Changes in the Amygdala Produced by Viewing Strabismic Eyes

Jatta Berberat, PhD,1 Gregor P. Jaggi, MD,2 Frederick M. Wang, MD,3,4 Luca Remonda, MD,1 Hanspeter E. Killer, MD2,5

**Purpose:** The aim of this study was to look for the response to strabismus images in the limbic network (amygdala, hippocampus, parahippocampus) of healthy volunteers and to compare it with their reaction to viewing normal eyes.

**Design:** Prospective, observational study.

**Participants:** Thirty-one healthy volunteers underwent functional magnetic resonance imaging (fMRI).

**Methods:** Functional magnetic resonance imaging data and blood oxygen level dependent signal changes were analyzed using the BrainVoyager QX software package (Brain Innovation, Maastricht, The Netherlands).

**Main Outcome Measures:** Responses to viewing strabismus images were compared with those observed while viewing normal eye images.

**Results:** Strabismus images led to significant activation of the amygdala, hippocampus, parahippocampal, and fusiform gyri in 30 of 31 subjects compared with normal eye images, indicating a negative emotional response.

**Conclusions:** These fMRI results confirm that strabismus influences organically not only the patient with nonparallel eyes but also observers. Treatment of strabismus therefore changes the interpersonal dynamic for patients with strabismus on a demonstrable organic basis.

**Financial Disclosure(s):** The author(s) have no proprietary or commercial interest in any materials discussed in this article.

Strabismus is an ophthalmic disorder with a prevalence of up to 4% in a population.1,2 It is associated with functional and social handicaps. Eye contact is of essential importance for verbal and especially nonverbal social interaction. Up to 60% of the time spent looking at a face is used for scanning the eyes. In this study, we used images of normal eyes and strabismic eyes to investigate the emotional response of subjects examined with functional magnetic resonance imaging (fMRI).

Neuroimaging studies suggest that emotional processing in the brain involves the prefrontal cortex (PFC),3–5 anterior cingulate gyrus, parietal cortex, amygdala,3,6–8 and cerebellum.8 The amygdala is thought to play an important role in processing negative, fearful, and aversive emotions.3,6,9 Both the PFC and amygdala are suggested to be the main elements in emotional cognition, behavior, and processing feelings.9 However, an overlap in regions involved in the processing of pleasant and unpleasant stimuli exists, and the neural network for each is unique.8

Most of the neuroimaging studies that have investigated emotional processing maps in the human brain have used emotional faces, pictures, or words as emotional visual stimuli.3,8,10,11 Music and aversive sounds also have been used to evoke emotional responses in the brain.12,13

Strabismus is associated with functional as well as social handicaps. The object of interest in studies on strabismus is almost always the patient. This study focused on the observer. Using fMRI, we used images of normal and strabismic eyes to investigate the emotional response of a subject. The study was designed to assess the difference in responses in the limbic network of observers viewing strabismus images compared with images of normally aligned eyes.

**Methods**

**Subjects**

This study was approved by the local ethical commission and followed the tenets of the Declaration of Helsinki. All studied individuals were volunteers (17 men and 14 women; mean age, 39±10 years; age range, 27–65 years). All subjects gave written informed consent. Each subject had normal brain MRI results. Of the 31 subjects, 29 were not aware of the purpose of the study.

**Stimuli and Paradigm**

The visual stimuli consisted of normal and strabismic eyes and a neutral picture (Fig 1). To investigate only the response based on the eyes presented on the images, the upper and lower part of the face were covered. The neutral picture consisted of a crosshair presented in the middle of the screen. We used a total of 42 images: 21 normal images and 21 strabismus images. The experimental paradigm consisted of 168 blocks of eyes as visual stimuli with a duration of 21 seconds, followed by a baseline condition in which a crosshair presented in the middle of the screen. The use of a crosshair is based on earlier emotions studies.8 During each block of the emotionally evocative stimuli, 7 normal eyes or 7 strabismic eyes were presented for 3 seconds and then followed by the baseline condition. The visual stimulus was programmed by using E-Prime software (Psychology Software Tools, Sharpsburg, PA). Subjects lay in the MRI scanner and viewed, via a mirror, large stimuli projected on a screen.
Functional Magnetic Resonance Imaging Data Acquisition

Block-designed, blood oxygenation level–dependent (BOLD) fMRI was applied to the volunteers using the 1.5-Tesla whole-body scanner with a 12-channel head array coil (MagnetomAvanto; Siemens Healthcare, Erlangen, Germany). Functional MRI was performed using an echo planar imaging sequence (repetition time, 3000 ms; echo time, 50 ms; flip angle, 90°; voxel size, 3×3×3; slice thickness, 3 mm; matrix, 64×64). T₁-weighted anatomic, 3-dimensional, volumetric, interpolated brain examination sequence followed (fat saturated; scan duration, 3 minutes; repetition time, 6300 ms; echo time, 2380 ms; voxel size, 1×1×1; matrix size, 256×256; flip angle, 12°; slice thickness, 1.0 mm; 192 slices).

