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ORIGINAL ARTICLE

Modulation of the Emotional Response to Viewing Strabismic Children in Mothers—Measured by fMRI

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Abstract
Purpose Strabismus influences not only the individual with nonparallel eyes but also the observer. It has previously been demonstrated by fMRI that adults viewing images of strabismic adults have a negative reaction to the images as demonstrated by limbic activation, especially activation of the left amygdala. The aim of this study was to see if mothers would have a similar reaction to viewing strabismic children and whether or not that reaction would be different in mothers of strabismic children.
Methods Healthy mothers of children with strabismus (n = 10, Group I) and without strabismus (n = 15, Group II) voluntarily underwent fMRI at 3T. Blood oxygen level dependent signal responses to viewing images of strabismic and non-strabismic children were analyzed.
Results Group II, while viewing images of strabismic children, showed significantly increased activation of the limbic network ($p < 0.05$) and bilateral amygdala activation. Group I showed considerably less limbic activation, compared to the group II, and had no amygdala activation. Both groups revealed statically significant activation in the FEF (frontal eye field) when they were viewing images of strabismic children as compared to when they were viewing children with parallel eyes. The activated FEF area for Group II was much larger than for group I.
Conclusion Mothers of non-strabismic children showed similar negative emotional fMRI patterns as adults did while viewing strabismic adults. Strabismus is an interpersonal organic issue for the observer, which also impacts the youngest members of our society.

Keywords Strabismus · Imaging · MRI · Emotions · Limbic lobe

Introduction

Far from being a mere cosmetic problem, strabismus has a strong influence on the lives of those individuals suffering from non-parallel eyes [1–5]. Strabismus influences not only the individual with nonparallel eyes but also the observer [1]. Reaction to strabismic adults has been shown to trigger a negative emotional response in the observer, activating the limbic lobe (parahippocampal gyri, hippocampus, and especially the left amygdala) [1]. Activation of the left amygdala occurs when facial expressions showing anger, fear, or disgust are viewed, while viewing frightening images, or as a response to phobias [6]. Aldhafeeri et al. showed bilateral amygdala involvement in the processing of negative emotions but not positive ones [7]. On the other hand, some neuroimaging studies have reported amygdala activation as a response to pleasant facial expressions as well [8].

Face perception is one of the most highly developed visual perceptual skills in humans and is central to human social interaction; providing critical information about sex, age, emotions, intentions, and the identity of another. Darwin felt that all primates have similar facial expressions for

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similar emotions and that this trait was of common evolutionary origin [9]. Various neuropsychological and neuroimaging studies exist regarding face perception [10]. Primarily, three bilateral brain regions are involved: the inferior occipital gyri, superior temporal sulcus, and lateral fusiform gyri [10].

The frontal eye field (FEF) is the area in the brain most responsible for generating saccadic eye movements [11]. These saccadic eye movements are used to scan objects. When dealing with a strabismic person, establishing eye contact is challenging. This may result in increased activation in the FEF.

The classic model of amygdala functioning with regard to identification of emotional expression proposes that the amygdala contributes to emotional expression recognition and empathy by encoding the level of threat or distress [12]. Reaction to viewing strabismic adults has been shown, by fMRI, to trigger negative emotional response in the observer [1], making strabismus a significant interpersonal problem. The aim of this study was to see if mothers would have a similar negative reaction to viewing strabismic children and whether or not that reaction would be different in mothers of strabismic children. This may shed some light on the maternal–child interaction.

