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Abstract

Previous studies have observed a sex-dependent lateralization of amygdala activation related to emotional memory. Specifically, it was shown that the activity of the right amygdala correlates significantly stronger with memory for images judged as arousing in men than in women, and that there is a significantly stronger relationship in women than in men between activity of the left amygdala and memory for arousing images. Using a large sample of 235 male adolescents and 235 females matched for age and handedness, we investigated the sex-specific lateralization of amygdala activation during an emotional face perception fMRI task. Performing a formal sex by hemisphere analysis, we observed in males a significantly stronger right amygdala activation as compared to females. Our results indicate that adolescents display a sex-dependent lateralization of amygdala activation that is also present in basic processes of emotional perception. This finding suggests a sex-dependent development of human emotion processing and may further implicate possible etiological pathways for mental disorders most frequent in adolescent males (i. e., conduct disorder).

Keywords: hemisphere; interaction; gender; emotional; angry; faces

1. Introduction

In the processing of emotional faces as well as in emotional processing in general, the amygdala is frequently described as the key structure (Adolphs, 2010; Costafreda et al., 2008; Hamann & Canli, 2004; Sergerie, Chochol, & Armony, 2008). Previously, the amygdala has been more often associated with the processing of fearful faces (Morris et al., 1996), but more recently, it has been shown that the amygdala is generally involved in the processing of faces (Adolphs, 2010; Fitzgerald et al., 2006; Kesler-West et al., 2001). There have been various attempts to relate individual differences or differences in task design to specific patterns of activation in emotional processing (Costafreda et al., 2008; Fusar-Poli et al., 2009a; Hamann & Canli, 2004; Wager et al., 2003). For example, it has been proposed that the left hemisphere is dominant for positive emotions, while the right hemisphere predominantly processes negative emotion (Davidson, 1992; Gur, Skolnick, & Gur, 1994). However, this hypothesis did not withstand recent meta-analyses (Fusar-Poli et al., 2009a; Wager et al., 2003). Altogether, the left amygdala was found to be more often engaged in emotional processing (Baas, Aleman, & Kahn, 2004), even though this difference seemed to appear mainly in block design studies (Sergerie et al., 2008), supporting the notion of a short-duration response in the right amygdala and a more sustained one in the left amygdala (Sergerie et al., 2008). Sex differences in the neural correlates of emotional processing have been studied extensively with mixed results (Fusar-Poli et al., 2009a; Hamann & Canli, 2004; Kesler-West et al., 2001; Lee et al., 2002; McClure et al., 2004; Proverbio et al., 2009; Wager et al., 2003). Meta-analyses were not able to resolve this issue: While Wager et al. (2003) reported a more lateralized amygdala response in males, but no significant difference in the dominance of one specific hemisphere, Fusar-Poli et al. (2009b) reported a stronger activation in a cluster spanning the right amygdala and parahippocampal gyrus in males, but did not show a formal sex by hemisphere interaction. In their meta-analysis of 148 studies reporting amygdala activation in emotional processing, Sergerie et al. (2008) did not detect any significant difference in the proportion of amygdala activations between male- and female-only studies, but a significantly larger mean effect size of amygdala activation in studies involving only men than in those testing only women. They explicitly did not find evidence for an amygdala lateralization as a function of sex.

