

Eye Dominance in Visual Cortex in Amblyopia Using Functional Magnetic Resonance Imaging

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In a previous article,¹ we described a functional magnetic resonance imaging (fMRI) technique at 1.5 T (magnetic field strength) that could be used to study primary visual cortex (V1) in patients with amblyopia. Our methodology characterized the distribution of eye dominance of voxels (small volumes) in V1 based on the Student *t* statistic in an OS-versus-OD contrast. Only control individuals were studied, and the technique was found to be sensitive to neutral-density filtering but relatively insensitive to visual blur. In the present study, the eye dominance of voxels in V1 in 2 patients with anisometropic amblyopia and 1 patient with monocular suppression was studied using this technique. The eye-dominance histograms were shifted toward the unaffected eye, and the magnitude of the change seemed to be correlated with the visual acuity deficit in the amblyopic eye. Our technique complements other fMRI methodologies,²⁻⁷ including 1⁶ that was recently described in this journal and is now being used to study cortical abnormalities associated with amblyopia.

METHODS

Two volunteer subjects with anisometropic amblyopia (ages 11 and 13) and 1 volunteer subject with monocular suppression (age 33) were studied, and each signed a consent form approved by the Institutional Review Board of The Children's Hospital of Philadelphia. Patient demographics and ophthalmic history are shown in Figure 1.

We described the details of the fMRI methodology in our previous article.¹ Briefly, a 1.5-T MRI scanner (Siemens; Erlangen, Germany) was used to obtain T2*-weighted echo planar images (voxel size $3.75 \times 3.75 \times 5$ mm³) of area V1. Epochs consisted of right eye (OD), left

eye (OS), and both eyes (OU) stimulation with a 1-cycle/degree checkerboard (8 Hz), and rest periods. Monocular stimulation was achieved by using a red filter over the OD and a green filter over the OS and alternating identical filters over the video projector lens. A 0.9-log neutral-density filter over the OS was used to make the stimuli to each eye equiluminant. In the 2 subjects with amblyopia and the 1 subject with monocular suppression, the full refractive correction was given in the amblyopic eye. The eye dominance of each voxel within each subject's V1 was determined using the Student *t* statistic from the OS-versus-OD contrast. Eye-dominance distribution was plotted, and the mean Student *t* statistic was used to describe the histogram asymmetry. Total time in the MRI scanner for each subject was approximately 30 minutes. Because of the relatively older ages of the subjects, all were able to cooperate for the study.

RESULTS

The results are displayed in Figure 1. For comparison, the results in a control individual are also shown.

DISCUSSION

In the 2 patients with anisometropic amblyopia (Figure 1B and C), the eye-dominance histogram was shifted toward the sound eye, and the shift was more pronounced in the patient with the poorer acuity. In our original article,¹ the average mean Student *t* value for the control subject undergoing this test paradigm was +0.13 (SD +0.34). Therefore, the mean Student *t* values for the 2 subjects with anisometropic amblyopia (+0.92 and -2.47, respectively), which were >2 SD from the mean in the control subject, can definitely be considered abnormal. The patient with accommodative esotropia, monocular suppression OS, and relatively normal visual acuity (OD) had no relative shift in the histogram. The mean Student *t* value of this subject (-0.21) was not abnormal.

Thus, these data, albeit small in number, suggest that the eye-dominance histogram shifts toward the sound eye in patients with amblyopia. Although the amount of shift appeared to be related to visual acuity, our previous study showed that visual blur alone (created artificially in control subjects) does not shift the eye-dominance histogram significantly. In fact, the mean Student *t* value (+0.92) of our first subject with milder amblyopia (20/70) was still

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Submitted April 4, 2003.

Revision accepted November 21, 2003.

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J AAPOS 2004;8:184-186.

