Interocular suppression in strabismic amblyopia results in an attenuated and delayed hemodynamic response function in early visual cortex

Athinoula A. Martinos Center for Biomedical Imaging, Charlestown, MA, USA, & Harvard Medical School, Boston, MA, USA

Reza Farivar

Department of Optometry and Vision Science, University of Auckland, Auckland, New Zealand

Benjamin Thompson

Division of Neurology, Department of Internal Medicine, University of Manitoba, Winnipeg, Canada

Behzad Mansouri

McGill Vision Research Center, McGill University, Montreal, Canada

Robert F. Hess

Factors such as strabismus or anisometropia during infancy can disrupt normal visual development and result in amblyopia, characterized by reduced visual function in an otherwise healthy eye and often associated with persistent suppression of inputs from the amblyopic eye by those from the dominant eye. It has become evident from fMRI studies that the cortical response to stimulation of the amblyopic eye is also affected. We were interested to compare the hemodynamic response function (HRF) of early visual cortex to amblyopic vs. dominant eye stimulation. In the first experiment, we found that stimulation of the amblyopic eye resulted in a signal that was both attenuated and delayed in its time to peak. We postulated that this delay may be due to suppressive effects of the dominant eye and, in our second experiment, measured the cortical response of amblyopic eye stimulation under two conditions where the dominant eye was open and seeing a static pattern (high suppression) or where the dominant eye was patched and closed (low suppression). We found that the HRF in response to amblyopic eye stimulation depended on whether the dominant eye was open. This effect was manifested as both a delayed HRF under the suppressed condition and an amplitude reduction.

Keywords: functional imaging, visual cortex, visual development, hemodynamic modulation, hemodynamic response


Introduction

Amblyopia is a visual disorder caused by a difference in the images seen by each eye during early development (Holmes & Clarke, 2006). The visual loss typically occurs in one eye and is characterized by a reduction of sensitivity to high spatial frequencies (Hess, 1979; Hess & Howell, 1977), positional uncertainty (Levi, Klein, & Yap, 1987), and a range of higher level deficits including impaired global motion processing (Simmers, Ledgeway, Hess, & McGraw, 2003). Importantly, these visual deficits cannot be corrected optically or surgically, as the visual loss is not due to a problem with the eye but rather due to neural processing of information from the eye (Hess, 2001; Wiesel & Hubel, 1965). In addition to this monocular loss of function, amblyopia is also associated with impaired or absent binocular vision (Sireteanu, 2000). The major contributing factor to this binocular loss is suppression of the amblyopic eye input to the visual cortex (Baker, Meese, Mansouri, & Hess, 2007; Harrad, Sengpiel, & Blakemore, 1996; Mansouri, Thompson, & Hess, 2008; Sengpiel & Blakemore, 1996; Sengpiel, Blakemore, Kind, & Harrad, 1994; Sengpiel, Jirmann, Vorobyov, & Eysel, 2006).

While interocular suppression can be generated in the normal visual system using binocular rivalry paradigms (Tong, Meng, & Blake, 2006), in amblyopia, the suppression is typically chronic (de Belsunce & Sireteanu, 1991). This means that while during normal binocular viewing the amblyopic eye is open and providing neural input to the lateral geniculate and the visual cortex, this input does not reach awareness. This is evidenced clinically by a general lack of double vision in strabismic amblyopes without anomalous retinal correspondence and the experience of a single focused image in anisometropic amblyopes. Importantly, in the strabismic form of the disorder, chronic...
suppression is considered to cause the loss of perception in the amblyopic eye (Holmes & Clarke, 2006) raising the possibility that neural input from the amblyopic eye may still be subject to residual suppression under monocular viewing conditions.