Material and Methods

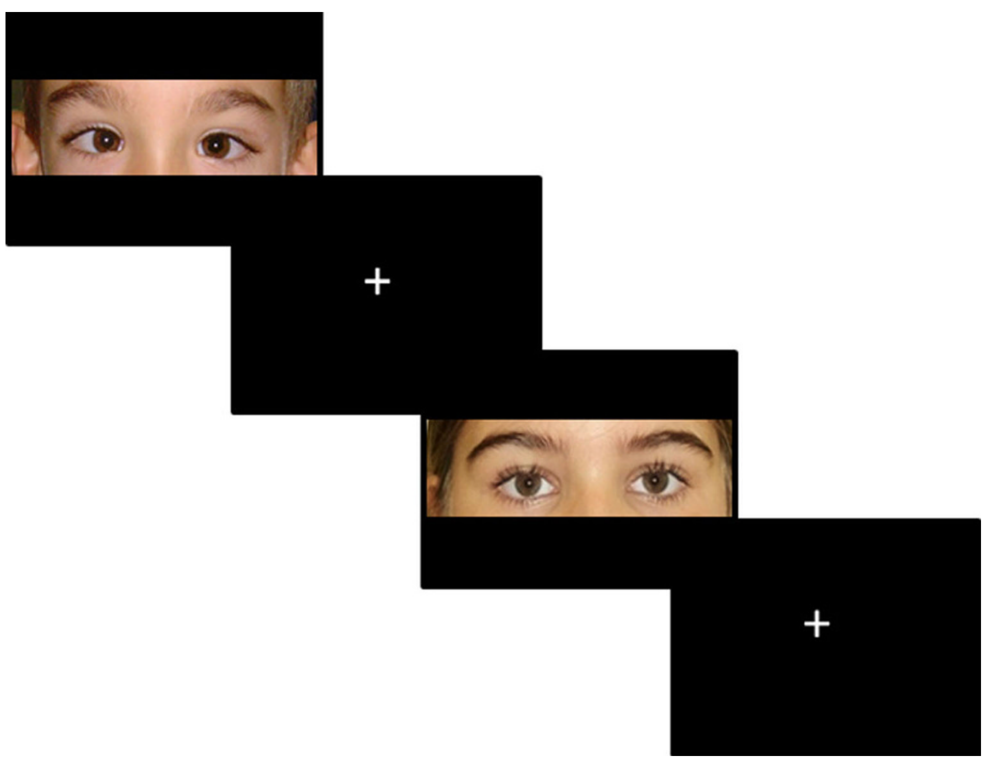
Subjects

This study was approved by the local ethical commission and follows the tenets of the Declaration of Helsinki. All studied individuals were healthy mothers; some with children without ocular misalignment (Group I, $n = 15$, age range from 24–52 years, mean 39.5 ± 7.4 years) and some with strabismic children (Group II, $n = 10$, age range from 29–52 years, mean 39.2 ± 7.5 years). All subjects were volunteers and gave written informed consent. For each subject the magnetic resonance imaging (MRI) scan of the brain was normal. The purpose of the study was explained only after the functional MRI (fMRI) examination to guarantee spontaneous reaction to the stimuli.

Stimuli and Paradigm

The visual stimuli consisted of alternating normal or strabismic children's faces as well as a neutral picture, presented as previously described (Fig. 1; [1]). The neutral picture consisted of a crosshair presented in the middle of the screen [1, 7]. A total of 43 images: 22 images of non-strabismic children and 21 images of strabismic children were used. The experimental paradigm consisted of 4 blocks of eyes, as emotionally evocative visual stimuli, followed by the baseline condition in which a crosshair was presented. During each block of the visual stimuli, 8 normal eyes or

Fig. 1 Schematic diagram of the experimental paradigm



8 strabismic eyes were presented for 3 s, followed by the baseline (24 s). The visual stimulus was programmed using E-Prime software (Psychology Software Tools, Sharpsburg, PA, USA). Subjects laid in the scanner and viewed the stimuli displayed on a monitor via a mirror (NordicNeuroLab SA, Bergen, Norway).

MRI Examination

All subjects underwent fMRI at 3 T (Skyra, Siemens Healthcare, Erlangen, Germany) with a 32-channel head coil. fMRI was performed utilizing an echo planar imaging sequence (slice thickness 3 mm, repetition time (TR) = 3000, echo time (TE) = 30, flip angle 90^o). T1-weighted anatomical, 3-dimensional, volumetric, interpolated brain examination sequence followed (fat saturated, TR = 1940, TE = 3.67, IT = 900, voxel size 1 × 1 × 1, matrix size 256 × 256, flip angle 9, 192 slices).

