Amygdalar Activation Associated With Happy Facial Expressions in Adolescents: A 3-T Functional MRI Study

TONY T. YANG, M.D., PH.D., VINOD MENON, PH.D., AMY J. REID, B.A.,
IAN H. GOTLIB, PH.D., AND ALLAN L. REISS, M.D.

ABSTRACT

Objective: To study the possible role of the amygdala in the recognition of happy and sad facial expressions in adolescents aged 13 to 17 years. **Method:** Twelve healthy adolescents (6 females and 6 males) underwent noninvasive 3-Tesla functional magnetic resonance imaging while viewing pictures of happy, sad, and neutral facial expressions. **Results:** Happy faces produced significant bilateral amygdalar activation when compared with neutral faces ($p < .05$, corrected). Sad faces relative to neutral did not produce significant amygdalar activation. **Conclusions:** These results extend the role of the amygdala in adolescents to include the recognition of happy facial expressions. They demonstrate the feasibility of using happy facial expressions to noninvasively study amygdalar function in adolescents and establish a baseline against which the amygdalar response to emotional stimuli in several psychiatric conditions may be compared. *J. Am. Acad. Child Adolesc. Psychiatry*, 2003, 42(8):979–985. **Key Words:** amygdala, adolescence, functional magnetic resonance imaging, emotion, neuroimaging.

Darwin and Ekman (1998) theorized that primary or basic emotions represented important evolutionary adaptations. Ekman et al. (1969) characterized these basic emotions as facilitating rapid responses to fundamental life tasks in ways that have improved our survival fitness. They found that facial expressions for certain, basic emotions were universally recognized and displayed in different cultures. The primate amygdala is thought to be involved in social behavior, emotion, and the processing of facial expressions. The nonhuman primate evidence suggests that the amygdala is involved with emotional and social responses to the face (Rolls, 2000) and processing the affective information conveyed by the face (Tovee, 1995). In adult humans, the evidence indicates that the amygdala plays an important role in learning how to evaluate social cues (Phelps and Anderson, 1997) and in the processing of facial expressions (Adolphs et al., 1994). Human lesion studies in adults have demonstrated that damage to the amygdala greatly impairs the processing and recognition of fearful faces (Adolphs et al., 1994, 1995; Broks et al., 1998; Calder et al., 1996), but they have been less clear regarding other emotions. Animal studies have emphasized the role of the amygdala in fear conditioning (Cahill et al., 2000; Falls and Davis, 1995; LeDoux, 1996, 2000; Meunier et al., 1999; Parkinson et al., 2000; Pitkanen et al., 1997).

To date, the vast majority of functional neuroimaging studies in humans have mainly focused on the study of the amygdalar response to fear in adults. The positron emission tomography (PET) (Morris et al., 1996, 1998) and functional magnetic resonance imaging (fMRI) (Phillips et al., 1998b) literatures have been generally consistent in demonstrating the involvement of the adult human amygdala in the perception of fearful faces. For the perception of other basic emotions such as sadness and happiness, functional neuroimaging studies have not been as extensive in number or positive in their findings.

Sadness is a potentially strong negative emotion that one might expect to elicit a response from the amygdala, but the neuroimaging and human lesion studies have

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Dr. Yang is with the Department of Psychiatry, Division of Child and Adolescent Psychiatry, University of California-San Diego School of Medicine and Children's Plaza. Dr. Menon is with the Departments of Psychiatry and Behavioral Science, Program in Neuroscience, Stanford University School of Medicine. Ms. Reid is with Stanford University. Dr. Gotlib is with the Department of Psychology and Dr. Reiss is with the Departments of Psychiatry and Behavioral Science and Pediatrics, Program in Neuroscience, Stanford University School of Medicine, Stanford, CA.

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Correspondence to Dr. Yang, 3020 Children's Way, Children's Plaza, MC 5018, San Diego, CA 92123-4282; e-mail: tyang@ucsd.edu.

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been less extensive and conclusive relative to the studies of fear. In a PET study, Blair et al. (1999) found enhanced amygdalar activity in response to the perception of sad facial expressions. This finding is consistent with reports that human subjects with amygdalar lesions are impaired in recognizing negative emotions, especially fear and sadness (Adolphs et al., 1996).