Although much research has been carried out on the monocular loss of function in amblyopia, very little is known about the nature of interocular suppression. For example, a considerable number of functional magnetic resonance imaging (fMRI) studies have been conducted on humans with amblyopia (for example, Algaze, Roberts, Leguire, Schmalbrock, & Rogers, 2002; Anderson & Swettenham, 2006; Barnes, Hess, Dumoulin, Achtman, & Pike, 2001; Choi et al., 2001; Conner, Odom, Schwartz, & Mendola, 2007a, 2007b; Goodyear, Nicolle, Humphrey, & Menon, 2000; Goodyear, Nicolle, & Menon, 2002; Hess, Li, Lu, Thompson, & Hansen, 2010; Hess, Li, Mansouri, Thompson, & Hansen, 2009; Hess, Thompson, Gole, & Mullen, 2009; Lerner et al., 2006; Li, Dumoulin, Mansouri, & Hess, 2007; Lv et al., 2008). In general, studies have revealed an attenuated neural response to amblyopic eye stimulation within the visual cortex and, more recently, the lateral geniculate (Hess, Li et al., 2009). While these findings are consistent with a cortical suppression of amblyopic eye inputs, the inference cannot be made directly. This is because the vast majority of these studies used monocular stimulus presentation paradigms whereby the eye not being stimulated was occluded, therefore minimizing suppression. At least one study, however, did employ a dichoptic stimulus presentation paradigm, which allowed for a direct comparison between monocular viewing with the dominant eye occluded and dichoptic stimulation with the dominant eye viewing a uniform mean luminance field (Conner et al., 2007b). For one amblyopic participant, foveal suppression was clearly evident as an absent phase-encoded response to retinotopic mapping stimuli at the occipital pole during dichoptic but not monocular stimulation, although it is unclear whether the absence of a phase map is due to BOLD attenuation or modification of the BOLD hemodynamic response function so as to produce a poorer fit. As noted by Conner et al. (2007b), however, mean luminance is unlikely to drive interocular suppression to the same extent as viewing a pattern with the dominant eye.

Direct neurophysiological investigations of amblyopic suppression have been conducted in strabismic cats with stimuli presented to the amblyopic and dominant eyes simultaneously (Harrad et al., 1996; Sengpiel & Blakemore, 1996; Sengpiel et al., 1994, 2006). These studies demonstrate that strabismic suppression is cortical rather than thalamic and is mediated by GABAergic inhibition of amblyopic eye ocular dominance columns in the striate cortex. Particularly strong support for this hypothesis comes from the finding that the GABA_A antagonist bicuculine greatly reduces the suppression of amblyopic eye neurons in the primary visual cortex of strabismic cats (Sengpiel et al., 2006).

Therefore, while there is strong evidence from human fMRI studies to suggest that the cortical response to amblyopic eye inputs is reduced under monocular viewing, the neural basis of amblyopic suppression in humans is yet to be elucidated. This is an important issue as impaired binocularity is a key feature of human amblyopia (Holmes & Clarke, 2006) and the suppressive effects that are thought to play a causal role in the development of amblyopia are, by definition, most evident during binocular viewing. In this study, we used fMRI to investigate both the nature of the hemodynamic response function generated by amblyopic eye stimulation and the effects of dominant eye stimulation on the response of the early visual cortex to amblyopic eye stimulation. It has previously been found that excitatory and inhibitory neural interactions are represented differently by the blood oxygenation level dependent (BOLD) signal that forms the basis of fMRI measurements (Shmuel, Augath, Oeltermann, & Logothetis, 2006; Shmuel et al., 2002). We therefore used an event-related design and measured both the magnitude and the temporal characteristics of the hemodynamic response function (HRF) in the early visual cortex. In Experiment 1, we compared the response of the visual cortex to stimulation of the amblyopic vs. the dominant eye when the non-viewing eye was occluded. In Experiment 2, we then compared this response to stimulation of the amblyopic eye when the dominant eye was either (1) occluded or (2) viewing a static pattern under dichoptic viewing conditions.

**Methods**

**Participants**

In total, 11 observers with strabismic amblyopia (6 with a mixed strabismic/anisometropic etiology) participated in the experiments. All participants granted informed consent, in accordance with the McGill University Guidelines on Research Ethics. A standard clinical workup was performed on all patients. Their visual acuity was measured with a Sloan letter chart, their binocular status was assessed with a synoptophore and cover test, and their fundus was examined ophthalmoscopically. All subjects were refracted and wore their best correction. Clinical details of our participants are given in **Table 1**.

