Robust sensory gating in the cortical visual evoked potential using two spatially separated stimuli

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1. Introduction

Sensory gating is the phenomenon whereby the electroencephalographic response to one stimulus is reduced in magnitude by the presentation of a preceding (‘conditioning’) stimulus. It is sometimes referred to as a “recovery function” or “recovery cycle”. Sensory gating has been commonly seen in the cortical evoked potential response to auditory stimuli (Adler et al., 1982; Hong et al., 1985). However, a previous study using flashes of light viewed diffusely through closed eyelids found no evidence for sensory gating (Adler et al., 1985), and another, using large overlapping white circles, found gating effects that were statistically significant but small in magnitude (Gjini et al., 2008). A study using diffuse flashes of light found sensory gating in the human VEP which was strong for flashes separated by 20 ms or less but which became much less robust for longer inter-stimulus intervals (Schwartz and Shagass, 1964). Another study using large-field contrast-reversing checkerboard gratings found no consistent effect of one stimulus on the magnitude of the response to a following stimulus, although there were significant latency effects for inter-stimulus intervals of 30 ms or less (Mitchell et al., 1983). The goal of this study was to explore the degree of sensory gating in the VEP to two spatially separated stimuli, which instead of activating the same cortical regions in sequence, should sequentially activate different retinotopically organized areas of visual cortex regions. Using spatially separated stimuli could elicit different behaviors than those of spatially congruent stimuli.

Despite many years of research, it is still not clear precisely what aspects of neuronal activity are reflected in the scalp-surface recorded cortical visual evoked potential (VEP) (Fahle and Bach, 2006). Intracortical recordings of the local field potential (LFP) have identified a fast local component, which in visual cortex has been referred to as “retinotopic”, and a slow-distributed component, which has also been referred to as “non-retinotopic” (Bringuier et al., 1999; Doty, 1958; Ebersole and Kaplan, 1981; Gawne, 2010; Kitano et al., 1994, 1995; Kasamtsu et al., 2005; Mitzdorf, 1985). Because the slow-distributed component of the LFP is widely distributed across cortex, it might be expected to contribute strongly via volume conduction to the surface-recorded VEP. What is most relevant to the current study is that the slow-distributed component is highly nonlinear: the response to a stimulus at one location suppresses the response to a stimulus at another location (Kitano et al., 1994; Nauhaus et al., 2009). The purpose of this study was to explore how sensory gating in the VEP is affected by the sequence and timing of two spatially separated stimuli.
study was to determine if the nonlinearity present in the slow-distributed component of the LFP is also present in the scalp-surface-recorded VEP.

### 2. Materials and methods

Subjects were 18 adults between the ages of 23 and 52, of normal health, and with acuity corrected to normal. They were seated in a Faraday cage that had a viewing port made of electrically conductive glass. Three gold cup electroencephalogram (EEG) electrodes were placed on the skin in standard EEG locations O2, Pz, and Cz. The skin was scrubbed with Lemon Prep (Mavidon, Lake Worth, FL) until good contacts were made, and then gold pastes were applied. Zeiss (Oberkochen, Germany) ER-42 disposables were used for the EEG. The entire filtering chain was constructed to close their eyes and relax, that prominent alpha-band rhythms were observed. Electrode gel (Grass, EC2 West Warwick RI) was used to ensure good electrode contact. Two additional pairs of electrodes were used to monitor the horizontal and vertical electro-oculogram (EOG). A custom-built EEG amplifier was used with Oz referred to Cz, and Pz ground. In some experiments, however, we only used a single vertical channel of EEG but two channels of EEG, O1 and O2, both referenced to Cz. The amplifier had a gain of 200 and a flat passband between the frequencies of 0.1 and 1000 Hz. The output of the EEG amplifier was further amplified and filtered by a four-pole low-pass linear-phase Bessel filter (Warner Instrument Corp., Model LF202, Hamden, CT) set at a cutoff frequency of 200 Hz. No notch filters were used. A post-recording software filter was used that had a Gaussian kernel with a standard deviation of 6 ms, which acts as a linear-phase low-pass filter with a cutoff frequency of 20 Hz. The entire filtering chain did not create any phase distortion or ‘ring’ in any way.

