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Occlusion therapy improves phase-alignment of the cortical response in amblyopia ☆

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ABSTRACT

The visual evoked potential (VEP) generated by the amblyopic visual system demonstrates reduced amplitude, prolonged latency, and increased variation in response timing (phase-misalignment). This study examined VEPs before and after occlusion therapy (OT) and whether phase-misalignment can account for the amblyopic VEP deficits. VEPs were recorded to 0.5–4 cycles/degree gratings in 10 amblyopic children (2–6 years age) before and after OT. Phase-misalignment was measured by Fourier analysis across a limited bandwidth. Signal-to-noise ratios (SNRs) were estimated from amplitude and phase synchrony in the Fourier domain. Responses were compared to VEPs corrected for phase-misalignment (individual epochs shifted in time to correct for the misalignment). Before OT, amblyopic eyes (AE) had significantly more phase-misalignment, latency prolongation, and lower SNR relative to the fellow eye. Phase-misalignment contributed significantly to low SNR but less so to latency delay in the AE. After OT, phase-alignment improved, SNR improved and latency shortened in the AE. Raw averaged waveforms from the AE improved after OT, primarily at higher spatial frequencies. Correcting for phase-misalignment in the AE sharpened VEP peak responses primarily at low spatial frequencies, but could not account for VEP waveform improvements in the AE after OT at higher spatial frequencies. In summary, VEP abnormalities from the AE are associated with phase-misalignment and reduced SNR possibly related to desynchronization of neuronal activity. The effect of OT on VEP responses is greater than that accounted for by phase-misalignment and SNR alone.

1. Introduction

Unilateral amblyopia is typically defined as reduced visual acuity in one eye due to anisometropia, strabismus, or visual deprivation resulting from ptosis or media opacity. For each of these disorders a suboptimal retinal image in one eye, interocular disparity of visual inputs, or both limit the postnatal visual development of one eye resulting in decreased visual acuity. Additional visual deficits include reduced contrast sensitivity, reduced Vernier acuity, temporal instability, motion, and global motion deficits, and abnormal contour interactions (Altmann & Singer, 1986; Giaschi, Regan, Kraft, & Hong, 1992; Hess & Holliday, 1992; Ho et al., 2005; Levi & Klein, 1983; Levi & Klein, 1985; Simmers, Ledgeway, Hess, & McGraw, 2003; Sireteanu, Lagreze, & Constantinescu, 1993). Treatment for amblyopia includes detection and correction of the underlying ocular disorder. To recapture optimal vision in the amblyopic eye, monocular occlusion therapy, or pharmacological or optical blurring, of the fellow eye is performed during the critical period of visual development (Epelbaum, Milleret, Buisseret, & Dufier, 1993; Flynn et al., 1999; Vaegan, 1979).

Animal models using induced anisometropia or strabismus have provided important insights into the cortical mechanisms underlying amblyopic visual loss (Crewther & Crewther, 1990; Hendrickson et al., 1987; Kiorpes, Kiper, O'Keefe, Cavanaugh, & Movshon, 1998; Movshon et al., 1987; Roelfsema et al., 1994; Singer, von Grünau, & Rauschecker, 1980). Recordings in visual striate cortex (V1) show a change from predominately binocularly encoded cells to approximately the same number of neurons being driven by the amblyopic eye as the fellow eye. However, neurons driven by the amblyopic eye can show similar spatial response properties and similar firing rates as the fellow eye despite behavioral measures showing reduced spatial resolution in the amblyopic eye (Bi et al., 2011; Kiorpes, Kiper, O'Keefe, Cavanaugh, &

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Movshon, 1998; Kiorpes & Movshon, 2003). This finding suggests that deficits in V1 neurons are insufficient to account for behavioral vision loss at high spatial frequencies in the primate model. An emerging view is that integration of cortical areas downstream from V1 play a significant role in the visual defects imposed by early strabismus or anisometropia (Bi et al., 2011; Chino, Bi, & Zhang, 2003; El-Shamayleh, Kiorpes, Kohn, & Movshon, 2010; Imamura et al., 1997; Kiorpes & Movshon, 2003; Kiorpes et al., 1998; Li, Mullen, Thompson, & Hess, 2011; Singer et al., 1980).