Data Analysis

Data was analyzed individually for both groups I and II (Group I = mothers with non-strabismic child, Group II = mothers with strabismic child). Blood oxygen level dependent (BOLD) signal changes were analyzed and resulting contrast maps were created for a response to (1) strabismic children images vs. non-strabismic children images, (2) strabismic children images vs. crosshair and (3) non-strabismic children images vs. crosshair.

BOLD clusters were assessed individually with respect to the anatomic locations. First, the fMRI images were processed using the Brainvoyager QX software (Brain Innovation, Maastricht, The Netherlands). Data processing included the following steps: motion correction (trilinear or sync interpolation by spatial alignment for all acquired volumes by rigid body transformation), coregistration of functional imaging and 3-dimensional isovoxel anatomic data and spatial smoothing (Gaussian filter of 2.5 mm full width half maximum). Anatomical images were transferred to Talairach space. At the first level of analysis, a general linear model was computed for each experiment, applying separate predictors for each subject. Then, multi-subject analysis was applied by averaging all the data. Activation maps were corrected for multiple comparisons using false discovery rate (FDR) approach with $p < 0.05$, considering a minimum cluster of more than 20 contiguous voxels in terms of t-statistics based on BOLD signal changes.

For population-based statistics, random-effect (RFX) analysis was executed. RFX takes into account the between-subject and intra-subject variability. The different subjects are treated as random samples from the possible selection of subjects. The RFX analysis calculates beta (β) weights per subject and predictor. The resulting BOLD activation map shows a comparison of the individual betas of all subjects. In this way, the variability between the different subjects can be calculated and, thus, conclusions can also be drawn for the general population.

Furthermore, a ROI analysis focused on the whole amygdala was carried out. A 2-sample t-test based on the average β-value from amygdala was additionally performed using SPSS Statistics Software version 24 (IBM Corporation, Armonk, NY, US).

Results

Groups I and II were age matched and the Student's t-test did not reveal any significant age differences ($p = 0.922$).

Table 1 Regions of increased blood oxygen level dependent (*BOLD*) activation while viewing of strabismic children images vs. parallel eyes based on the pooled data from the mothers of a non-strabismic child ($n = 15$, Group I) and from mothers with strabismic child ($n = 10$, Group II). Voxels are presented in terms of t-statistics (False Discovery Rate threshold of q[FDR] < 0.05)

Region		Group I						Group II					
		Talairach			No. of voxels	BA	T	Talairach			No. of voxels	BA	T
		x	y	z				x	y	z			
Amygdala	R	27	1	–15	48	–	2.49	–	–	–	–	–	–
	L	–16	–6	–11	40	–	2.35	–	–	–	–	–	–
Hippocampus	R	27	–12	–14	98	–	2.30	–	–	–	–	–	–
	L	–	–	–	–	–	–	–30	–17	–14	63	–	2.42
Parahippocampal gyrus	R	23	–14	–14	146	28	2.99	24	–9	–24	39	35	2.29
	L	–21	–17	–14	66	28	2.29	–22	–13	–15	38	28	2.56
Fusiform gyrus	R	47	–8	–23	52	20	2.25	40	–21	–25	75	20	2.69
	L	–47	–27	–27	69	20	2.36	–	–	–	–	–	–
Frontal eye field (FEF)	R	2	54	51	164	8	2.49	8	19	47	70	8	2.37
	L	–30	30	51	198	8	2.37	–18	35	48	114	8	2.21

BA Broadman area, *R* right, *L* left

Table 2 Blood oxygen level dependent (*BOLD*) signal increase with different stimuli in Group I (mothers of a parallel viewing child, $n = 15$) and Group II (mothers with a strabismic child, $n = 10$). Voxels in terms of t-statistics (False Discovery Rate threshold of q[FDR] < 0.05) are presented in Talairach space