For visual activation of the occipital lobe, there is generally one dominant response vector which is readily picked up by the electrode configurations used here. For this reason the multifocal VEP typically only uses a single active recording site (Fortune and Hood, 2003). Additionally, as will be covered in the Section 4, testing the linearity of summation that might occur via volume conduction is independent of either the number or configuration of recording electrode pairs. Thus, high-density recording would not have altered our results.

Signals were digitized for 500 ms intervals at a rate of 1000 Hz using a 16-bit A/D converter and custom software written in MATLAB (The Mathworks, Natick, MA) using custom-written routines.

Subjects were instructed to fixate on a small (0.08° square) white dot presented in the middle of a video monitor (Korea Data Systems, Garden Grove, CA). The monitor was displayed at a refresh rate of 85 Hz, measured 54.3 cm diagonally, and was positioned 57 cm from the subject’s eye. Two stimuli, each 1.6 degrees square, were presented centered 2.26 degrees from the fixation point. Stimulus 1 was located in the lower left, and stimulus 2 in the upper left, visual field. Stimuli were flashed on either separately or together with different inter-stimulus delays. There were eight distinct conditions presented in shuffled random order with an inter-trial interval that varied randomly from 500 to 750 ms. The stimulus timings were constrained by the 85 Hz video refresh rate. Stimulus 1 was always flashed on at time = 43 ms, and stimulus 2 at time = 90 ms, for an inter-stimulus delay of 47 ms. There were three stimulus pairings: a checkerboard followed by a checkerboard (Fig. 1A), and checkerboard followed by a red circle (Fig. 1B), and a red circle followed by a checkerboard (Fig. 1C). This allowed us to investigate whether the interactions between stimuli were affected by the stimuli having the same or different forms. The gray background had a luminance of 6.96 cd/m², the black and white of the checkerboard stimuli had luminances of 0.74 and 87.58 cd/m², and the red circle had luminance of 27.38 cd/m². Additionally, the single stimuli making up each combination were presented separately, as well as a blank control stimulus (Fig. 1D–H). The responses to the blank control stimuli as a function of time were subtracted off from all other responses to cancel out a small but consistent effect that was due to the initiation of the recording epoch.

For 13 subjects we performed a similar experiment, except that we only used the checkerboard stimuli, and we presented the stimuli at three different delays: simultaneously, 47 ms, and 90 ms. Additionally, the stimuli were larger, subtending 2.4° each. Using longer inter-stimulus delays is problematic, because the number of trials (100 trials for each of 18 subjects) we performed a similar experiment, except that we only used the checkerboard stimuli, and we presented the stimuli at three different delays: simultaneously, 47 ms, and 90 ms. Additionally, the stimuli were larger, subtending 2.4° each. Using longer inter-stimulus delays is problematic, because the number of trials the eyes do not move decreases rapidly with longer recording epochs, and with longer inter-stimulus delays it is hard to rule out small-magnitude stimulus-dependent eye movements. For this experiment, we used only the horizontal channel of the EOG, and we only used the vertical channel of the EOG, and recorded two channels of VEP data, with both O1 and O2 referred to Cz.

Responses were discarded when the EOG signal indicated a blink or eye movement, and when the peak-to-peak VEP amplitude was greater than 80–120 μV (VEP thresholds set separately for each subject). We presented the stimuli 200 trials per unique stimulus condition for each subject, but rejecting bad trials meant that the median value for the smallest number of trials for any single condition for each subject was 167, with a range from 75 to 193.

For the purposes of this study we were only concerned with the first strong positive peak, which is by far the strongest and most prominent component of the VEP.
consistent part of the VEP, at least under these conditions. The latency was quantified by either the time from stimulus onset to the peak, or as time from stimulus onset to the point where the voltage had reached 50% of the peak. This latter measure is similar to that used by many researchers to quantify the onset of the activity of single neurons (Levick, 1973; Lee et al., 2007).

All experiments were performed with the understanding and written consent of the subjects, and were approved by the UAB Institutional Review Board.