**Stimuli**

The visual stimulus used to drive the HRF response consisted of a flashing spatial frequency fractal noise pattern covering approximately 26° of visual angle horizontally and 20° vertically. A Perlin noise algorithm was used to construct the spatial frequency fractal noise patterns. The algorithm begins by taking an array of
values randomly drawn from a uniform distribution and rescaling the array to the final image size, using cubic spline interpolation. Subsequently, larger arrays, with array sizes defined by powers of two (2^n, up to image size that was 1024, or 2^{10}), are then constructed in the same manner—by drawing from a uniform random distribution and rescaling to final image size with cubic interpolation. Finally, all images are summed and rescaled by drawing from a uniform random distribution (mean = 1 s, SD = 2 s). In the dichoptic viewing condition of Experiment 2, where only the amblyopic eye saw the dynamic fractal noise pattern stimulus, the dominant eye viewed a single static fractal noise pattern of the same size that never changed. Experimental presentation was realized using the psychophysics toolbox (Brainard, 1997; Pelli, 1997) with the stimuli generated using Matlab (The Mathworks) and the Image Processing Toolbox.

Table 1. Clinical details of the amblyopic observers participating in the experiments. The following abbreviations have been used: strab for strabismus, aniso for anisometrope, mixed for mixed strabismic–anisometropic, Sq for squint, Obs for observers, RE for right eye, LE for left eye, ET for esotropia, XT for exotropia, DS for diopter sphere.

<table>
<thead>
<tr>
<th>Obs</th>
<th>Age/Sex</th>
<th>Type</th>
<th>Refraction</th>
<th>Acuity</th>
<th>Squint</th>
<th>History, stereo</th>
</tr>
</thead>
<tbody>
<tr>
<td>ML</td>
<td>20/F</td>
<td>RE</td>
<td>+1.0–0.75</td>
<td>90°</td>
<td>20/80</td>
<td>ET 6° Detected at age 5 years, patching for 2 years, no stereopsis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE mixed</td>
<td>–3.25</td>
<td>DS</td>
<td>20/20</td>
<td></td>
</tr>
<tr>
<td>GN</td>
<td>30/M</td>
<td>RE mixed</td>
<td>+5.00–2.00</td>
<td>120°</td>
<td>20/70</td>
<td>ET 8° Detected at age 5 years, patching for 3 m, no glasses tolerated, 2 strabismus surgery RE, no stereopsis, age 10–12 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE</td>
<td>+3.50–1.00</td>
<td>75°</td>
<td>20/20</td>
<td></td>
</tr>
<tr>
<td>PH</td>
<td>33/M</td>
<td>RE</td>
<td>–2.0 + 0.50</td>
<td>DS</td>
<td>20/25</td>
<td>XT 5° Detected at age 4 years, 6 m, no strabismus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE strab</td>
<td>+0.50</td>
<td>DS</td>
<td>20/63</td>
<td></td>
</tr>
<tr>
<td>VD</td>
<td>23/F</td>
<td>RE</td>
<td>+0.25</td>
<td>DS</td>
<td>20/20</td>
<td>ET 3° Detected at age 5–6 years, patching for 6 m, no surgery, no stereopsis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE mixed</td>
<td>+2.75–1.25</td>
<td>175°</td>
<td>20/40</td>
<td></td>
</tr>
<tr>
<td>XL</td>
<td>31/F</td>
<td>RE</td>
<td>–2.50</td>
<td>DS</td>
<td>20/20</td>
<td>ET 15° Detected at age 13 years, no treatment, no stereopsis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE strab</td>
<td>–2.75 + 0.75</td>
<td>110°</td>
<td>20/400</td>
<td></td>
</tr>
<tr>
<td>WM</td>
<td>20/M</td>
<td>RE</td>
<td>0</td>
<td>20/20</td>
<td>XT 1° Detected at age 12 years, no patching, no surgery, no stereopsis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE strab</td>
<td>+1.75–0.5</td>
<td>180°</td>
<td>20/63</td>
<td></td>
</tr>
<tr>
<td>GH</td>
<td>45/M</td>
<td>RE</td>
<td>–1.75 + 0.5</td>
<td>90°</td>
<td>20/20</td>
<td>ET 6° Detected at 11 years, no surgery, no patching, eye exercise 1–2 years, glasses since 12 years, no stereopsis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE mixed</td>
<td>+1.25</td>
<td>DS</td>
<td>20/63</td>
<td></td>
</tr>
<tr>
<td>SS</td>
<td>32/M</td>
<td>RE mixed</td>
<td>+3.00</td>
<td></td>
<td>20/50</td>
<td>XT 5° No stereopsis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE</td>
<td>+3.00</td>
<td></td>
<td>20/25</td>
<td></td>
</tr>
<tr>
<td>AS</td>
<td>25/F</td>
<td>RE strab</td>
<td>0</td>
<td>20/160</td>
<td>ET 15° Detected at 4 years, strabismus corrected surgically at 7 years, intermittent patching, no stereopsis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE</td>
<td>–0.5</td>
<td></td>
<td>20/25</td>
<td></td>
</tr>
<tr>
<td>KS</td>
<td>43/M</td>
<td>RE mixed</td>
<td>+5.00–1.00</td>
<td>20/125</td>
<td>ET 4° Detected at 4 years, patching and training for 1 m, glasses for 1 year. At 15 years, glasses again for 2.5 years. No stereopsis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE</td>
<td>+0.5</td>
<td></td>
<td>20/25</td>
<td></td>
</tr>
<tr>
<td>SH</td>
<td>24/F</td>
<td>RE</td>
<td>–0.5</td>
<td>90°</td>
<td>20/25</td>
<td>XT 6° Detected at birth, glasses at 6–7 years, not patched, no stereopsis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE strab</td>
<td>+2.5 + 2</td>
<td>180°</td>
<td>20/63</td>
<td></td>
</tr>
</tbody>
</table>