Region		Group I					Group II					Group I					Group II				
		Strabismic children images vs. crosshair										Non-strabismic children images vs. crosshair									
		No. of voxels	T	Talairach			No. of voxels	T	Talairach			No. of voxels	T	Talairach			No. of voxels	T	Talairach		
				x	y	z			x	y	z			x	y	z			x	y	z
Amygdala	R	171	2.38	25	−3	−14	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	L	152	2.66	−23	−3	−14	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Hippocampus	R	83	2.44	27	−12	−14	57	2.65	27	−15	−14	–	–	–	–	–	–	–	–	–	–
	L	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Parahippocampal gyrus	R	195	2.43	27	−12	−11	105	2.62	27	−8	−11	–	–	–	–	–	130	2.40	30	−9	−22
	L	120	2.74	−28	−8	−11	112	2.29	−28	−8	−11	76	2.48	−20	−19	−17	–	–	–	–	–
Fusiform gyrus	R	102	2.76	40	−21	−25	161	2.88	38	−22	−25	102	2.76	40	−21	−25	156	2.74	40	−21	−25
	L	78	2.63	−43	−8	−25	130	2.50	−38	−24	−25	178	2.63	−42	−9	−25	154	2.33	−51	−32	−27
Frontal eye field (FEF)	R	282	2.36	2	54	51	486	2.59	10	46	48	–	–	–	–	–	217	2.37	5	38	51
	L	433	2.85	−26	31	51	405	2.50	−26	31	51	584	2.88	−26	31	51	474	2.91	−18	35	48

R right, *L* left

Limbic Lobe Activation

A list of activated limbic system brain regions and other structures of interest with respective *t*-values are listed in Table 1 for both groups of mothers viewing the strabismic vs. non-strabismic images. Table 2 extends the results to the strabismic vs. crosshair and non-strabismic vs. crosshair images.

Group I

All subjects in Group I had significant limbic lobe activation when viewing the strabismus images as compared to viewing the straight eyes. Reaction to strabismus images compared to normal eye images showed a statistically significant ($p < 0.05$) increase in BOLD signal on pooled data for Group I in the amygdala bilaterally, the right hippocampus, the parahippocampal gyri bilaterally, and the fusiform gyri bilaterally.

When comparing strabismus images to the neutral image of a crosshair, significant increased BOLD signal on pooled data was again observed bilaterally in the amygdala, in the right hippocampus, bilaterally in the parahippocampal gyri, and bilaterally in the fusiform gyri.

When viewing parallel eyes vs. crosshair, a signal difference was evoked only in the left parahippocampal gyrus, and bilaterally in the fusiform gyri. There was no signal difference in the amygdala.

Group II

The mothers in Group II, while viewing images of strabismic children vs. non-strabismic children images, revealed considerably less limbic activation as compared to Group I (based on active voxel count: 36% less activation in the hippocampus, 42–73% less activation in the hippocampal gyri, and 44% more activation in the fusiform gyri) and had no amygdala activation (Fig. 2). Reaction to strabismus images vs. non-strabismic images showed a statistically significant ($p < 0.05$) increase in BOLD signal on pooled data for Group II in the left hippocampus, the parahippocampal gyri bilaterally, and the right fusiform gyri (Fig. 2).

When comparing strabismus images to the neutral image of a crosshair, significant increased BOLD signals on pooled data were observed in the right hippocampus, bilaterally in the parahippocampal gyri, and bilaterally in the fusiform gyri. There was no amygdala signal difference.

Viewing parallel eyes versus viewing the neutral crosshair revealed signals only in the right parahippocampal gyrus and right fusiform gyrus.