More specific than these general approaches to emotional processing, there has been research relating amygdala activation to subsequent emotional memory. In a PET study using emotionally proactive films as stimuli, Cahill and colleagues (2001) demonstrated for the first time that left amygdala activation during encoding was associated with subsequent memory for the emotional films only in women. Men, on the other hand, exhibited stronger right amygdala activation in relation to enhanced emotional memory. Their result was replicated in several fMRI studies using pictures of emotionally arousing negative scenes as stimuli (Cahill et al., 2004; Canli et al., 2002; Mackiewicz et al., 2006). Additionally, Cahill et al. (2004) demonstrated a significant sex by hemisphere interaction for memory-related amygdala activation. Armony and Sergerie (2007) extended these results by demonstrating that not only the sex of the observer but also the sex of the stimulus face play a role in this lateralized processing: while the left amygdala was more engaged in memory for fearful female faces in women, right amygdala activation was associated with successful remembered male faces in men. Using EEG, Gasbarri et al. (2006, 2007) could show a significant sex by hemisphere interaction with a female-left and male-right direction in the P300 evoked by either emotionally arousing pictures or stories. The findings described above were further enhanced by a study by Kilpatrick and co-workers (2006), providing evidence for the corresponding sex difference in functional connectivity during resting conditions. In particular, the authors found the left amygdala associated with greater functional connectivity in women than in men, and the right amygdala associated with greater functional connectivity in men than in women. In addition, the regions displaying connectivity with the right or left amygdala, respectively, showed sex-specific differences. The authors speculate that these findings might in part explain the different prototypical emotional coping mechanisms in males vs. females ("fight and flight" vs. "tend and befriend", Taylor et al., 2000). Savic and Lindström (2008) replicated the results concerning a greater connectivity in the left amygdala than in the right amygdala in females and the reverse pattern in males. Additionally, they demonstrated that the amygdala connectivity pattern of homosexual men resembles the female one, and that homosexual women exhibit a greater connectivity in the right amygdala than in the left amygdala, similar to males. Another finding specifically pointing in the direction of a sex-specific amygdala lateralization comes from animal research. Investigating stress-induced dopamine release in the rat, Sullivan and colleagues (2009) found a significant sex by hemisphere interaction in the basolateral amygdala. While males showed a right-sided bias in dopamine release, females displayed a left-sided dominance. This finding extends previous research using purely male rat samples, robustly demonstrating a right-lateralized basolateral amygdala function in fear conditioning (Baker & Kim, 2004; Berlau & McGaugh, 2006; LaLumiere & McGaugh, 2005) as well as the predominant effect of pharmacological stressors on the right amygdala in male cats (Adamec, 2000). In sum, a male-right/female-left amygdala lateralization has been generally supported by recent findings in the domains of emotional memory, functional connectivity as well as in dopamine release in the rat, but not in human functional brain response to emotional stimuli per se.

The studies cited above are typically based on samples within broad age ranges. However, emotional processing differs between different age groups, for example between adults and adolescents (Chung & Thomson, 1995; Monk et al., 2003; Pine, Cohen, & Brook, 2001; Williams et al., 2009). Specifically, adolescents do not only display an enhanced emotional reactivity, but also a greater amygdala activation during the processing of emotional faces compared to adults and children (Guyer et al., 2008; Hare et al., 2008; Monk et al., 2003; Passarotti, Sweeney, & Pavuluri, 2009). This is in line with the notion that adolescence is a time of emotional vulnerability (Ernst, Pine, & Hardin, 2006). Additionally, amygdala functional connectivity with medial prefrontal cortex and hippocampus seems to be reduced in comparison to adults, suggesting a weaker link between emotion, memory and higher cognitive processes (Guyer et al., 2008; Hare et al., 2008). These findings may point towards an adolescent neural system not yet capable to adequately integrate emotional events into previous experience. Thus, the results of studies with adults do not automatically apply to adolescent samples.

It could be speculated that certain neural mechanisms in adolescence relate to the development of mental disorders. Moreover, sex differences in basic neural processes can give information about sex-specific vulnerabilities for such disorders. For example conduct disorder, characterized by a range of behaviors such as physical aggression, stealing, lying, and destruction of property, is more frequent in adolescent males (Maughan et al., 2004; Nock et al., 2006). This is of particular interest as prior studies investigating the neural correlates of conduct disorder have found irregularities in amygdala activation (Decety et al., 2009; Herpertz et al., 2008; Sterzer et al., 2005).

However, sex differences in amygdala activation have rarely been studied in adolescents. McClure et al. (2004) conducted an fMRI study to investigate the sex-related processing of emotional faces in adults as well as in adolescents. While the activation pattern of adult women as compared to men was more specific with regard to certain emotions, the adolescents did not display any sex differences but as a group resembled adult men. Another study examining the neural correlates of emotional faces processing in adolescents (Guyer et al., 2008) also failed to detect any sex differences in amygdala response. However, Killgore and colleagues (2001) studied the age-related amygdala response in male and female children and adolescents in a cross-sectional design. They found that females showed a progressive increase in prefrontal relative to amygdala activation in the left hemisphere, whereas males failed to show a significant age-related difference. However, all of these studies with adolescents are based on small to medium sample sizes, and none of them directly addressed the issue of amygdala lateralization.