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1091-8531/2004/\$35.00 + 0

doi:10.1016/j.jaapos.2003.11.011

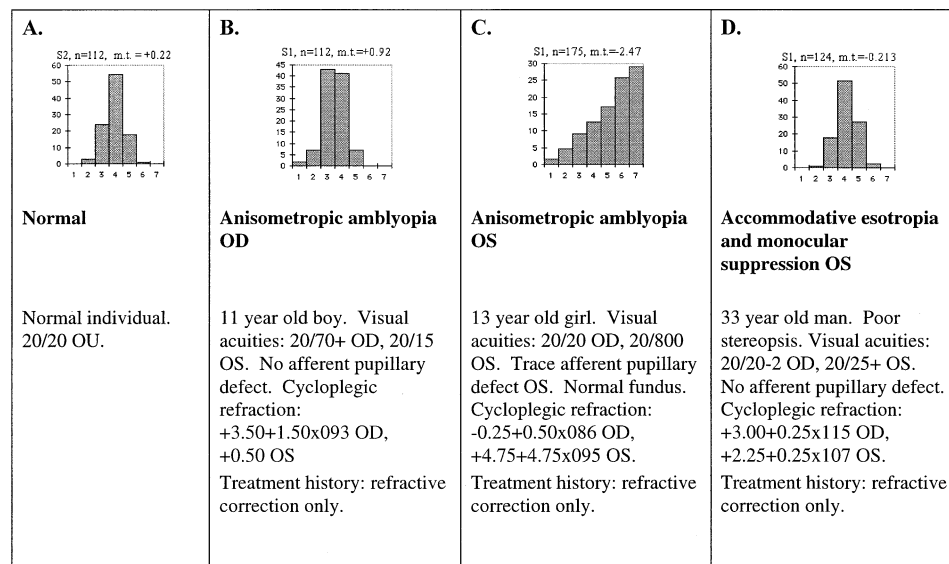


FIG 1. Eye-dominance distributions in visual cortex using fMRI at 1.5T in amblyopia. The mean Student *t* statistic was used to describe the histogram asymmetry. (A) Control subject with relatively symmetric distribution. (Reprinted with permission from Liu GT, Miki A, Goldsmith Z, et al. Eye dominance in visual cortex using functional MRI at 1.5 T. An alternative method. *J AAPOS* 2002;6:40-8). (B and C) Subjects with anisometropic amblyopia. (D) Subject with accommodative esotropia. *n*: number of voxels analyzed; *mt*: mean Student *t* statistic; *y*-axis: percentage of *n*; *x*-axis: ocular dominance number (1 = OS dominant, 7 = OD dominant).

slightly greater than any of the control subjects visually blurred to 20/200 (range of mean Student *t* values +0.26 to +0.81). Therefore, there must be some other pathophysiologic mechanism other than visual blur underlying the shift in the ocular-dominance histogram in these patients with amblyopia. The exact nature of this mechanism is unclear. It is possible that the abnormality lies within neurons in V1. However, because of connections from extrastriate cortex on V1, alternatively, the defect may be located outside of the primary visual cortex.

There are many real and potential drawbacks to this study as well as the original one. The subjects with amblyopia were younger than most of the original article's control subjects who were primarily college and graduate students. Younger individuals (age range 10–40) not being able to sit still for the testing would lead to compromised data. However, the young subjects we included in the current study were able to remain still for the testing. Creating an fMRI template using binocular stimulation may not be valid in patients with amblyopia because there may be a decrease in binocular interaction in their visual cortex. An alternative template using a logical OS-versus-off or OD-versus-off technique may have been preferable. Finally, the statistical cutoff for defining the regions of interest is somewhat arbitrary. A *z* score cutoff of 4.0 is conservative for visual cortex stimulation.

There are also ways to improve our studies. For instance, it would have been desirable to have more subjects blurred and filtered in the original control study to enhance its statistical power. In addition, an ideal control for

subjects 1 and 2 would have been a subject with anisometropia but no amblyopia.

Other groups of investigators have used fMRI techniques to study cortical abnormalities in patients with amblyopia. Although each has approached the problem slightly differently, to some extent abnormalities in V1 activation were shown in all. Goodyear et al² found a decreased number of activated voxels in V1 when the amblyopic eye was stimulated. Barnes et al³ studied 10 subjects with strabismic amblyopia and found decreased V1 activation when affected eyes viewed high-contrast stimuli. Lee et al^{4,5} used reversing checkerboards in subjects with strabismus and anisometropic amblyopia. They found that fewer voxels in V1 were activated by both eyes during monocular stimulation in patients with strabismic amblyopia than in subjects with anisometropic amblyopia, and they attributed this to a loss of binocular interaction. In contrast, subjects with anisometropic amblyopia had decreased primary visual cortex activation when the affected eye was stimulated by higher spatial frequencies compared with patients having strabismic amblyopia.^{4,5} Algaze et al⁶ found decreased levels and areas of activation in amblyopic eyes. They also determined that the difference between monocular and binocular responses in subjects with amblyopia was larger than that observed in control subjects. fMRI at a spatial resolution of the cortical columns showed that patients whose amblyopia developed during infancy showed a decreased number of pixels within the visual cortex activated by stimulation of the affected eyes.⁷ In contrast, patients with late-onset ambly-

opia (developed after 2 years of age) showed lack of the shift in ocular dominance in the unaffected eye. This finding suggests that the effect of early-onset and late-onset amblyopia on ocular dominance columns may be different.

Our study confirms that fMRI, which is noninvasive and nonradioactive, offers temporal and spatial resolution for studying the eye dominance of small volumes of visual cortex in patients with amblyopia by measuring the relative activation by stimulation of the OS or OD. Our approach may have future usefulness in the further study of amblyopia in humans.

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