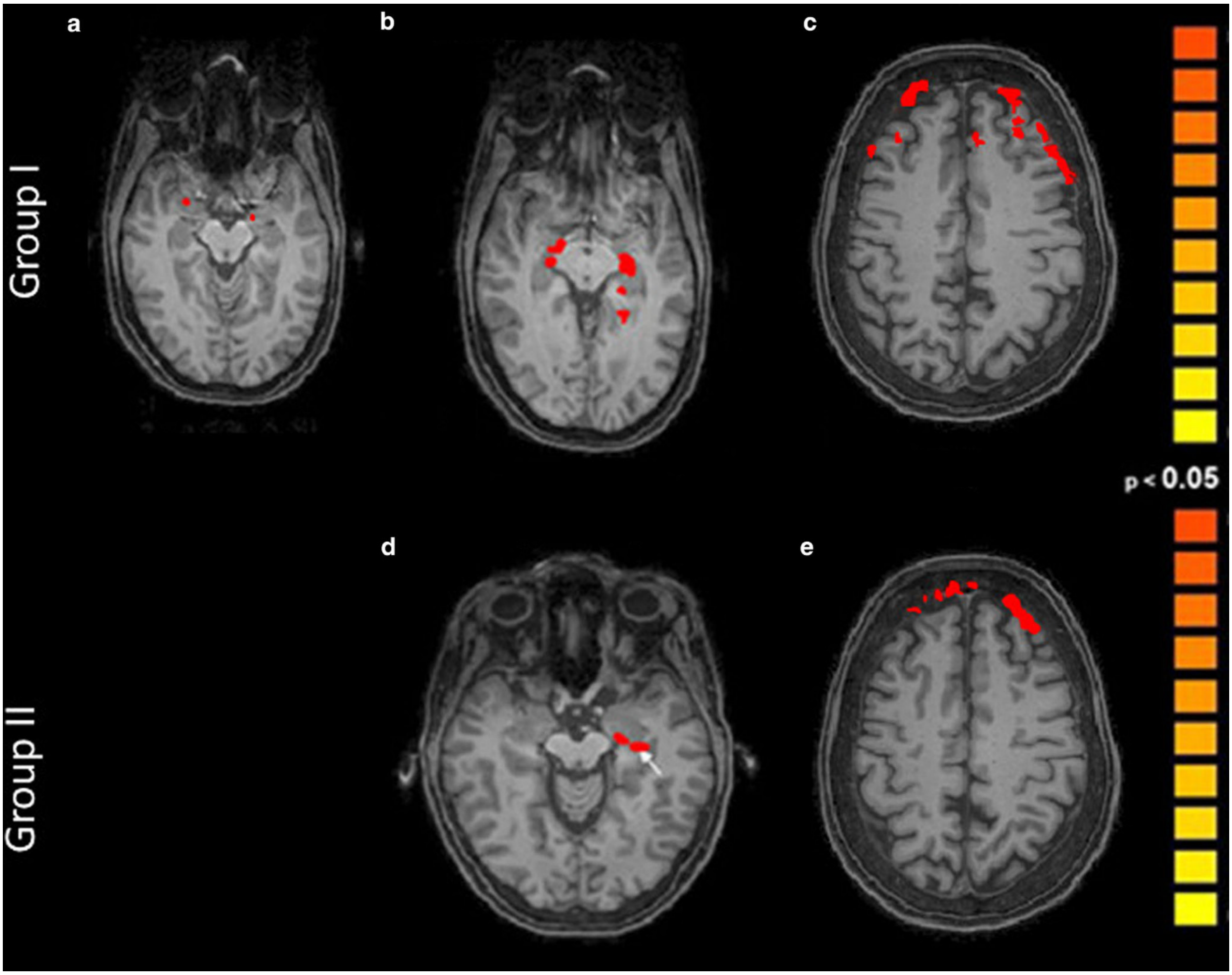


Fig. 2 fMRI scan showing statistically significant limbic lobe activation ($p < 0.05$) by pooled data of mothers with a non-strabismic child (Group I) at **a** amygdala, **b** parahippocampal gyri, and **c** frontal eye field (*FEF*) when viewing images of strabismic children compared to viewing images of children with parallel eyes. Group II represents the pooled data of mothers with a strabismic child at **d** hippocampus (*white arrow*) as well as in the parahippocampal gyri and **e** *FEF* when viewing images of strabismic children compared to viewing images of children with parallel eyes

Frontal Eye Field and Visual Cortex Activation

Both groups revealed statically significant greater activation in the FEF while viewing images of strabismic children as compared to viewing children with parallel eyes or the crosshair (Fig. 2). The activated FEF area for mothers with parallel viewing children (Group I) was much larger than for mothers with strabismic children (Group II). Based on the voxel count, Group II had 42–57% less activation on FEF than Group I (Fig. 2). When comparing non-strabismic children images to the crosshair, bilateral FEF activation was observed in Group II, and left-sided FEF activation by Group I.