In the present study, we addressed this issue and investigated lateralization of amygdala activation associated with viewing angry and neutral faces in a large, age-homogeneous sample of adolescent males and females. In particular, we were interested whether a sex-dependent lateralization of amygdala activation – which seems to appear only in relation with memory in adults – already exists in adolescents on a basic level of emotional processing.

2. Methods

2.1 Participants

The participants were obtained from the IMAGEN study, a large European multicentre genetic-neuroimaging study of reinforcement behavior in adolescence (for a detailed description of the sample see Schumann et al., 2010). For the present study, 235 adolescent male and 235 females were drawn from the first group of IMAGEN-subjects available for data analysis. The groups were matched concerning handedness as reported by the participants (each group comprised 30 left-handers, all others were right-handed) and age (mean age 14.47 and 14.48 years (5287 and 5289 days), respectively; $SD = 0.39$, $p > 0.8$).

2.2 Task design

There are two main reasons why angry faces were found particularly suitable for the present study. Firstly, anger was the emotion that elicited the largest effect size of amygdala activation among all negative emotions as found in the representative meta-analysis of Sergerie et al. (2008). Secondly, sex differences in emotion recognition were not supposed to bias our results. In their large analysis of emotion identification in 1,000 participants, Williams et al. (2009) found a significant sex-by-emotion interaction in recognition accuracy (more accurate recognition by females than by males) for the emotions fear and sadness, but not for anger. As stimuli, a sequence of video clips designed by Grosbras & Paus (2006) was chosen that the volunteers were requested to view passively. They consisted of short (2-5 s) black-and white video clips showing faces that always started from a neutral expression, and then either turned angry or displayed a neutral movement without a particular emotional content (for example, twitching the nose). These stimuli were arranged in 18 s blocks, each block including 4-7 video clips depicting faces of the same emotion (either angry or neutral). Altogether, there were five blocks of neutral faces and five blocks containing angry faces. In between two blocks of face clips, an 18 s non-biological control video clip was presented that was originally developed for a study by Beauchamp et al. (2003). The control stimuli consisted of expanding and contracting black-and-white concentric circles of various contrasts, roughly matching the contrast and motion characteristics of the faces clips. Prior to functional MR scanning, participants were instructed that they would be presented with short video clips showing faces with angry and neutral expressions as well as moving circles. They were asked to watch the video clips carefully and lie as still as possible during the task. The same instruction was given to them directly before the task started.

Please insert figure 1 here

2.3 Imaging parameters

All MRI data were acquired using 3T MRI scanners made by several manufacturers (Siemens, Philips, General Electric, Bruker) in the eight IMAGEN assessment sites (London, Nottingham, Dublin, Mannheim, Dresden, Berlin, Hamburg, and Paris). Important scanning parameters were identical across sites (i. e., field of view, flip angle, matrix; see Schumann et al., 2010). Moreover, the same Quality Assurance (QA) protocol was implemented regularly at each site, using two different procedures. Firstly, the American College of Radiology phantom as well as a custom phantom (Tofts et al., 2000) were scanned every two months Secondly, *in vivo* QA was conducted with healthy human volunteers twice a year. In addition, both phantom and *in vivo* QA scans were performed before and after every software and/or hardware upgrade. In order to minimize a site effect in the fMRI results, all sites were modeled as covariates in the statistical analyses (see section 2.4). In the present task, 160 volumes per subject were obtained, each comprising 40 slices. The slices were aligned to the connecting line between the anterior and posterior commissure (2.4 mm thickness, 1 mm gap, TR = 2.20 s, TE = 30 ms). The scanning procedure required 5 minutes, followed by a brief dialogue between participant and investigator ensuring the participant's well-being as well as more tasks specified in Schumann et al. (2010).

2.4 Image analysis

All image analysis procedures were conducted using SPM8 (Wellcome Department of Cognitive Neurology). In a first step, EPI images were coregistered with the T1 structural image. Functional images were realigned and resliced to the first volume. Second, EPI images underwent an affine normalization to Montreal Neurological Institute (MNI) space via the custom SPM8-EPI-template. Accordingly, the two hemispheres were extracted as separate images for each scan. The left hemisphere was flipped to the right side so that all images were oriented as right hemispheres. Thereafter, all images underwent a final, non-linear spatial normalization to the same EPI-template.