Limited neuroimaging and human lesion literature exist regarding the role of the amygdala during the perception of positive facial expressions such as happiness. In an fMRI study of normal adults, Breiter et al. (1996) observed amygdalar activation in response to the perception of fearful versus neutral faces. Moreover, they unexpectedly found that the amygdala responded to the perception of happy versus neutral faces, suggesting a possibly more generalized response of the amygdala to emotionally valenced stimuli. More recently, Yang et al. (2002) also found significant amygdalar activation to happy versus neutral faces in 17 healthy adults. These fMRI results are consistent with the findings of at least one human lesion study in which facial processing was examined following amygdalotomy. In this study, Young et al. (1995) found that in the facial expression matching and recognition tasks, the patient was significantly impaired in matching and identifying several emotions including happiness.

Although the examination of the amygdalar response to the perception of different facial expressions is fairly limited in adults, it is virtually nonexistent in adolescents. To our knowledge, only one fMRI study of the role of the amygdala in normal adolescents has been performed. In this study of 12 normal adolescents, Baird et al. (1999) found significant amygdalar activation in response to the perception of fearful facial expressions. In the discussion of the limitations of their study, they suggested that "additional categories of emotional expression (i.e., happiness, sadness, etc.)" (p. 198) should be examined in future studies.

Thus, based upon the neuroimaging studies (Blair et al., 1999; Breiter et al., 1996) and human lesion data (Adolphs et al., 1996; Young et al., 1995), we hypothesized that the human amygdala would show significant activation during the perception of happy and sad faces.

The purpose of this 3-T functional study was to assess whether the adolescent amygdala might have a broader role in the processing of affective information beyond just responding to fearful faces. To this end, we examined the amygdalar response to the perception of happy and sad facial expressions compared with neutral.

METHOD

Subjects

Twelve healthy, right-handed adolescent subjects (6 females and 6 males; aged 13–17 years; mean age 15.69 years; standard deviation 1.57 years) participated in this study. Each subject received a structured clinical interview, the Schedule for Affective Disorders and Schizophrenia for School Aged Children (K-SADS-PL) (Puig-Antich and Ryan, 1986). In addition, each subject received the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999) and Montgomery Asberg Depression Rating Scale (MADRAS) (Montgomery and Asberg, 1979). Finally, each subject completed the following questionnaires: (1) demographic questionnaire, (2) medical and developmental history form, (3) Tanner stage (Tanner, 1962), (4) Child Behavior Checklist for Ages 4–18 (CBCL) (Achenbach, 1991), (5) Edinburgh Handedness Inventory (Oldfield, 1971), (6) family history, and (7) Beck Depression Inventory-II (BDI-II) (Beck et al., 1996). Subjects with any history of substance abuse, head injury, seizures, or Axis I disorder were excluded. Subjects who scored in the clinical range or borderline clinical range (syndrome scale *t* score >66) on the CBCL or who had a Full-Scale IQ score <90 on the WASI were excluded from the study. Family history was obtained from the subject and subject's parent/guardian(s); subjects were excluded if there were any first-degree relative(s) with an Axis I disorder. All subjects and their parent/guardians gave written consent for their participation in this study. This study was approved by Stanford University's Institutional Review Board.

Stimuli

A set of more than 1,600 photographs of faces of people posing different emotions was assembled from a number of sources, including photograph collections of other researchers (Laura Carstensen, Ruben Gur, Paula Niedenthal, Stephen Nowicki, and Robert Zajonc), standardized sets of emotional faces developed by Ekman and colleagues (Ekman and Friesen, 1976; Matsumoto and Ekman, 1988), and sets of photographs developed by Lang and colleagues (Lang et al., 1997). In addition, photographs were taken of 27 undergraduate, graduate, and postdoctoral student volunteers posing different emotions. All of the images were digitized and edited to be monochromatic and of approximately the same size (260 × 300 pixels, or approximately 9 × 10 cm).

Stimulus Rating

All photographs were independently rated by 14 right-handed, healthy students (7 females and 7 males, aged 15–38 years, mean 21 years, standard deviation 5.93 years) with respect to happiness, sadness, anger, and fear, using scales ranging from 1 (no emotion) to 7 (extreme emotion). Faces were categorized as a particular target negative expression if they received a mean rating of >4 (with 4 representing moderate intensity) on the target scale, <4 on the other two negative expression scales, and <2 on the Happiness scale. Faces were categorized as "happy" if they received an average rating of >4 on the Happiness scale and <2 on the Sadness, Anger, and Fear scales. Faces were categorized as "neutral" if they received an average rating of <2 on all four emotion scales (Happiness, Sadness, Anger, and Fear).