Data Analysis

Blood oxygenation level–dependent clusters were assessed individually for anatomic localization. The images obtained from fMRI were processed using the BrainVoyager QX software package (Brain Innovation, Maastricht, The Netherlands). Anatomic images were transformed to Talairach space. All image data from the functional sessions for each subject underwent the following preprocessing steps: head motion correction was performed using trilinear or sync interpolation by spatial alignment of all acquired volumes to the first volume by rigid body transformations. All functional images for each subject were spatially smoothed using Gaussian filter of 3 mm full width at half maximum. Functional images were coregistered with the 3-dimensional isovoxel anatomic data. At first-level analysis, a general linear model was computed for each experiment, applying separate predictors for each subject. Then, multisubject analysis was applied by averaging all the data. Activation maps were corrected for multiple comparisons using a false discovery rate approach with \( P < 0.05 \), considering a minimum cluster of more than 12 contiguous voxels.

Questionnaire

After undergoing the fMRI, each observer answered a questionnaire. Each observer was asked, Did the pictures evoke any emotions?

Results

A list of activated limbic system brain regions and structures, Talairach coordinates, and \( t \) values are listed in Table 1 for the
normal eyes versus strabismus eyes (Table 1). Thirty of 31 subjects had significant limbic activation when viewing the strabismus images compared with viewing the straight eyes. Reaction to strabismus images compared with normal eye images showed a statistically significant ($P<0.05$) increase in BOLD signal on pooled data in the left amygdala and bilaterally in the parahippocampal gyri, hippocampus, and fusiform gyri (Fig 2). Increased activation also was noted in the visual cortex. When comparing strabismus images with the neutral image of a crosshair, a significant increased BOLD signal on pooled data was observed in the left amygdala and bilaterally in the parahippocampal gyri and hippocampus. However, viewing parallel eyes versus viewing the neutral crosshair evoked signal only in the parahippocampal gyri and not in the amygdala or hippocampus. There was no significant difference in the activation pattern between male and female observers (Fig 3).

On the questionnaire, 23 subjects (10 women, 13 men) stated they were emotionally evoked by the strabismus images, and 8 subjects (4 women, 4 men) claimed to have a neutral response to the stimuli. However, when looking at the BOLD signal response among the 31 candidates, there was only 1 candidate with no or little limbic activation. The lone observer without limbic activation is an ophthalmologist who helped design the study. After dividing the data into 2 subgroups, male and female, and averaging for analysis (Fig 3), both subgroups showed similar activation of the parahippocampal area and the limbic lobe as a response to the stimuli.

### Discussion

Based on ethnologic studies, facial expressions and emotions are innate and of critical importance for social interaction.\(^{14}\) The amygdala receives input from temporal visual-association areas with a strong anatomic link to the autonomic nervous system and is involved in the acquisition and expression of conditioned fear.\(^{15}\) According to LeDoux et al\(^{15}\) the amygdala serves as a warning system. In a meta-analysis of positron emission tomography and fMRI studies, Costafreda et al\(^{16}\) and Breiter et al\(^{17}\) found that the activation of the amygdala was more pronounced for fear and disgust than for happiness. Damage to the amygdala results in impaired recognition of fearful facial expression and therefore inhibits the development of conditioned fear.\(^{18}\) A functional amygdala is, therefore, important for social interaction.

This fMRI study is focused on the response in the amygdala and other parts of the limbic system of observers viewing strabismus images compared with their reactions while viewing normal (parallel) eyes. Strabismus images led to significant activation of the left amygdala, the hippocampus, the fusiform gyri, and the parahippocampal gyri when compared with normal eye images in 30 of 31 subjects.

Activation of the amygdala previously was shown in studies of facial expressions, such as anger, fear, and joy, as well as in response to phobic and frightening images.\(^{19}\) A neural network for disgust involves the amygdala and the insula.\(^{20}\) Activation of the amygdala also was demonstrated after viewing phobic images (spiders and snakes) and fear-inducing pictures.\(^{21,22}\) Network activation including the occipitotemporal cortex, the orbitofrontal cortex, and the amygdala was demonstrated as a response to pictures of mutilation and contamination.\(^{22}\)

Because the amygdala is the fundamental structure in the processing of negative, fearful, and aversive emotions,\(^{3,23,24}\) the results of this study strongly suggest that healthy individuals are reacting in a negative fashion to strabismus. The strong reaction to strabismus seems to be based on a system for face recognition hardwired during early infancy. Even with a relatively poor level of visual resolution, infants are able to recognize different faces and different facial expressions.\(^{25}\) The strongest stimulus for the visual system in infants is the human face. Studies with infants demonstrate that infants prefer to look at faces rather than other objects.\(^{25}\) Face recognition is an essential tool for survival, and therefore, the neural network can be explained by hardwired neuronal systems that deal primarily with face recognition.\(^{26}\)