3. Results

Fig. 2 panels A–E illustrate the mean VEP responses for a single subject whose responses closely matched the population mean (example). Panel A shows the response to a single stimulus turned on in the upper left visual field: there is a modest positive response with a latency of 111 ms. Panel B illustrates the response to a single stimulus presented in the upper visual field: the response has a larger positive peak with a latency of 117 ms. Panel C shows the mean response to both stimuli presented with a temporal separation of 47 ms, and panel D is the overlay of panels A, B, and C. Note that the curves representing the response of the first stimulus presented by itself (dashed line) and the response of both stimuli in sequence (thick black line) follow each other very closely, especially through the point where the first positive peak to the second stimulus would have occurred. In panel E, the thin black line represents the response elicited by the second stimulus alone (same as panel B), and the thick gray line is the difference between the response to both stimuli presented in sequence (Panel D) and the first stimuli presented by itself (Panel A). If the response to both stimuli presented in sequence was the same as the linear sum of both stimuli presented by themselves, these two curves should have tracked each other; instead, the presentation of one stimulus almost completely suppresses the initial short-latency peak response to the second stimulus, although the second stimulus does appear to have some effect later in the recording epoch.

Fig. 2 panels F–J are laid out the same as panels A–E, except that these are the mean responses (mean of the means, n = 18) for all subjects in the study. The population mean shows the same response pattern as the single example.

Fig. 3 Panel A is the same data as Fig. 2 Panel J, except that the standard error of the mean is shown for the response to the second stimulus in the sequence, and a significant point-by-point paired t-test comparison between the two curves is shown via the extent of the heavy horizontal bars near the bottom of the Panel. Panels B and C have the same layout as panel A, expect that in Panel B the
These results are all similar, demonstrating that the suppressive effect of the first stimulus on the response to the second does not require that the two stimuli be of identical form.

Fig. 4 illustrates the mean results for the 13 subjects where the stimuli were presented at different relative onsets, and recordings were made at electrode locations O1 and O2. The second stimulus does have some effect on the response to both stimuli combined (the thick gray line is not completely flat), but the strong initial transient response to a stimulus is almost completely wiped out by another stimulus. This response suppression occurs independent of inter-stimulus timing over the range studied here. We were surprised that, averaged across subjects, the VEP was of similar magnitude in both O1 and O2, as previous results suggested that we should have had a stronger response in O2 (Barrett et al., 1976). We can only point out that the precise form of the VEP can vary substantially with the details of the visual stimulation. Nonetheless, the suppression of the response to the second stimulus was equally robust regardless of electrode location.

For the mean waveform across all subjects the latency to the positive peak varied from 111 to 135 ms for the paradigm illustrated in Figs. 2 and 3 (the longest latency was for the response to the red circle), and 114–126 ms for the paradigm in Fig. 4. The response onset time (time to 50% of the peak) varied from 86 to 100 ms for the paradigm of Figs. 2 and 3 (again, the red circle gave the response with the longest latency) and from 92 to 104 ms for the paradigm in Fig. 4.

4. Discussion

It is important to understand how the physics of volume conduction relates to these results. Consider a container filled with a conductive medium such as saline, two voltage sources embedded in it, and two recording electrodes. Unless you are at a null position, when you turn one voltage source on, you will generate a voltage difference between the two recording electrodes via volume conduction. If you turn the second voltage source on, you will generate another voltage difference between the two recording electrodes. If you turn both voltage sources on, you will record the linear sum of the voltages generated by the two sources activated separately. Linear summation will be obtained no matter how many electrodes you record from, what position they are in, how complex the shape of the container, whether the voltages induced by the different sources are equal or unequal, or the degree of inhomogeneity of the conductive media. Linear summation will also be unaffected by any linear time invariant filtering. Therefore, as regards testing whether linear summation via volume conduction of spatially separated sources is concerned, the results are independent of the details of electrode number, position, or the variability or complexity of cortical folding of the individual subjects. Because it is independent of so many factors, a test of linearity may be a useful general technique for analyzing electroencephalographic data.