Following the procedures of Bradley et al. (1997), pairs of one emotional and one neutral photograph of the same poser were used as stimuli. Using the same poser ensured that the pictures in each pair were matched exactly with respect to age, gender, race, physical appearance, attractiveness, etc., and that the only difference between the two pictures was the emotional expression. Within each emotion face cat-

egory, half of the pictures were male and half were female. The pictures were carefully matched with respect to the intensity of the dominant emotion displayed in the picture, both across the gender of the poser and across the different types of emotional expression. For additional details, please see Yang et al. (2002).

The set of facial stimuli presented in the current study have been used in another fMRI experiment that has been published elsewhere (Canli et al., 2002).

Experimental Design

The scan was composed of 18 24-second epochs. Within each epoch of scrambled faces and faces posing a particular target emotion, eight faces were presented contiguously for 2,800 ms each with a 200-ms interstimulus interval. A rest, neutral, or scrambled epoch was placed between each affect epoch. This was done to allow the BOLD signal to decay to baseline levels between the presentation of different affective stimuli. The Happy (H), Sad (S), Neutral (N), Scrambled (SC), and Rest (R) epochs were presented in the following order: R-H-N-S-SC-H-N-S-R-SC-H-N-S-SC-S-N-H-R. No comparisons with the scrambled epochs were used in this study.

fMRI Acquisition

Images were acquired on a 3-T GE Signa scanner (General Electric, Milwaukee, WI) with EchoSpeed gradients using the standard GE coil. A sagittal T1-weighted localizer with the following parameters was first acquired: TR = 535 ms; TE = 7 ms; field of view = 24 cm; 10 slices; slice thickness = 5 mm; 0 mm skip. To reduce blurring and signal loss arising from field inhomogeneities, an automated high-order shimming method based on spiral acquisitions was used before acquiring fMRI scans (Kim et al., 2002). A spiral sequence was used to reduce susceptibility-related loss of signal and warping in or near the amygdala. A custom-built head holder was used to minimize head movement. Eighteen axial slices (4-mm thick, 0.5-mm skip) parallel to the anterior and posterior commissure covering the whole brain were imaged with a temporal resolution of 3 s using a T2-weighted gradient echo spiral pulse sequence (TE = 30 ms, TR = 2000 ms, flip angle = 89° and 1 interleave). Number of slices (28), slice thickness (4.0 mm), epoch length, and voxel size remained the same for all subjects. Field of view was 200 mm and the in-plane spatial resolution was 3.125 mm. To aid in localization of functional data, high resolution T1-weighted spoiled grass gradient recalled three-dimensional MRI sequence with the following parameters was used: TR = 35 ms; TE = 6 ms; flip angle = 45°; 24 cm field of view; 124 slices in coronal plane; 256 × 192 matrix; acquired resolution = 1.5 × 0.9 × 1.2 mm. The images were reconstructed as a 124 × 256 × 256 matrix with a 1.5 × 0.9 × 0.9 mm spatial resolution.

Behavioral Task

Subjects were instructed to perform a gender discrimination task while inside the scanner to assure attention to the stimuli. They were given the following instructions: "Press the left button if you see a female face. Press the right button if you see a male face." All subjects used their dominant, right hand during the behavioral task.

During the "rest" epoch, subjects were instructed to lie still and focus on the crosshair fixation point on the screen. During the "scrambled" epoch, subjects were instructed to alternate their button presses between the left and right buttons starting with the left button.

The task was programmed using Psyscope (Cohen et al., 1993) on a Macintosh (Sunnyvale, CA) notebook computer. Initiation of scan and task was synchronized using a TTL pulse delivered to the scanner timing microprocessor board from a 'CMU Button Box' microprocessor (*http://psyscope.psy.cmu.edu/bbox/index.html*) connected to the Macintosh. Stimuli were presented visually at the center of a screen using a custom-built magnet-compatible projection system (Resonance Technology, Northridge, CA).