With the normalized right hemisphere images, a first level analysis on the single subject level was performed. For each individual, right hemisphere images and images of the left – flipped to right – hemisphere were concatenated as two scanning sessions. As contrasts, we included 'angry, right hemisphere > control', 'angry, left hemisphere > control', 'angry, right hemisphere > angry, left hemisphere' as well as 'angry, left hemisphere > angry, right hemisphere', and the same for neutral faces as well as for all – angry and neutral – faces together.

The single-subject contrast images were smoothed with a 4mm Gaussian isotropic kernel and then taken to a second level random effects analysis (two-sample T-test male vs. female). Additionally, a 2-by-2-full-factorial analysis with the factors sex and hemisphere was performed in order to confirm and further visualize the sex by hemisphere interaction. In these analyses, all scanning sites were included as covariates of no interest. As we were explicitly interested in amygdala responses, we based the correction of multiple comparisons for the analyses regarding the amygdala on this region. Specifically, the threshold was set to $p < 0.05$, FWE corrected, for right and left – flipped to right – amygdala with a mask of the right amygdala taken from the Harvard-Oxford subcortical structural atlas (Smith et al., 2004) with a probability threshold at 0.5. For visualization purposes, all images are displayed with a threshold of $p < 0.001$, uncorrected, and an extent threshold of 5 voxels projected onto the mean structural scan of 552 volunteers that provided usable data for the IMAGEN study.

3. Results

In the angry as well as in the neutral condition, the adolescents activated the network commonly associated with emotional face processing in both hemispheres (amygdala, superior temporal sulcus, fusiform gyrus, inferior frontal, and medial prefrontal cortex). During the perception of faces irrespective of emotional content (all faces > control), the global maxima of both hemispheres were located in the amygdala (peak at *x, y, z* = 20, -6, -20 in the right, and *x, y, z* = 18, -6, -20 in the left – flipped to right – hemisphere, T (462) = 29.78 and T (462) = 26.58, respectively, both $p < .0001$, FWE corrected). In the whole sample, there was no significant difference in amygdala activation between the angry and the neutral condition (angry > neutral).

Collapsing both conditions, we investigated the difference between male and female participants during the perception of faces compared to the control condition. There was a significant sex difference in the right, but not in the left hemisphere such that the male participants showed a stronger activation in the right amygdala (all faces, male (right>control) > all faces, female (right>control), *x, y, z* = 20, -10, -14, T (461) = 4.69, $p < .0005$, FWE corrected). Furthermore, the sex by hemisphere interaction was significant: the right amygdala compared to the left amygdala was significantly stronger activated in male participants than in female participants (all faces, male (left>right) > all faces, female (left>right), *x, y, z* = 18, -10, -14, T (461) = 3.52, $p < .05$, FWE corrected; see figure 2). Investigating this interaction in more depth, it became clear that the right amygdala in males showed a stronger activation as compared to the left male and to both female amygdalae, this being an effect more pronounced in the angry condition (see figure 2).

Please insert figure 2 here

By comparing male and female participants in both hemispheres and both conditions separately, we found a significant difference in amygdala activation only in the right hemisphere for the angry condition (angry, male (right>control) > angry, female (right>control), *x, y, z* = 20, -10, -16, T (461) = 5.40, $p < .0001$, FWE corrected). By excluding the neutral condition from the interaction analysis (see figure 2) and investigating only the angry condition (angry, male (right>left) > angry, female (right>left)), we detected an enhanced sex by hemisphere interaction (x, y, z = 20, -8, -16, T (461) = 3.79, p < .01, FWE corrected; see figure 3).

Please insert figure 3 here

4. Discussion

The present study aimed to examine sex differences in the neural processing of emotional faces in a large, age-homogeneous sample of adolescents. Specifically, we could elucidate whether the sex-dependent lateralization of amygdala activation that has been shown for emotional memory in adults already exists in adolescents during the sole perception of emotional faces.

