximal sensitivity difference occurred during state changes for the S-cones whereas a minimal difference emerged for the L- and M-cones. This can be achieved by using colors which stimulate the L- and M-cones with dissimilar spectral distributions and cannot be distinguished by the visual system – so-called metameric colors. Concerning the stimulator (LCD-display), the quantum absorption of L- and M-cones remained constant during state changes whereas a maximal absorption and thus a maximal activation were reached for the S-cones. Consequently, the contribution of M- and L-cones to the VEP response was minimal whilst the contribution of the S-cones was maximal due to flashes (state changes). To ensure an excitation of the entire fovea and the regions close by we

used the 10° observer for stimulation. A central, monofocal visual field stimulation with flashes of color specific composition was applied as excitation method. The SST sequences were presented in a full circle with eccentricity of 25° within a central fixation point whereas the stimulation area outside of the circle was used to suppress rod responses. Each eye was stimulated separately. The stimulation rate of 0.7–1.25 Hz was randomized in order to exclude habituation. A total of 200 stimuli was applied for each sequence.

C. *Data Recording*

For visualization of the stimulation sequences and electroencephalogram (EEG) recording we utilized a Theraprax® system (neuroconn, Ilmenau, Germany) with a 64 channel amplifier (ground Cpz). To allow spatial coregistration of VEP and MRI data, anatomical landmarks (PAL, PAR, nasion, inion) and channel positions were digitalized with a Polhemus Fastrack® digitizer (Neurosoft, Inc.). Analog-to-digital conversion was performed with a sampling frequency of 512 Hz.

D. *Data Preprocessing*

The raw data was first filtered to remove electrode drifts and parasitic frequencies. We developed detectors for electrooculogram (EOG), electromyogram (EMG) and alpha artifacts under Matlab® to reject artifact trials. Then a verification algorithm was applied to receive the 100 best sweeps (highest SNR after artifact rejection) of the 200 recorded responses for averaging. Finally, the preprocessed data were referenced to common average reference. An artifact occurred after trigger onset, caused by the hardware trigger. This artifact was faded out (0–50 ms) using the mean value of the first two samples after the artifact appeared. The fade-out did not affect following investigations because it was located outside the relevant analyzed interval. The data of all subjects were standardized and averaged to obtain the grand average datasets.

E. *Source Localization*

The preprocessed data were analyzed with the source localization software CURRY (version 4.6). For each subject the volume conductor was modeled by a BEM consisting of 3 compartments. A T1 weighted anatomical MRI-scan of the head was recorded for three probands. For the remaining 8 subjects the Average-MRI dataset, available in CURRY, was matched to the real head shapes. The anatomical landmarks were used for linear scaling of the three space dimensions. Next, we constructed BEM models from the segmented and triangulated compartments skin, skull and liquor with a triangle size of 7, 9 and 10 mm, respectively. A homogeneous conductivity of 0.33, 0.0042 and 0.33 S/m was assumed. A mirrored moving dipole for source modeling with a spatial restriction in occipital cortex was applied [9], [10]. Furthermore, the reconstructed sources were constrained to the inner BEM compartment. We allowed the two mirrored dipoles to move within a spherical region with a maximal radius of 30 mm to the defined seed point. Based on the time-domain of the mean global field power (MGFP), the reconstruction intervals were defined from beginning to maximal activity (MGFP-Peak). Before reconstruction, we performed a singular value decomposition (SVD) on the analyzed interval and only components with positive signal to noise ratio (SNR) within the analyzed time interval were used for further calculations. The noise was estimated in the interval from 600 to 800 ms since no noticeable signal was observed in this interval. We used the Talairach space to compare the localization results between both color channels and for coregistration with the anatomical structures of the Talairach brain. The Talairach-Daemon-Client was applied to obtain the distances of the dipole coordinates to visual areas. A two-tail paired t test was used for statistical evaluation.

III. Results

A. *Right-Left Comparison*

As a result of the stimulation of the right and left eye with both stimulation sequences, 44 data sets were available for