**Design**

During all experiments, subjects were asked to fixate on a centrally presented cross and reported conforming to this instruction. For Experiment 1, participants viewed the dynamic fractal noise stimulus monocularly while wearing a tight-fitting eye patch over their non-viewing eye. Three scanning runs, each consisting of twenty-four stimulus presentation events, were conducted for each eye. When the dynamic fractal noise pattern was not present, a mean luminance gray screen with the central fixation cross was presented and the participant was required to maintain fixation.

For Experiment 2, a dichoptic stimulus presentation system consisting of aligned polarized filters was employed to achieve full-field dichoptic presentation with
For this experiment, the dynamic event-related fractal noise pattern was always presented to the amblyopic eye while the dominant eye was either occluded with a tight-fitting eye patch (condition 1—minimal suppression) or viewed a constantly presented static fractal noise pattern (condition 2—full suppression). The experimental design is shown in Figure 1. Since the static fractal noise pattern was presented constantly to the dominant eye, we could identify the visual cortex activity due to the stimulation of the amblyopic eye—induced by the brief dynamic stimulus presented independently to the amblyopic eye—by using an event-related design. Three scanning runs were conducted with the dominant eye patched and three under dichoptic viewing conditions, with twenty-four stimulation events presented to the amblyopic eye per run.

**Acquisition and analysis**

All measurements were made using a Siemens Sonata 1.5 Tesla MRI scanner with a flexible receive surface coil positioned on the posterior of the head. Following an anatomical scan (MPRAGE), 415 frames were captured for each functional run using an EPI sequence (TE = 50 ms, flip angle = 90°, voxel size = 3 × 3 × 4 mm, 64 × 64 matrix, TR = 1.0 s, descending acquisition, 11 slices, no slice gap). The slices were centered on the calcarine and the FOV covered most of the occipital lobe. Because of the random length of the interstimulus intervals (see above) and assuming a linear and time-invariant response function, we were able to subsample the HRF at a temporal resolution finer than the TR, thus allowing us to make estimates of delays that are shorter than the TR itself.

All preprocessing and statistical analyses were performed using SPM2 (http://www.fil.ion.ucl.ac.uk). Following slice-time correction by sinc interpolation, all frames in a session were aligned to the fourth frame in the first run. GLM of the canonical HRF convolved with the stimulus onsets was used to select activated voxels.
proximal to the calcarine cortex for subsequent extraction and analysis. Figure 2 represents an ROI for a sample subject. Extracted time courses were high-pass filtered and temporal autocorrelations were modeled with the SPM AR (1) model. Average HRFs were estimated for each run using finite impulse response filters with 0.5-s bins. This deconvolved HRF was subsequently fitted as the difference of two gamma functions using the Curve Fitting Toolbox in Matlab (Mathworks). Each gamma function has three parameters for amplitude, width, and time to peak. While many fMRI analysis packages make use of only one gamma function, two gamma functions have been found to better fit the HRF, particularly the HRF undershoot (Friston et al., 1998). Here, we took the time-to-peak estimate of the first gamma function as the measure of HRF delay for the inferential statistical tests.