The adolescents' task was to passively view short videos of angry and neutral faces. As expected, the task activated the neural network typically associated with emotional face processing including the amygdala, superior temporal sulcus, fusiform gyrus, inferior frontal, and medial prefrontal cortex (Adolphs, 2002; Allison, Puce, & McCarthy, 2000; Batty & Taylor, 2006; Grosbras & Paus, 2006; Williams et al., 2005). As we were mostly interested in the activation within the amygdala, the fact that the global maximum in the main effect of faces processing was located within the amygdala assured the high validity of the task for our purpose.

The main finding of this study was the confirmation of a sex-dependent amygdala lateralization during the processing of faces. The right amygdala was significantly more strongly activated than the left amygdala in males but not in females. Specifically, males showed a stronger activation of their right amygdala compared to their left amygdala in contrast to females. This effect was enhanced when viewing angry faces, suggesting that emotional content enhances this differential activation.

The present study provides the first evidence of a sex-related lateralization in general amygdala function during face processing. Even though many studies based on adult samples have investigated the neural processes during face perception, recent meta-analyses do not confirm a consistent pattern of sex differences in amygdala activation (Fusar-Poli et al., 2009b; Sergerie et al., 2008; Wager et al., 2003). In particular, no study reported a sex by hemisphere interaction in the amygdala during face perception. Moreover, in their large meta-analysis, Sergerie et al. (2008) explicitly tested this hypothesis and could not support it.

However, to date no meta-analyses on emotional processing in adolescent samples have been conducted. Other studies investigating the neural correlates of emotional face processing in adolescents are based on small and /or age-heterogeneous samples (Guyer et al., 2008; Hare et al., 2008; Monk et al., 2003; Passarotti et al., 2009).

The sex-dependent amygdala lateralization in emotional memory first reported by Cahill and co-workers (2001, 2004; Canli et al., 2002) is mostly compatible with our results as in the present study, the right hemisphere was more activated in males as well. Thus, it can be speculated that the sex-dependent amygdala lateralization during basic emotional processes in adolescence is the precursor of the lateralization in emotional memory observed in adulthood. This interpretation is also in line with the finding by Killgore et al. (2001) showing that females exhibit a progressive increase in prefrontal relative to amygdala activation in the left hemisphere with age. It could be that in early stages, the amygdala exhibits a sex-dependent lateralization in reactivity but this differential reactivity becomes undermined as cortical processes (i. e., cognitive control) get more and more involved in emotional processing later in development. Consistently, the sex difference outlasts adulthood only in basic emotional processes such as emotional memory, which is mostly mediated within the early developed limbic system without the involvement of higher cognitive processes. This would also correspond to the findings by Kilpatrick et al. (2006) who found not only a female-left/male-right difference in amygdala connectivity but also differential neural networks associated with this connectivity, interpreting those with regard to the differential emotional coping mechanisms of men and women. Expanding these ideas, it would be very interesting to investigate the impact of menstrual cycle phase on the laterization effect, especially since recent research indicates that amygdala function in females differs between different phases of their menstrual cycle (Dreher et al., 2007). Another point to keep in mind is the possibility that neural sex differences – for example in amygdala lateralization – could also prevent behavioral sex differences or differences in emotional processing instead of creating them (De Vries, 2004). However, besides such speculations about developmental and hormonal aspects, it is possible that the enhanced right-lateralized amygdala activation in adolescent males also plays a role in vulnerability for disorders that typically take their onset at this age, and that are more frequent in males. This applies to conduct disorder, which is of high societal relevance as it is prevalent in more than 40% of juvenile delinquents (Colins et al., 2010; Karnik et al., 2009). Moreover, conduct disorder has been associated with aberrant amygdala activation, even though there is no consensus on the question whether this abnormality is a matter of hypo- or hyper-activation (Decety et al., 2009; Herpertz et al., 2008; Sterzer et al., 2005). A recent review (Crowe & Blair, 2008) suggests that the direction of amygdala abnormalities might be explained by a differentiation between reactive and instrumental aggression. While a tendency towards impulsivity and reactive aggression may be related to an amygdala hyper-activation, instrumental aggression could be associated with a hypo-activation of the amygdala. As adolescents displaying conduct problems are at high risk to retain these problems until adulthood, insights in the underlying mechanisms of their behavior are of particular relevance (Vloet et al., 2010).