fMRI Analysis

fMRI data from each subject were analyzed using SPM99 (*www.fil.ion.bpmf.ac.uk/spm*). Prior to statistical analysis, images were corrected for movement using least square minimization without higher-order corrections for spin history and normalized to Montreal Neurological Institute (MNI) coordinates. Images were then resampled every 2 mm using sinc interpolation and smoothed with a 4-mm Gaussian kernel to reduce spatial noise. MNI coordinates were transformed to Talairach (Tal) coordinates using a nonlinear transformation (Brett, 2000) (*http://www.mrc-cbu.cam.ac.uk/Imaging/mnispace.html*). For each subject, voxel-wise activation during each of the conditions (happy and sad) compared with neutral was determined using regression analysis with correction for temporal autocorrelations in the fMRI data (Friston et al., 1995). Confounding effects of fluctuations in global mean were removed by proportional scaling, and low frequency noise was removed with a high pass filter (0.5 cycle/minute). A regressor waveform for each condition, convolved with a 6-s delay Poisson function accounting for delay and dispersion in the hemodynamic response, was used to compute voxel-wise *t* statistics, which were then normalized to *Z* scores to provide a statistical measure of activation that is independent of sample size. This voxel-by-voxel random effects model analysis ensured that only brain voxels that were consistently activated across subjects, rather than within subjects, emerged as significant population activation. Hence, the results generated from using this model provided a better generalization to the (normative) population from which the sample was acquired (Friston et al., 1999; Holmes and Friston, 1998).

Brain activation was determined for each of the two facial emotions (happy and sad) contrasted with the neutral condition.

For the predicted regions of activation (the left and right amygdala), functional analyses were based on the average activation of voxels after small volume correction (SVC) ($p < .05$, corrected) (Worsley et al., 1996). This method of analysis has been used in other fMRI studies (Canli et al., 2002; Winston et al., 2002).

Finally, as an added level of statistical stringency, the presence of significant clusters of activation was also determined by using the joint expected probability distribution of height and extent of *Z* scores (Poline et al., 1997) with height ($Z > 1.67$; $p < .05$) and extent threshold ($p < .05$) to correct for spatial correlations in the data.

Amygdala Regions of Interest for SVC Analyses

For the purpose of performing the SVC analyses in SPM99, left and right amygdalae regions of interest (ROIs) were drawn for the normalized, group-averaged anatomical image in this study using a highly reliable method described elsewhere (Kates et al., 1997). ROIs were demarcated separately in the left and right hemispheres from T1-weighted Talairach normalized images for the normalized, group-averaged anatomical image. Drawing of the amygdala was performed coronally, beginning on the slice where the anterior commissure first crosses the midline of the brain. Drawing began inferolaterally, moving medially at the border between the amygdala and the white matter tract inferior to it. The medial border of the ROI was drawn at the CSF/gray border. The ROI continued superomedially at the gray/white border and around the lateral amygdala to the starting point. In the posterior regions of the amygdala, the superior border was partially defined by the presence of the entorhinal sulcus. The amygdala was drawn until it disappeared posteriorly.

Behavioral Data Analysis

The percentage of correct and incorrect button presses was computed for each of the three facial expressions (happy, sad, neutral). Reaction times for the correct and incorrect responses were also recorded.

RESULTS

Behavioral Data

All 12 subjects performed the gender discrimination task with a high level of accuracy. The average percentage correct ranged from 0.948 to 0.966 (mean ± SD: happy, 0.961 ± 0.036; sad, 0.948 ± 0.052; neutral, 0.966 ± 0.040). The average reaction times ranged from 902.5 to 927.7 ms (mean ± SD: happy, 906.2 ± 179.2; sad, 927.7 ± 173.9; neutral, 902.5 ± 183.6).

Amygdalar Activation

Compared with neutral faces, happy faces were associated with significant bilateral activation in the amygdala. Functional analyses based on the average activation of voxels after SVC ($p < .05$, corrected) demonstrated significant left (Talairach coordinates x, y, and z = –20, –8, and –13, respectively; $Z = 3.32$; cluster size = 62; cluster $p = 0.012$, after SVC; cluster size = 62) and right (Talairach x, y, and z = 26, –1, and –13, respectively; $Z = 3.67$; cluster $p = .040$, after SVC; cluster size = 45) amygdalar activation (Fig. 1).

In addition to the SVC analyses, we also examined the data for significant clusters of activation corrected at the whole-brain level. Significant clusters of activation were determined using the joint expected probability distribution of height and extent of Z scores, with height ($Z > 1.67$; $p < .05$) and extent threshold ($p < .05$). This analysis showed a significant cluster of activation at the same Talairach coordinates as the SVC analysis with a primary activation peak in the right amygdala (Talairach x, y, and z = 26, –1, and –13, respectively; $Z_{max} = 3.67$; p-corrected = 0.024; cluster size = 293) and a secondary activation peak in the left amygdala (Talairach x, y, and z = –20, –8, and –13, respectively; $Z_{max} = 3.32$; p-corrected = 0.024; cluster size = 293).