Results

Experiment 1: Monocular viewing, amblyopic eye vs. dominant eye

The HRFs for amblyopic eye and dominant eye stimulation under monocular viewing conditions are shown in Figure 3. While the magnitude of the effects varied across participants, two main differences in the HRFs between the two eyes were apparent. First, the response of the amblyopic eye to our high-contrast, briefly presented dynamic stimulus was significantly reduced compared to the response of the dominant eye ($t(5) = 2.62, p < 0.03$). This is consistent with previous fMRI studies of amblyopia (see Introduction section for sample references). The novel finding was that the HRF of the amblyopic eye was delayed by an average of 500 ms compared to the response of the dominant eye. This delay was reliable across subjects ($F(1,10) = 8.372, p < 0.034$) and did not differ across sessions ($F(2,10) = 0.47, p > 0.95$) and there was no session by eye interaction ($F(2,10) = 0.055, p > 0.9$). To measure correlation of HRF delays and amplitudes and visual acuity, we converted acuity measures to logMAR values. We excluded the results from one participant because the individuals’ acuity was more than 2 standard deviations from the group average. The HRF delay measured here correlated strongly and negatively with logMAR acuity difference of the dominant vs. amblyopic eye ($r = 0.91$) and the relationship was significant ($p < 0.03$)—the worse the acuity in the amblyopic eye, the greater the delay in the response of that eye. In addition, the correlation between the relative amplitude of the HRF (amblyopic eye amplitude/dominant eye amplitude) and relative acuity was also strong and significant ($r = 0.96$, $p < 0.03$).
Experiment 2: Dichoptic viewing, dominant eye patched vs. dominant viewing a static stimulus

In Experiment 2, the amblyopic eye was presented with the event-related flashing fractal noise stimulus while the dominant eye was either occluded (minimal suppression) or viewing a static, constant fractal noise pattern (suppression; see Figure 1). Across the nine subjects we tested, a comparison between the HRFs generated by amblyopic eye stimulation under low or high suppression conditions revealed that when the dominant eye was open and seeing a static pattern, the HRF response in the amblyopic eye was not only significantly lower in amplitude relative to when the dominant eye was patched (21% lower, \( t(8) = 3.637, p < 0.003 \)) but was also significantly delayed (mean delay = 0.670 s, \( t(8) = 2.525, p < 0.017 \)). The correlation between the amplitude reduction and delay was weak (\( r = 0.05, p > 0.9 \).) Figure 5 presents individual data from the nine subjects who took part in the second experiment. Surprisingly, the suppression-induced delay and amplitude reduction observed here did not correlate with interocular acuity difference (Figure 6), suggesting that the neural suppression measured using fMRI and relative acuity differences observed in amblyopia are separable factors. Exclusion of outliers had no effect on the strength or significance of these correlations.

Discussion

We measured the event-related HRF in the early visual cortex of observers with strabismic amblyopia under both monocular and dichoptic viewing conditions in order to assess the effect of interocular suppression on cortical responses. When the amblyopic and dominant eyes were compared under monocular presentation conditions (non-tested eye occluded, Experiment 1), we found that the response of the amblyopic eye was both reduced in amplitude and delayed in time relative to the dominant eye. The reduced amplitude is consistent with previous studies of amblyopia using fMRI and is indicative of a cortical loss of function (Algaze et al., 2002; Anderson & Swettenham, 2006; Barnes et al., 2001; Choi et al., 2001; Conner et al., 2007a, 2007b; Goodyear et al., 2000, 2002; Hess et al., 2010; Hess, Li et al., 2009; Hess, Thompson et al., 2009; Lerner et al., 2006; Li et al., 2007; Lv et al., 2008). The temporal delay in the amblyopic eye response is novel and may be indicative of chronic suppression of the ocular dominance columns representing the amblyopic eye even under monocular viewing conditions. To further explore this temporal delay and its relationship to suppression, we compared the cortical response to amblyopic eye stimulation when the dominant eye was occluded to a condition where the dominant eye was open and viewed a static pattern. Presenting a static stimulus to
the dominant eye caused both a reduction in the magnitude of the amblyopic eye response and a significant delay in the time to peak of the response, suggesting that suppressive interactions underlie both of these effects.