Group I vs. Group II

The significant regions of BOLD contrast map of the population effect based on RFX analysis while viewing of strabismic children vs. normal eyes between Groups I and II revealed bilateral activation in the parahippocampal gyri and on the left FEF (Fig. 3). ROI analysis over the amygdala did not reveal statistically significant differences on the mean β-values of the right and left amygdala (p = 0.3260, p = 0.0923, respectively).

Discussion

Our results show a significant activation of the amygdala for Group I, indicating discomfort while viewing images

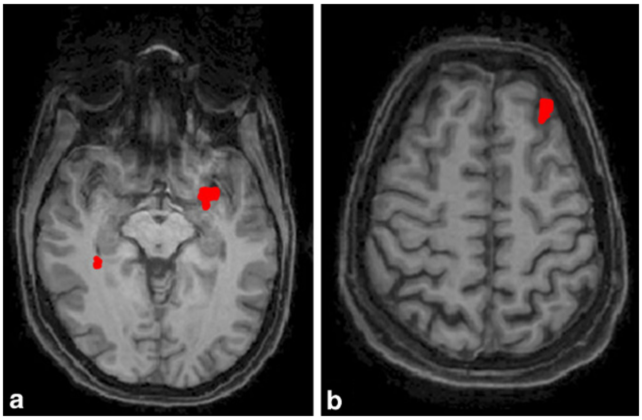


Fig. 3 The significant regions of blood oxygen level dependency (BOLD) contrast map of the population effect based on random-effect (RFX) analysis while viewing of strabismic children vs. normal eyes between Groups I and II revealed activation **a** bilateral on parahippocampal gyrus and on **b** left frontal eye field (FEF)

of strabismic children. Assessment of human emotion by fMRI is complex and related to many variables including what images are being compared and the emotional state of the observer [13, 14]. It has been shown that the emotional state of a test person influences fMRI results and that well-balanced subjects in a neutral mood achieve the best fMRI results [15]. The amygdala is preferentially activated in response to fearful versus neutral faces [8]. Studies have shown that significant bilateral amygdala activation occurs in the processing of negative emotions, but not positive ones [7, 16]. Others have found that although the amygdala is preferentially and more strongly activated by fearful, aversive stimuli, it may be activated by other emotionally valenced stimuli, even pleasant ones, especially in the condition where pleasant stimuli are compared to neutral ones [8, 13]. Right amygdala activation has also been linked to empathy for pain [17]. The amygdala plays a key role in guiding social behaviors, from emotional judgment to social cognition [18]. It has been shown that amygdala activation is more pronounced for the emotions of fear and disgust than for happiness [6, 19]. Damage to the amygdala results in impairment in recognizing fearful facial expression and therefore inhibits the development of conditioned fear [20]. A functional amygdala is, therefore, essential for social interaction.

The strong limbic lobe activation in Group I, especially left amygdala activation, might indicate possible discomfort by those mothers who do not have strabismic children to viewing strabismic children. Similar to the adults viewing strabismic adults in our previous study [1], mothers without strabismic children—when viewing strabismic children—showed higher activation of the amygdala, the hippocampus, the fusiform gyri, and the parahippocampal gyri, suggesting a negative emotional state. The right amygdala activation by the Group I may indicate, in addition to the possible negative reaction, a degree of empathy for strabismic children. No right amygdala activation was noted when adults viewed adults with strabismus [1]. Cognitive processing of facial expression is demanding. Our study involved viewing fairly simple facial expressions so that even though there was an overall negative reaction to the strabismus, there may also be some empathetic reaction to the strabismus or positive reaction to the children's other features. Viewing non-strabismic children vs. the crosshair evoked a limited limbic activation in both groups (Table 2), demonstrating a limited emotional response to these stimuli. These findings are in line with the literature [1].