In this study, we found that activation of the left amygdala was dominant. Twenty-nine of 31 of the involved individuals were right handed, so left hemisphere dominance seems to be feasible using pooled data. Asymmetry in the right and left PFC in emotional processing has been addressed in neuroimaging studies involving healthy and psychiatric patients.\(^{7,8,23}\) In one study, bilateral amygdala activation was associated with the processing of negative emotions but not with the processing of positive ones.\(^{8,27}\)

Another major finding is that viewing the strabismus images resulted in significant activation in the hippocampus, parahippocampal gyri, and fusiform gyri bilaterally. The hippocampus is known to be related to memory formation, and it interconnects with other parts of the limbic system and PFC.\(^{28,29}\) Because the amygdala is connected extensively to other cortical and subcortical structures, including the hippocampus and parahippocampal areas, stimulating the amygdala may cause such a pattern of activation in the hippocampal region.

Strabismus surgery has 2 aims: to maximize binocular function and improve cosmesis.\(^{30,31}\) Beauty, of course, is subjective. Functionality is a factor in assessing beauty. We likewise find dysfunctional traits such as strabismus to be detracting.\(^{32}\) Strabismus yields a lower functionality of eye use and may signal a number of pathologic conditions that produce strabismus.

Our fMRI results contrast with the subjective answers of some of the candidates. Although we found activation in the

### Table 1. Significant Regions Blood Oxygen Level-Dependent Activation in Healthy Subjects (n = 31) during Viewing of Strabismic Eyes Contrasted with Normal Eyes

<table>
<thead>
<tr>
<th>Region</th>
<th>Voxels in Talairach Coordinates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>x</td>
</tr>
<tr>
<td><strong>Right hemisphere</strong></td>
<td></td>
</tr>
<tr>
<td>Amygdala</td>
<td>–20</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>–27</td>
</tr>
<tr>
<td>Parahippocampal gyrus</td>
<td>–34</td>
</tr>
<tr>
<td>Fusiform gyrus</td>
<td>–35</td>
</tr>
<tr>
<td><strong>Left hemisphere</strong></td>
<td></td>
</tr>
<tr>
<td>Amygdala</td>
<td>27</td>
</tr>
<tr>
<td>Fusiform gyrus</td>
<td>24</td>
</tr>
<tr>
<td>Parahippocampal gyrus</td>
<td>44</td>
</tr>
</tbody>
</table>

Voxels in terms of t-statistics are presented in Talairach space.
*P<0.05.
amygdala and the parahippocampus in virtually all candidates (30 of 31), one quarter of the observers reported experiencing no emotions while viewing the strabismic images. Whether this is conscious or unconscious needs further investigation. Perhaps trying to be politically correct or understanding plays a role in this.

Although the results of this study clearly demonstrate the activation of the amygdala and the parahippocampal gyri while viewing strabismus images, there are some limitations to the study that need to be addressed. The most important of these is our choice of targets. The eyes in the strabismus and normal target images were not standardized. In future studies, the eyes will be more comparable. The response to full-face images is being planned because this, too, would add data about the observer’s reaction. This would allow the possibility of ignoring the strabismus, a possibility we did not want to occur for this study. Although 2 of the subjects knew the purpose of the study, none of the conclusions would have changed if they were deleted from the study. This study demonstrates for the first time the organic effect of strabismus on the observer. The strong reaction in the limbic system of the observer confirms that strabismus is indeed viewed negatively. Therefore, strabismus is a significant interpersonal problem. This study helps elucidate why those with strabismus may have social and psychological difficulty as well as difficulty gaining employment.32–34

A strong limbic activation while viewing strabismus is demonstrated with fMRI, suggesting that strabismus not only affects the visual function of the patient, but also has a negative organic effect on the observer as well. Strabismus surgery
can improve quality of life by improving interpersonal relationships by virtue of its organic effect on both parties.

References


Footnotes and Financial Disclosures

Originally received: December 24, 2012.
Final revision: March 13, 2013.
Accepted: March 15, 2013.
1 Department of Neu-ro-radiology, Cantonal Hospital Aarau, Aarau, Switzerland.
2 Department of Ophthalmology, Cantonal Hospital Aarau, Aarau, Switzerland.
3 Department of Ophthalmology, Albert Einstein College of Medicine, Bronx, New York.
4 Department of Ophthalmology, New York Eye and Ear Infirmary, New York, New York.
5 Department of Ophthalmology, University of Basel, Basel, Switzerland.

Financial Disclosure(s): The author(s) have no proprietary or commercial interest in any materials discussed in this article.

Correspondence: Hanspeter E. Killer, MD, Department of Ophthalmology, Kantonsspital Aarau, CH-5001 Aarau, Switzerland. E-mail: Killer@ksa.ch.