It would appear therefore that the signature of amblyopic suppression, as detected with fMRI, is an attenuated and delayed BOLD response. What does this tell us about the underlying neural mechanisms? Although our data do not allow for a conclusive answer to this question, in the following section, we propose a possible explanation for these effects.

**Local summation of positive and negative BOLD**

One possibility for the delay observed in our two experiments is the summation of two opposing BOLD responses: one negative BOLD response representing local neural inhibition and one positive BOLD response representing neural activation (Figure 7). While negative and positive BOLD are likely extremes of a continuum of possible BOLD responses, for the sake of discussion, it may be helpful to consider them as separate. Specifically,

---

**Figure 5.** Hemodynamic responses of visual stimulation of the amblyopic eye under conditions of low and high suppression. Both red and blue lines depict stimulation of the amblyopic eye but under conditions of high suppression (red line) and low suppression (blue line). Suppression by means of static visual stimulation of the dominant eye increased the delay and further reduced the amplitude of the HRF resulting from amblyopic eye stimulation. Each panel depicts the responses of one subject.
we speculate that under conditions of high suppression, increases in inhibition within a given voxel bring about an increase in the negative BOLD amplitude. Given the shape and timing of the two BOLD functions as described recently (Shmuel et al., 2006), this negative response summed with the positive BOLD response from within that same voxel would give rise to an appearance of a delayed response (see Supplementary Figure 2).

In the second experiment, we only stimulated the amblyopic eye. By way of a dichoptic stimulation setup, we were able to selectively stimulate the amblyopic eye while the dominant eye either viewed a static random pattern or was patched (no stimulation). Given the constant suppression of the amblyopic eye by the dominant eye, if columns representing the amblyopic eye were to respond to stimulation under this ongoing suppression, they would need to countersuppress the dominant eye columns—in other words, they would have to suppress their suppressor. This would bring about a reduction in neural activity in the dominant eye columns and, thus, a negative BOLD response. Future studies with high-resolution functional imaging may allow us to test such a model directly.

Another possibility is that negative BOLD is induced in some voxels while positive BOLD is observed in others, and the ratio of these changes is a result of suppression. However, the number of voxels exhibiting negative beta values (as estimated by the canonical HRF) in the high suppression condition did not differ substantially with that observed in the low suppression condition. Yet the possibility remains that negative BOLD may be exhibited in cortical patches larger than a column but smaller than our voxels during high binocular suppression. This may need to be assessed in future studies. Another alternative explanation is that a neural delay underlies the HRF delay, or neural modulation by the lateral geniculate nucleus of the thalamus is the source of the HRF delay. We find the argument for a neural delay unlikely, given the fact that the neurons in early visual areas have very short response latencies. Thus, even in the presence of inhibitory inputs, it is unlikely that neurons delayed their responses by the amount observed in the HRF delay. While we believe that the HRF delay is due primarily to suppressive activity in the early visual cortex, it is possible and even likely that such a suppression arises from recurrent modulation between early visual areas and the LGN. Thus, while we do not believe that the LGN is the source of the HRF delay observed due to the argument against a neural delay, we do not exclude the possibility that the LGN plays an important role in the suppressive processes carried out in the early visual cortex.

The results of Experiment 1 could also be explained in the context of physiological changes brought on by chronic suppression. It is conceivable that chronic suppression of amblyopic eye representations by that of the dominant eye over a lifetime resulted in degeneration of neurons, reduced synapses, or reduced capillary density. Such changes would then contribute to a difference in HRF of the amblyopic eye as opposed to the dominant eye. However, these putative changes would not explain the results of Experiment 2, where all stimulation was in the amblyopic eye.

Finally, it is possible that the HRF delay is not related to a neural difference but simply a difference in the vascular response. Given that BOLD is an indirect measure of neural function and foremost a measure of blood oxygenation, flow, and volume, the possibility may exist that the neural response to amblyopic eye stimulation is left intact, but the vascular response is affected, hence the affected HRF. While we have no direct electrophysiological evidence to test this possibility, patients do report suppression of vision in their amblyopic eye when their
dominant eye is open, suggesting that our measurements are at least correlated with the subjective effects of suppression.