When Group II viewed the strabismic children vs the non-strabismic children, BOLD contrast map analysis of the limbic lobe region revealed a 36–73% decrease in pixels (i. e., less emotional activation) than when Group I viewed these same images. Striking was the amygdala activation in Group I versus the lack of it in group II while these mothers viewed the strabismic images. However, when making group comparisons based on ROI analysis over amygdala, no significant differences were found between the activation pattern of the right and left amygdala. We also found a higher activation in the lateral fusiform gyrus in Group II when viewing images of strabismic children as compared to when they were viewing non-strabismic images. Several fMRI studies [10, 22] revealed that the fusiform gyrus is an important area in the perception of invariant aspects of faces as identity. Based on these findings, we hypothesize that mothers of strabismic children—while observing images of strabismic children—have a conscious or unconscious association with their own children through the activation of these areas of facial identity. This association with their own children is likely the reason for the lower activation of the negative emotional limbic network. These mothers' lower limbic activation indicates less emotional reaction to the strabismus and a lack of negative feelings toward strabismic children due to their acceptance of the entity of strabismus in their own children.

An alternative interpretation of results is that the amygdala is a part of the neural reference space for discrete emotions and it is likely for the amygdala to have increased activation when a person is experiencing any emotion [21]. This could mean that for mothers without strabismic children, photos of strabismic children are novel and motivationally salient, as suggested by the pronounced amygdala activation.

The significant regions of BOLD [23–25] contrast map of the population effect based on RFX analysis while viewing of strabismic children vs. normal eyes between groups I and II revealed activation of the parahippocampal gyrus bilaterally and the left FEF. Group comparison based on the ROI analysis over amygdala did not reveal a statistically significant difference between the activation patterns of the right or left amygdala. The RFX analysis has been recommended for groups with a minimum of 10 subjects. Thus, taking this into account with our relatively small number of subjects, it is normal to expect "minimized" results in the case of the random effects group analysis. The RFX contrast maps show only regions that are significantly consistently different between our groups. Also, using a cluster thresholding approach might be potentially dangerous due to the relatively small size of the amygdala.

Furthermore, to conclusively interpret the participant's emotional responses cannot be determined without behavioral or physiological data. Finally, the differences based on active voxel count are not based on formal statistical comparison.

During the analysis of the MRI images, statistically significant activation of the FEF area was noted when either group of mothers was viewing strabismic children. This area is involved in the preparation and triggering of all intentional saccadic eye movements [11, 26]. These saccadic eye movements allow for volitional scanning, which plays an important functional role in human face learning [27]. Humans tend to focus on the eyes of another when looking at them, rather than other areas of the face or the body [28]. Moreover, as proposed by Yarbus et al. [29] and others [27, 30–33], the eyes are one of the most important areas of visual focus during human nonverbal communication. Activation of the FEF occurs on viewing a face. Adding an element of strabismus to the face produces hyperactivation.

We believe the hyperactivation in the FEF area results when mothers try to establish eye contact with the strabismic image. This task becomes hard because of the difficulty in choosing which eye of the image to make the object of fixation. The observing mother may alternately shift the focus of her visual attention from eye to eye and intermittently avoid eye contact with the strabismic image; either maneuver produces the FEF hyperactivation.

The activated FEF area was significantly greater in mothers of children without strabismus than in mothers of strabismic children. Mothers of children with strabismus have learned to focus on the image's fixating eye, are used to not alternating their fixation between the eyes, and do not avoid eye contact with strabismic subjects, all of which leads to a lesser activation of the FEF than it is seen in mothers of strabismic children.

Conclusions

Understanding neural networks of negative and positive emotions in normal healthy subjects will help to unmask the neural correlates involved in human emotion and behavior. We previously showed that adults uniformly view strabismus with an organic negative reaction. In this study, we show that even mothers of non-strabismic children have a similarly strong negative reaction to strabismic children. Strabismus is, therefore, an interpersonal organic issue for the observer which impacts even the youngest members of our society. Fortunately, and expectedly, mothers of strabismic children overcome this reaction.

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Conflict of interest J. Berberat, M. Montali, P. Gruber, A. Pircher, M. Hlavica, F. Wang, H.P. Killer and L. Remonda declare that they have no competing interests.

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