The present study has several limitations. Within the IMAGEN protocol only two conditions could be investigated, which reduces the generalizability of our results. Although we think it is plausible that the laterization effect applies to other negative emotions as well because we found the effect to be significant even in the all faces condition, this cannot be concluded with certainty. In particular, it would have been of interest to investigate fearful faces as fear is the most thoroughly investigated emotion in the field (Sergerie et al., 2008). Furthermore, even though there exist plenty of data concerning the neural correlates of emotional face processing in adults, a similar large adult control group could potentially support developmental interpretations of our results. In addition, males and females might have different developmental gradients. This has been implicated in cognition, as females perform better in language-related tasks and males seem to have a visuospatial processing advantage, but also in cortical maturation as well as in regional gray and white matter trajectories (De Bellis et al., 2001; Raznahan et al., 2010; Stokes & Klee, 2009; Voyer, Voyer, & Bryden, 1995). Possibly, such differential developments may have influenced our results.

In summary, this study provides consistent evidence for a sex-dependent amygdala lateralization in a functional face processing task in an adolescent sample. This interaction was particularly strong when clear emotional content (i. e., angry faces) was involved. Our results hint towards a sex-specific neural development in emotional processing that might be important in the development of mental disorders affecting males more frequently than females.

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Disclosure Statement

All authors declare that they have no conflicts of interest.

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Figure Captions

Figure 1. Blocks of videos showing faces that turn from neutral to angry (a) or stay neutral (c), interspersed with blocks of control stimuli (b). Printed with permission from Grosbras & Paus (2006).

Figure 2. The image on the left shows the sex-by-hemisphere interaction in the amygdala during the perception of all faces (all faces, male (right>control) > all faces, female (right>control)). The bar plot describes this interaction in more detail by separating angry and neutral faces: it depicts the percent signal change at the peak activation in male (in blue) and female (in pink) participants, split up into left and right hemisphere as well as into angry and neutral faces (error bars indicate standard errors).

Figure 3. The sex-by-hemisphere interaction in the amygdala during the perception of angry faces only (angry faces, male (right>control) > angry faces, female (right>control)). The bar plot shows the percent signal change at the peak activation in male (in blue) and female (in pink) participants, split up into left and right hemisphere (error bars indicate standard errors).