Variability in amblyopia and comparison with normals

Our results point to a link between cortical suppression and the hemodynamic delay as observed in BOLD fMRI. The data from the second experiment demonstrate a simple paradigm within which such suppressive mechanisms may be measured. Amblyopic suppression has been studied previously in animal models and appears to be mediated by GABAergic mechanisms (Sengpiel & Blakemore, 1994; Sengpiel et al., 1994, 2006). A shortcoming of our study is that we were unable to visualize ocular dominance columns to directly assess our proposed model, given the limitations of current MRI technology. While we anticipate similar results in normal subjects under conditions of binocular suppression (e.g., continuous flash suppression, Tsuchiya & Koch, 2005), it is not known whether such a putative effect in normal subjects could be equally well ascribed to local suppressive mechanisms.

While a delay was not observed in every participant of Experiment 2, none showed the reverse effect—i.e., the results are not explicable as a random observation around a mean of zero delay. The variability of suppression...
Implications for fMRI studies of amblyopia

Our results have important implications for future fMRI studies of amblyopia, particularly those using event-related designs. Specifically, the present findings suggest that using the canonical HRF in the analysis of fMRI data in studies of amblyopia (i.e., studies comparing cortical responses to normal as compared to amblyopic eye) is intrinsically biased against finding “activations” in response to amblyopic eye stimulation, particularly if measured under dichoptic viewing conditions (e.g., Lerner et al., 2003). It follows that reduced t-contrasts in comparisons of normal to amblyopic eye responses may be due to a mismatch between the canonical HRF and the amblyopic eye HRF. Future studies should try and mitigate this difference by either estimating HRFs for the dominant and normal eyes independently or by employing correction terms such as the HRF temporal derivatives.

The correlation of relative acuity and HRF delay as observed in Experiment 1 and its absence in Experiment 2 suggest that some of the effects observed in Experiment 1 are due to differences between the sensory capacities of the amblyopic and dominant eyes. Experiment 1 did not control for differences in visual acuity or contrast sensitivity. Therefore, some of the differences seen between the response of the dominant eye and the amblyopic eye may have been due to these uncontrolled factors. In contrast, responses measured in Experiment 2 are always to stimulation of the amblyopic eye, thus relative acuity between the two eyes would not be a strong predictor of performance, unless the opening or closing of the dominant eye were to have a direct influence on the acuity of the amblyopic eye.

In summary, we observed a difference in the HRF amplitude and delay when the amblyopic and dominant eyes were stimulated monocularly. We then observed that the response in the amblyopic eye can be reduced and delayed as a function of suppression by the dominant eye. Our results have important methodological implications for future fMRI studies of visual processing in amblyopia and also lead to an interesting possibility for the source of the HRF delay as observed in many fMRI studies—that the HRF delay may serve as an index of local suppression. Future studies employing higher resolution imaging methods are needed to directly test this possibility.

Acknowledgments

This research was supported by an operating grant from the Canadian Institutes of Health Research (MOP-53346) to Robert F. Hess.

Commercial relationships: none.
Corresponding author: Reza Farivar.
Email: farivar@nmr.mgh.harvard.edu.
Address: Athinoula A. Martinos Center for Biomedical Imaging, Department of Radiology, Massachusetts General Hospital, 149 13th Street, Charlestown, MA, USA.

References


Conner, I. P., Odom, J. V., Schwartz, T. L., & Mendola, J. D. (2007b). Retinotopic maps and foveal suppression within the amblyopic population is known (Jampolsky, 1955; Travers, 1938) and also seen in fMRI (e.g., Conner et al., 2007b). For example, even in the patients with the same type of strabismus, there is a degree of variability in the density of the suppression. This is as true for small angle strabismics (Joosse et al., 1997) as it is for large angle strabismics (Joosse, Simonsz, van Minderhout, Mulder, & de Jong, 1999). It is thought that the age at which the strabismus first occurs may be the critical factor. A future objective will be to assess the correlation between the degree of suppression (Mansouri et al., 2008) and the amount of HRF delay in the amblyopic population.