It might appear that the results of this study would contradict the ability of the multifocal VEP to create a spatial map of sensitivity by flashing multiple stimuli in complicated pseudo-random patterns (Sutter, 2001; Seiple et al., 2005). Even though the stimuli used in multifocal VEPs are not identical to those used here, they nonetheless consist of multiple spatially separated stimuli, and our results suggest that presenting multiple stimuli in rapid succession should lead to a strong suppression of all responses after the first one. However, if the VEP to a single stimulus is usually dominated by the slow-distributed component of the LFP, then the multifocal technique would simply be selective for the fast local component of the LFP. If true, this would predict that the multifocal VEP would have a shorter latency than the classical VEP, that it would be smaller in magnitude (because it would be due...
Fig. 4. Mean VEP waveforms for all 13 subjects where the stimuli were presented either (A) simultaneously, (B) with an inter-stimulus delay of 47 ms, and (C) with an inter-stimulus delay of 95 ms, arranged as in Fig. 3. Panels on the left side are from electrode O1, and panels on the right side from O2. The thin black line is the mean response to the second stimulus in the sequence presented by itself, and the thick gray line is the difference between the responses to both stimuli presented in sequence and the first stimulus presented by itself. The interrupted heavy horizontal lines at the bottom of the plot indicate time points where these two curves were statistically different by paired t-test (P < 0.05, n = 18). On average, the first stimulus almost completely suppresses the effect of the second stimulus independent of whether the stimuli were presented at the same or different times.

It has been suggested that the early fast component of the VEP (and in particular, of the multifocal VEP) is dominated by primary visual cortical activity, and that later arriving components (the ‘classical’ VEP) are more strongly due to extra striate activity (Oostenveld and Spekreijse, 1991; Schroeder et al., 1991; Di Russo et al., 2002). However, our results suggest another possibility: the fast component of the VEP (likely a strong component of the multifocal VEP, and shown to have the same onset timing as V1 neuronal activity, typically around 40–50 ms for high-contrast stimuli, see Gawne, 2010) is generated by the fast local component of the LFP, and that the conventional VEP to an isolated stimulus is dominated more by a slow-distributed component of the LFP.

Most previous studies identifying a slow-distributed component of the LFP find response latencies somewhat faster than those identified here. For example, the latency to peak of the slow-distributed component of the LFP in the anesthetized cat was found to peak at about 74 ms (Kitano et al., 1994). This suggests that the scalp-surface VEP may not be driven by exactly the same processes identified by these studies, although it may still be driven by a process with similar properties. However, it is not clear that the absolute timings of field potentials responses can be directly compared between anesthetized cats and awake humans. A recent study performing intracortical recordings in awake primates using isolated checkerboard stimuli similar to those used here identified one distributed component of the LFP that had an onset latency of 90 ms (there was no obvious peak), and which also had a clear trend towards the sort of nonlinear behavior seen in the VEPs recorded here (Gawne, 2010). The similar onset times and nonlinear behavior in awake primates of the scalp-surface-recorded VEP and the intracortical slow-distributed component of the local field potential is evidence that these two phenomena are related.

If you turn a visual stimulus on, you will elicit a strong burst of neuronal activity in corresponding retinotopic regions of visual cortex, and this activity is largely unaffected by stimuli located in different retinotopic locations (Gawne, 2010). fMRI imaging yields a similar result: spatially discrete visual stimuli independently cause increases in aggregate neuronal activity in separate regions of cortex (Tootell et al., 1998). If the VEP were simply reflecting the spatial average of the electrical activity in visual cortex, we should have observed linear summation. But we did not. Therefore, at least under the condition used here, the scalp-surface-recorded VEP does not reflect the summation via volume conduction of the bulk of the overall neuronal activity in visual cortex. Rather, the
VEP appears to reflect a large-area mode of visual cortical activity, that only indicates that something occurred, but that is non-specific for the details of the stimulus, its location, or whether there are one or two stimuli, or if two stimuli, their relative timing over a range of up to 100 ms.

5. Uncited references

Gawne TJ. The local and non-local components of the local field potential in awake Fortune B, Hood DC. Conventional pattern-reversal VEPs are not equivalent to Adler LE, Pachtman E, Franks R, Pecevich M, Waldo MC, Freedman R. References supported by National Science Foundation and NIH Grant P90 EY03039 (Core).

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References


Fortune B, Hood DC. Conventional pattern-reversal VEPs are not equivalent to summed multifocal VEPs. Invest Opthalmol Vis Sci 2003;44:1364–75.