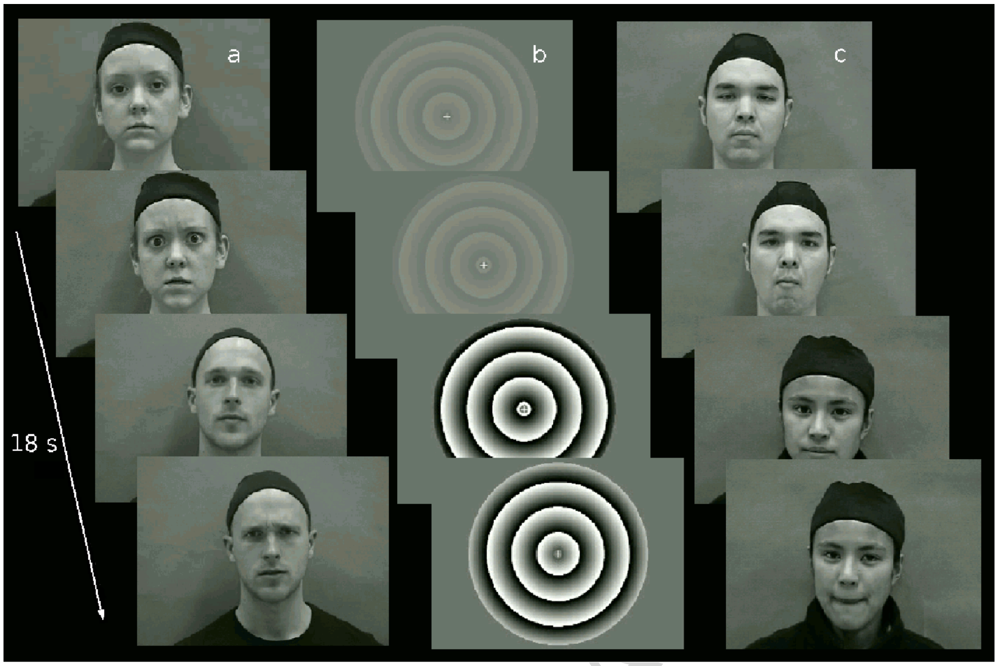

Figure 1

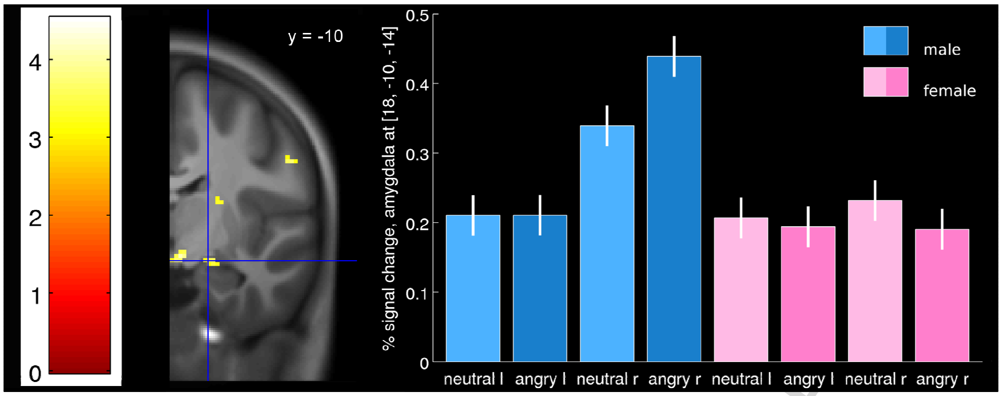
4
3
2
1
0
y = -10
% signal change, amygdala at [18, -10, -14]
0.5
0.4
0.3
0.2
0.1
0
male
female
neutral l
angry l
neutral r
angry r
neutral l
angry l
neutral r
angry r

Figure 2

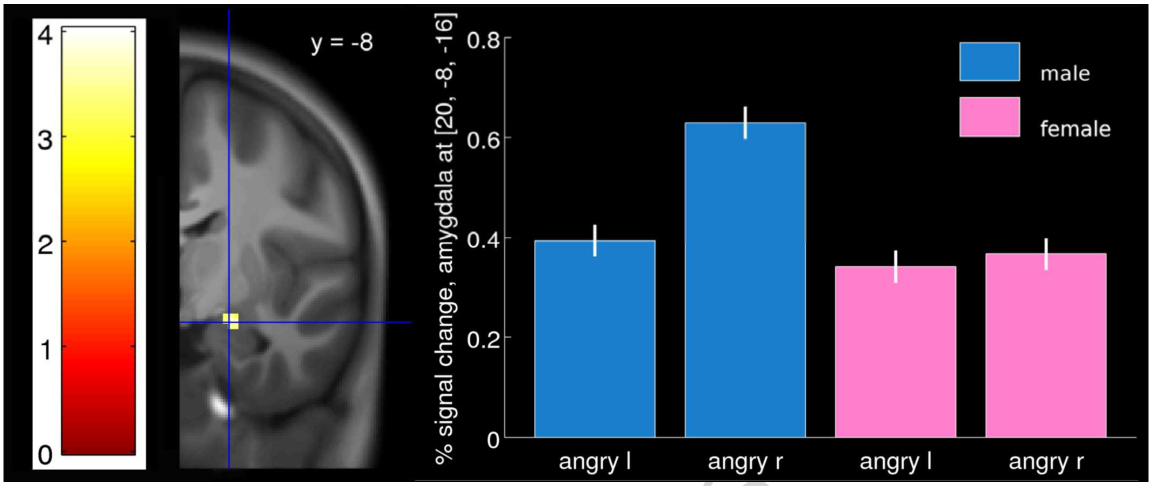
4
3
2
1
0
y = -8
% signal change, amygdala at [20, -8, -16]
0.8
0.6
0.4
0.2
0
male
female
angry l
angry r
angry l
angry r

Figure 3

Research Highlights

- sex by hemisphere interaction in basic face processing in a large adolescent sample
- significantly stronger right amygdala activation in males as compared to females
- difference in activation is enhanced when emotional content (anger) is involved
- implications for sex-dependent development of emotion processing and mental disorders