Using the same methods of analyses as described for happy faces, sad faces relative to neutral faces did not produce any significant amygdalar activation.

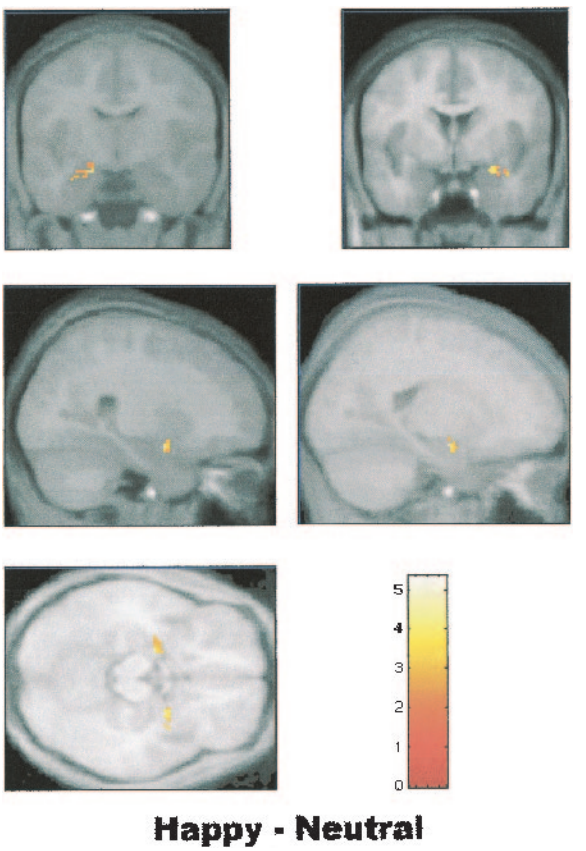

Fig. 1 Top: coronal views showing left and right amygdalar activation to happy faces compared with neutral. Middle: sagittal views of the same left and right amygdalar activations shown in the coronal images. Bottom: axial view showing the same bilateral amygdalar activations as seen in the coronal and sagittal slices. The color bar indicates the Z score of the activations seen in these images.

DISCUSSION

This study is the first to investigate amygdalar activation to happy and sad faces in adolescents using a within-subject design and a random effects analysis. These results were statistically significant using an SVC method and a more statistically stringent method of using the joint expected probability distribution of height and extent of Z scores. The results from the present study demonstrate that the perception of happy faces compared with neutral causes significant bilateral amygdalar activation in adolescents. These results are in agreement with the findings by Baird et al. (1999) who demonstrated that the amygdala is involved with affect recognition prior to adulthood. Their study was limited to the study of the amygdalar response to fearful faces. The current study extends the amygdala's role in adolescents to include affect recognition of happy faces. These results are also in agreement with the two fMRI studies of adult amygdalar activation (Breiter et al., 1996; Yang et al., 2002), and they extend these findings of amygdalar activation in response to happy faces to include adolescents as well as adults.

The results of the current study are particularly significant because most experiments and theories have emphasized the amygdala's role in negatively valenced emotions such as fear; much less is known about the amygdala's role in positively valenced emotions. Evidence from other types of studies suggests that the amygdala has a role in processing positively valenced emotions. These results are consistent with the human lesion findings by Young et al. (1995). In addition to this human lesion study, unit recordings in humans (Fried et al., 1997; Kreiman et al., 2000) and monkeys (Leonard et al., 1985; Nakamura et al., 1992; Wilson and Rolls, 1993) suggest that the amygdala may play a role in processing positive facial expressions. Lastly, in a 1.5-T fMRI experiment using stimuli selected from the International Affective Picture System, the amygdala was found to respond to both positively and negatively valenced stimuli (Garavan et al., 2001). Although Garavan et al. (2001) used International Affective Picture System stimuli rather than different facial expressions, their results support the idea that the role of the amygdala in processing emotional stimuli extends beyond just negatively valenced stimuli such as fear.