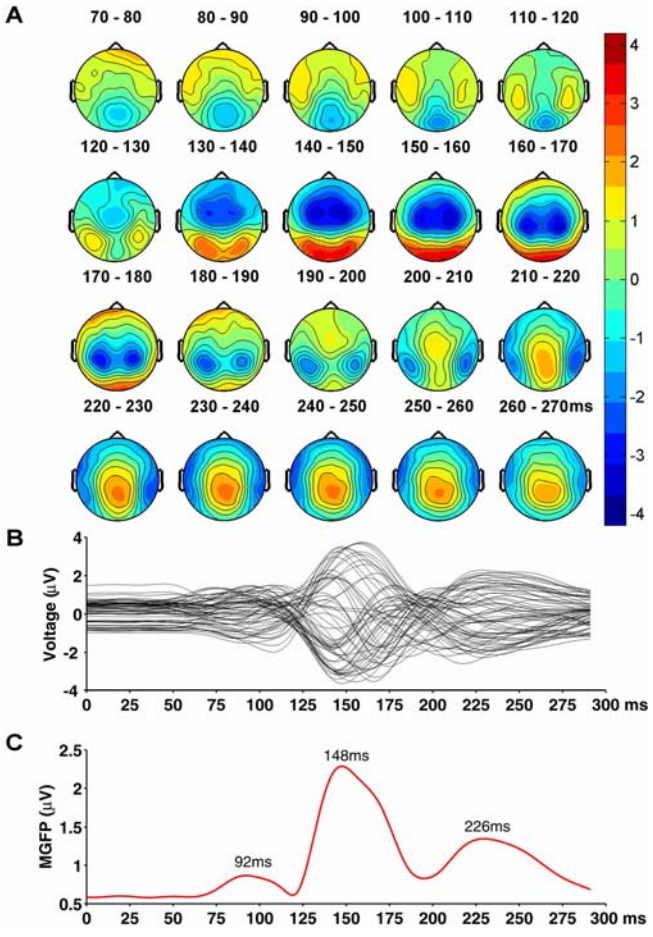

Fig. 1. Grand averages of the red-green color channel after stimulation of the right eye. (A) Scalp potential distribution as a function of time. The selected time interval (70–270 ms) comprises the topographical presentation of the main activities (components) N1 and P1 and a late component appearing unspecific among all subjects. (B) Waveforms of all 63 channels (Butterfly-Plot). (C) Mean global field power (MGFP) courses.

analysis. A comparison of the topographical distributions and the dipole coordinates of each eye obtained nearly similar results for all subjects. The reason for this was the central stimulation applied in this study.

B. Average Waveforms

In all subjects, the components N1 and P1 were observed since they were identified as the most robust components. The grand average MGFP curves are composed of three main peaks (see Fig. 1 C). Maximal activity of the first negative component (N1) appeared at 125 ms after stimulus for the blue channel and 92 ms for the red-green channel (see Fig. 1 C) whereas the maximum of P1 emerged at 170 ms for the blue channel and at 148 ms for the red-green channel. The paired t test showed significant temporal differences in latencies of MGFP maxima between both stimulation channels (right eye: $P < 0.05$ for N1 and $P < 0.001$ for P1; left eye: $P < 0.01$ for N1 and $P < 0.01$ for P1). These differences expressed themselves in a distinct time delay of the blue channel in comparison to the red-green channel. The third maximum of the MGFP curves was classified as a late component (> 200 ms), occurring unspecifically among all subjects. This manifested in a blurred temporal and spatial activity. Concerning the amplitudes, we found small differences in grand averages between both color channels in component N1 and clearly visible differences in component P1. The t test showed no significant differences between amplitudes in N1 for the stimulated right eye ($P = 0.2$) and significant differences for the left eye ($P = 0.01$). For P1 we found high significant differences for both eyes ($P < 0.001$).

C. Topographical Analysis

In the topographical EEG maps the negative activity centers were situated symmetrically above the occipital cortex for N1 and the positive center in temporal-parietal region. The positive activity center for P1 was also found above the occipital cortex whereas the negative part was located above central cortex (see Fig1 A). We used the centers of these activities to place the seed points for the dipole fits.

D. Source Localization

The field distribution of the fitted mirrored dipoles showed good agreement with measured data. Depending on the SNR a Goodness-of-Fit (GOF) of higher than 87 % was obtained. A comparison of Talairach coordinates of grand averages indicated no clear localization differences in the three planes (saggital, coronal, axial) between the color channels for both component N1 and component P1 (see Fig. 2, A–C). Furthermore, the difference was not significant between blue and red-green channel for all Talairach coordinates of all subjects (t test). Only small differences were found between the Talairach coordinates of grand averages and average coordinates of individual subjects. Dipole positions in general were close to area 18 (maximal distance 9 mm; Talairach-Daemon-Client). The component P1 had lower distances to area 18, with respect to N1. Significant differences were found in axial direction (z-coordinate Talairach space) between both components N1 and P1 for each stimulation channel ($P < 0.05$ for blue channel, $P < 0.01$ for red-green channel). This more superior location of P1 to N1 was also identifiable in grand average figures (see Fig. 2 D).