The visual evoked potential (VEP) provides an objective way to assess visual cortex in amblyopic children during the critical period (Arden, Barnard, & Mushin, 1974; Friendly, Weiss, Barnet, Saumweber, & Walker, 1986; Henc-Petrinovic, Deban, Gabric, & Petrinovic, 1993; Kubova, Kuba, Juran, & Blakemore, 1996; Levi & Manny, 1982; Lombroso, Duffy, & Robb, 1969; Sokol, 1983; Sokol & Bloom, 1973; Spekreijse, Khoe, & van der Tweel, 1972; Weiss & Kelly, 2004; Wright, Ary, Shors, & Eriksen, 1986). The VEP response is thought to be dominated by population summation of excitatory post-synaptic potentials from pyramidal cells in striate and extrastriate visual cortex (Mitzdorf & Singer, 1978; Nunez & Srinivasan, 2006). The VEP peak near 60 ms reflects initial activation of visual striate cortex whereas the VEP peak near 100 ms reflect combined activity of visual striate and extrastriate cortical areas (Clark, Fan, & Hillyard, 1995; Di Russo, Martinez, Sereno, Pitzalis, & Hillyard, 2002; Di Russo et al., 2005; Foxe & Simpson, 2002; Maier, Dagnelie, Spekreijse, & van Dijk, 1987; Nakamura, Kakigi, Okusa, Hoshiyama, & Watanabe, 2000; Ossenblok, Reits, & Spekreijse, 1992; Schroeder, Mehta, & Givre, 1998). Thus the VEP is ideal for measuring neuronal integration across multiple visual cortex areas in children during therapy. The VEP from the amblyopic eye consistently shows reduced amplitudes, altered waveforms, and prolonged latency at spatial frequencies below behavioral acuity thresholds. Although the amblyopic eye shows a small latency delay (10–20 ms), this timing is potentially important for integration between V1 and extrastriate cortex (Di Russo, Martinez, Sereno, Pitzalis, & Hillyard, 2002; Foxe & Simpson, 2002; Schroeder et al., 1998). After occlusion therapy, the amblyopic eye generates a VEP with increased amplitude, shorter latency, and sharper timing of peaks (Arden & Barnard, 1979; Arden, Barnard, & Mushin, 1974; Friendly et al., 1986; Furuskog, Persson, & Wanger, 1987; Henc-Petrinovic et al., 1993; Kubova, Kuba, Juran, & Blakemore, 1996; Odom, Hoyt, & Marg, 1981; Wilcox & Sokol, 1980; Weiss & Kelly, 2004). In comparison, after termination of therapy the treated fellow eye shows mild changes in amplitude reduction, latency prolongation, and waveform broadening that can persist for more than 3 months. The VEP changes in latency must be post-retinal since the pattern-electroretinogram shows no latency difference between the amblyopic and fellow eyes (Parisi, Scarale, Balducci, Fresina, & Campos, 2010; Teping, Kamps, & Reim, 1989).