The findings of the present study also support the theory that neuronal activation of the amygdala in response to fear-related stimuli represents only a portion of its more widespread role in modulating an organism's vigilance level (Davis and Whalen, 2001; Whalen et al., 2001). According to this theory, the amygdala should be considered as an integral component of a constant vigilance system that is preferentially invoked during ambiguous learning situations of biological relevance. The amygdala should be activated by a stimulus that requires additional information to be understood. Thus, fearful faces stimulate the amygdala because the source of the threat is perceived as ambiguous. Given this theory, other facial expressions that might be interpreted as ambiguous should also activate the amygdala. For example, a happy facial expression might be considered ambiguous in its interpretation. A happy facial expression might indicate that something wonderful has happened for everyone (i.e., the start of summer vacation) or that the adolescent's enemy (or alleged friend) is happy because something awful is about to happen to the adolescent. In this example, additional information is needed to understand the possible biological relevance of the perceived emotion to the observing adolescent.

Limitations

The perception of sad facial expressions did not cause significant amygdalar activation as compared with neutral. This finding is consistent with an fMRI study involving the presentation of alternating sad and neutral faces (Phillips et al., 1998a). In this study, Phillips et al. (1998a) found no brain regions with increased intensity during the presentation of sad faces. However, we had originally hypothesized that the amygdala would be activated by sad facial expressions. In their PET study of sad and angry facial expressions, Blair et al. (1999) found that increasing intensity of sad facial expressions was associated with enhanced amygdalar activity. Because this study did not use stimuli of varying emotional intensity, the failure to detect significant amygdalar activity may have been due to the lack of sufficient emotional intensity of the sad faces. Future studies may wish to use facial stimuli of varying intensities to confirm the PET findings by Blair et al. (1999) and to determine the optimal emotional intensity for observing amygdalar activation. Blair et al. (1999) also counterbalanced the order of presentation of sad and angry conditions across subjects. Because of the rapid habituation of the amygdala (Breiter et al., 1996), it is possible that since the happy faces blocks occurred before the sad faces in this study, the sad faces were at a disadvantage in terms of producing significant amygdalar activation. Subsequent studies should usey a counterbalanced design to address this possibility. This study purposely focused on the adolescent population. However, it is unknown whether these findings will apply to children. Thus, as suggested by Baird et al. (1999), additional studies that include a broader range of ages with a greater sample of subjects at each age should be done to assess the amygdala's role in children as well as adolescents. Finally, because this study is the first to report the finding of significant amygdalar activation during the perception of happy faces relative to neutral in adolescents, these results should be considered preliminary until replicated by others.

Clinical Implications

The results from this study have several important clinical implications. PET studies in depressed adult patients have found that amygdala metabolism is significantly increased in depressed adults relative to normal controls, and during antidepressant treatment that both induces and maintains symptom remission, amygdala metabolism decreases toward normal (Drevets et al., 1992). Using fMRI, Thomas et al. (2001) found decreased amygdalar activity in five depressed girls relative to healthy controls.

In addition to depression, fMRI studies have found abnormal amygdalar activity relative to normal controls in posttraumatic stress disorder (Rauch et al., 2000), obsessive-compulsive disorder (Breiter and Rauch, 1996), bipolar disorder (Yurgelun-Todd et al., 2000), autism (Pierce et al., 2001), generalized anxiety or panic disorder (Thomas et al., 2001), and schizophrenia (Schneider et al., 1998). Hence, the ability to reliably study amygdalar function in several major psychiatric disorders is key to being able to understand how the underlying neural circuitry is affected during the presence of a disorder and the recovery from it. Baird et al. (1999) demonstrated the feasibility of using fearful faces to study amygdalar function. The findings of the present study show that happy faces also may be applied to assay amygdalar function in adolescents. It is important to be able to examine the amygdalar response to different emotions because the amygdala may respond differentially to a particular emotion in a given psychiatric disorder (Schneider et al., 1998). Although the application of fMRI has mainly focused on the major Axis I disorders, the recent finding of amygdalar response to happy faces as a function of extraversion suggests the intriguing possibility of using fMRI to study personality disorders. In this fMRI experiment, Canli et al. (2002) found that amygdalar activation correlated positively and significantly with the degree of extraversion only to happy faces; extraversion did not correlate significantly with activation to fearful, angry, or sad facial expressions.

The present results establish a baseline against which amygdalar response to emotional stimuli in several clinical conditions may be compared. These results also demonstrate the feasibility of using happy facial expressions to noninvasively study the amygdala in adolescents. The ability to understand how the underlying neural circuitry in the limbic system is affected by different clinical conditions may provide additional insights into the possible early diagnosis and innovative development of more efficacious treatments for several major childhood and adolescent psychiatric disorders.

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