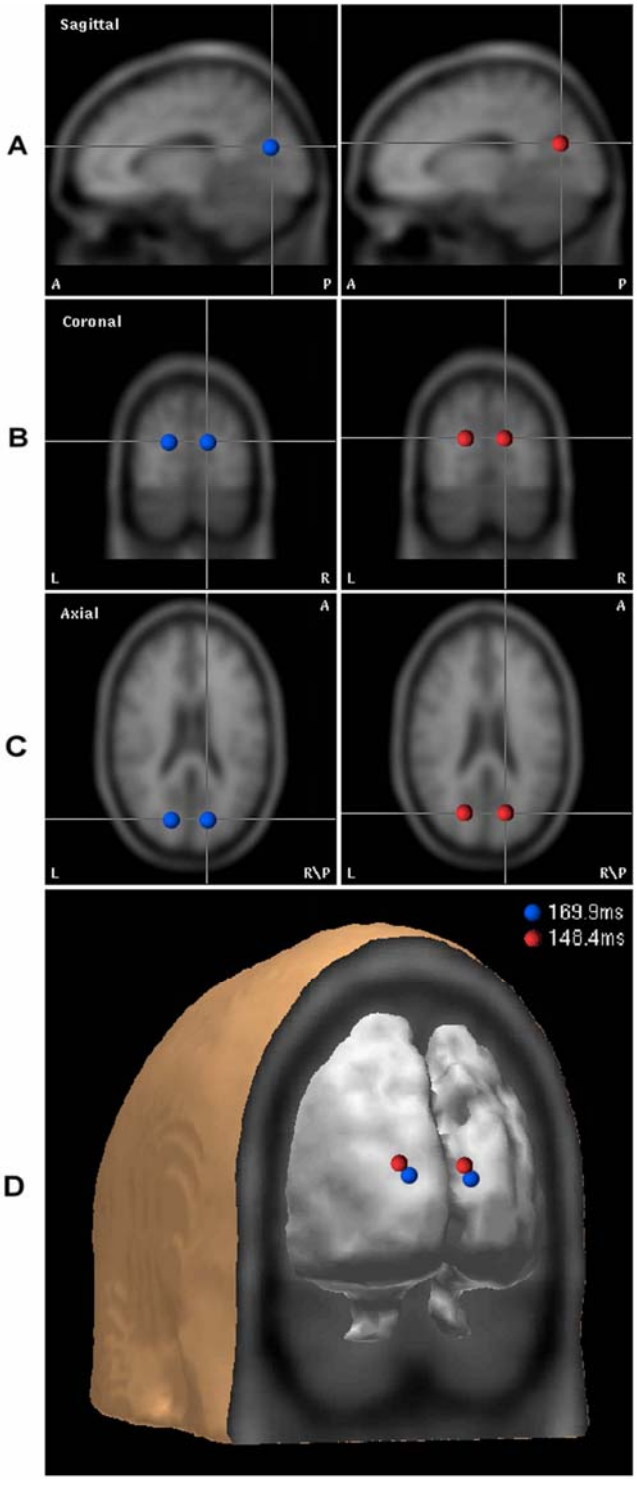

Fig. 2. Dipole positions of grand average of component P1 (right eye) at MGFP-Peak of the blue color channel (blue, 169.9 ms) and the red-green color channel (red, 148.4 ms) for sagittal (A), coronal (B) and axial (C) plane. (D) Shows the dipole positions projected on the cortex surface in the occipital region.

IV. 4 Discussion

Based on the selective excitation of particular cone types using the developed stimulation sequences and the 64-channel EEG, a VEP source reconstruction of blue- and red-green color channel was accomplished in our study. To summarize the major findings briefly, there were no significant differences in localization between both color channels and a significant time delay between the blue channel and the red-green channel.

Considering the anatomical and functional background, the parameters of VEP response are influenced along the entire visual pathway first by the retina, then the corpus geniculatum laterale (LGL) and finally the visual cortex where the incoming signal stream is processed in several visual areas. There are three distinct pathways, the magnocellular- (M), the parvocellular- (P) and the koniocellular- (K) system, all starting at retina [11]. These channels are functionally independent and transmitted in anatomically distinct retino-geniculo-cortical pathways [6]. The M-system is responsible for luminance information, the P-system for red-green information and cells of the K-system carry blue-yellow information [6]. The different visual attributes like color, shape, depth or motion are projected to the striate cortex (V1) and forwarded to several visual areas of the extrastriate cortex. Invasive studies with primates have shown that neurons sensitive to a specific color range exist in the visual cortex [12-14]. However, these neurons reside in the same visual areas. Surface records merely allow recording the accumulated activities of activated areas with an accuracy of about 0.5 to 1 cm at the given SNR. Thus, our EEG study can not resolve the perhaps different groups of neurons responsible for processing different colors within one cortical area.