Defects in temporal processing in the human amblyopic visual system have also been described using psychophysical techniques (Altmann & Singer, 1986; Huang, Li, Deng, Yu, & Hess, 2012; Spang & Fahle, 2009; Steinman & Levi, 1988). Studies in strabismic cats show V1 and extrastriate neurons driven by the amblyopic eye are sluggish, have impaired temporal structure, and have reduced population synchronization from the amblyopic eye (Crewther & Crewther, 1990; Eschweiler & Rauschecker, 1993; Roelfsema, König, Engel, Sireteanu, & Singer, 1994; Singer et al., 1980). These temporal processing defects in cortical neurons could be a significant factor in the amblyopic deficit since Roelfsema, König, Engel, Sireteanu, and Singer (1994) found no significant differences in the spatial resolution and firing rate of cells driven by the amblyopic and fellow eye. Reduced synchronization is also expected to decrease activity from one cortical processing stage to the next because integration of desynchronized synaptic potentials will be less effective in generating excitatory post-synaptic potentials (Oviedo & Reyes, 2002; Stevens & Zador, 1998). As a corollary in human amblyopia, recent studies in humans have shown increased latency variability in VEP epochs generated by the amblyopic eye compared to the fellow eye (Bankó, Körtvélyes, Németh, & Vidnyánszky, 2014; Bankó, Körtvélyes, Németh, Weiss, & Vidnyánszky, 2013), possibly related to increased internal neural noise within the amblyopic visual system. Furthermore, Weiss and Kelly (2004) found that the VEP waveform has a sharper peak tuning after occlusion therapy suggesting occlusion therapy may reduce temporal variance or reduce internal noise in the amblyopic visual system.

To address the impact of reduced synchronization and temporal noise in visual cortex, we propose a theoretical model for the VEP generated by the amblyopic and fellow eyes (Fig. 1). The simulated VEPs in the figure are characteristic of the VEPs generated by the amblyopic and fellow eye in children (Weiss & Kelly, 2004). The fellow eye VEP response (A) is simulated by a sum of sinusoidal wavelet functions with constant relationships between amplitude, frequency, and phase. When the underlying components have accurate temporal synchronization of phase across a range of temporal frequencies, the VEP generates a waveform with sharply defined peaks of large amplitude. In contrast, the amblyopic response with reduced amplitude, mild latency delay, and broader peaks can be simulated by desynchronization of phase across the

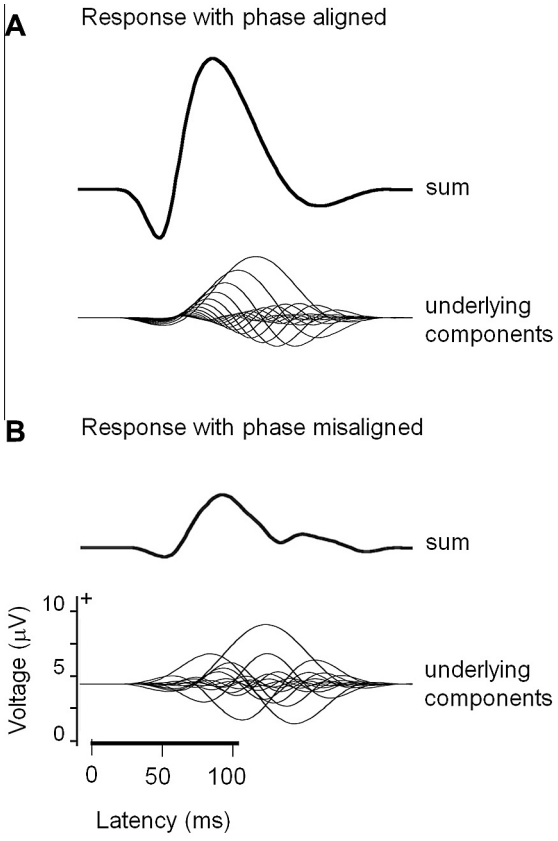

Fig. 1. (A) Simulated VEP waveform generated by multiple underlying sinewave components. The sinewaves have been multiplied by a Hamming window from 20 to 200 ms to reflect the transient nature of the evoked potential. When there is phase alignment of the underlying components, the VEP shows large amplitude with sharply tuned peaks. (B) Simulated VEP response generated by sinewave components with variable phase shifts at higher frequencies. The simulated VEP shows reduced amplitude, mild latency prolongation, and waveform distortion. Note amplitude of the underlying components in B is the same as in A but just shifted in time. The VEP waveform in A is characteristic of a control child; the VEP waveform in B is characteristic of children with amblyopic visual loss.