Regarding the significant temporal delay of the blue channel to the red-green channel, we suppose that these time differences emerge due to signal transmission within distinct visual pathways. However, the time delay decreased for successive peak components of the VEP. While the difference for N1 was 33 ms, it was 22 ms for P1, and 12 ms for N2. This might perhaps indicate converging information processing for the different colors. The dipole locations of both color channels and both components were in extrastriate cortex close to area 18, whereas component P1 had a significant more superior location. It has to be mentioned that the dipole coordinates describe the center of gravity. Hence, we do not believe that the components N1 and P1 were generated in only one cortical area. Regions close-by may also contribute to each component, particularly due to high parallel processing in involved visual areas. However, locations of the dipoles close to area 18 are in line with other studies using visual stimuli [7], [15].

Comparing the outcomes of both eyes, we found similar results. The synchronous, almost equal potentials in both hemispheres during stimulation of each eye were caused by the central stimulation used in this study. Both halves of the visual field were excited equally, thus the same information was transmitted across optic chiasm on the way to the cortex.

Examinations on patients suffering from glaucoma will be performed in further studies.

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References

[1] P. Martus, M. Korth, and N. X. Nguyen, "Value of blue-on-yellow VEP for early diagnosis in suspected glaucoma. Biostatistical considerations and results," *Ophthalmologe,* vol. 94, pp. 277-81, Apr 1997.

[2] M. Korth, N. X. Nguyen, A. Junemann, P. Martus, and J. B. Jonas, "VEP test of the blue-sensitive pathway in glaucoma," *Invest Ophthalmol Vis Sci,* vol. 35, pp. 2599-610, Apr 1994.

[3] P. A. Sample, "Short-wavelength automated perimetry: it's role in the clinic and for understanding ganglion cell function," *Prog Retin Eye Res,* vol. 19, pp. 369-83, Jul 2000.

[4] P. Beßler, S. Klee, P. Husar, and G. Henning, "Methodology and first results of selective cone stimulation of human eye via silent substitution technique," in *IFMBE Proc.*, Prague, 2005.

[5] O. Estevez and H. Spekreijse, "The "silent substitution" method in visual research," *Vision Res,* vol. 22, pp. 681-91, 1982.

[6] K. R. Gegenfurtner, "Cortical mechanisms of colour vision," *Nat Rev Neurosci,* vol. 4, pp. 563-72, Jul 2003.

[7] M. Stöhr, J. Dichgans, U. W. Buettner, and H. C. W., "Visuell evozierte Potentiale und Elektroretinogramm," in *Evozierte Potentiale*, 4. Auflage ed, M. Bach, T. Haarmeier, and J. Dichgans, Eds. Heidelberg: Springer Medizin, 2005, pp. 264 - 85.

[8] S. Klee, P. Beßler, P. Husar, and G. Henning, "Spectral distribution and dynamics of stimulators for selective cone excitation," in *IFMBE Proc.*, Prague, 2005.

[9] M. Fuchs, M. R. Ford, S. Sands, and H. L. Lew, "Overview of dipole source localization," *Phys Med Rehabil Clin N Am,* vol. 15, pp. 251-62, Feb 2004.

[10] M. Scherg and J. S. Ebersole, "Models of brain sources," *Brain Topogr,* vol. 5, pp. 419-23, Summer 1993.

[11] D. M. Dacey, "Parallel pathways for spectral coding in primate retina," *Annu Rev Neurosci,* vol. 23, pp. 743-75, 2000.

[12] T. Wachtler, T. J. Sejnowski, and T. D. Albright, "Representation of color stimuli in awake macaque primary visual cortex," *Neuron,* vol. 37, pp. 681-91, Feb 20 2003.

[13] D. C. Kiper, S. B. Fenstemaker, and K. R. Gegenfurtner, "Chromatic properties of neurons in macaque area V2," *Vis Neurosci,* vol. 14, pp. 1061-72, Nov-Dec 1997.

[14] J. B. Levitt, D. C. Kiper, and J. A. Movshon, "Receptive fields and functional architecture of macaque V2," *J Neurophysiol,* vol. 71, pp. 2517-42, Jun 1994.

[15] S. Arroyo, R. P. Lesser, W. T. Poon, W. R. Webber, and B. Gordon, "Neuronal generators of visual evoked potentials in humans: visual processing in the human cortex," *Epilepsia,* vol. 38, pp. 600-10, May 1997.