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Preferential Amygdala Reactivity to the Negative Assessment of Neutral Faces

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Abstract

Background—Prior studies suggest that the amygdala shapes complex behavioral responses to socially ambiguous cues. We explored human amygdala function during explicit behavioral decision making about discrete emotional facial expressions that can represent socially unambiguous and ambiguous cues.

Methods—During functional magnetic resonance imaging, 43 healthy adults were required to make complex social decisions (i.e., approach or avoid) about either relatively unambiguous (i.e., angry, fearful, happy) or ambiguous (i.e., neutral) facial expressions. Amygdala activation during this task was compared with that elicited by simple, perceptual decisions (sex discrimination) about the identical facial stimuli.

Results—Angry and fearful expressions were more frequently judged as avoidable and happy expressions most often as approachable. Neutral expressions were equally judged as avoidable and approachable. Reaction times to neutral expressions were longer than those to angry, fearful, and happy expressions during social judgment only. Imaging data on stimuli judged to be avoided revealed a significant task by emotion interaction in the amygdala. Here, only neutral facial expressions elicited greater activity during social judgment than during sex discrimination. Furthermore, during social judgment only, neutral faces judged to be avoided were associated with greater amygdala activity relative to neutral faces that were judged as approachable. Moreover, functional coupling between the amygdala and both dorsolateral prefrontal (social judgment > sex discrimination) and cingulate (sex discrimination > social judgment) cortices was differentially modulated by task during processing of neutral faces.

Conclusions—Our results suggest that increased amygdala reactivity and differential functional coupling with prefrontal circuitries may shape complex decisions and behavioral responses to socially ambiguous cues.

Keywords

Amygdala; cingulate; facial expressions; fMRI; prefrontal cortex; social decision making

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Successful navigation of complex social networks is critical for both mental and physical health. Paramount to such efforts is the ability to resolve the nature of socially ambiguous information or uncertain contexts, that is, social inputs that do not provide enough information about the social action to take, which may be interpreted as threatening. Recent studies have demonstrated that in addition to its critical contribution to fear-related behaviors (1), the amygdala, which is functionally connected with prefrontal and cingulate regions (2–4) and associated with regulation of emotional responses (5), contributes to more complex social behaviors and is sensitive to socially ambiguous stimuli (6). For example, lesions of the amygdala are associated with increased trustworthiness ratings of unfamiliar neutral faces (7), whereas the magnitude of amygdala activation observed with functional neuroimaging is associated with decreased trustworthiness ratings (8). Moreover, the amygdala exhibits a strong response to novel, emotionally neutral facial expressions that diminishes with familiarity (9,10), a pattern consistent with the initially ambiguous nature of such stimuli (i.e., neither emotionally positive nor negative and potentially threatening). In addition, the amygdala responds to increasing relative ambiguity of explicitly emotional facial expressions as a function of experimental manipulation (11).

These findings suggest that the amygdala, through its capacity to increase behavioral and physiological arousal, as well as through processing of both cue- and context-related information, may be recruited for explicit responses to socially ambiguous cues (6,12,13). In this study, we explored the contribution of the amygdala to explicit behavioral decisions about socially ambiguous stimuli. Forty-three healthy adults completed an event-related blood oxygen level–dependent (BOLD) functional magnetic resonance (fMRI) study during which they were required to make complex, explicit social decisions (i.e., approach or avoid) about facial stimuli with relatively unambiguous (i.e., angry, fearful, or happy) or ambiguous (i.e., neutral) emotional expressions. In a different session, subjects were required to make not social but simple, perceptual decisions (i.e., sex discrimination) of the same stimuli. Given the preferential involvement of the amygdala in processing of aversive stimuli (14), we focused our analysis on amygdala responses associated with processing of stimuli that subjects would choose to avoid. We hypothesized that both decision-making processes on unambiguous stimuli with negative valence (i.e., angry and fearful facial expressions) would be associated with amygdala response because they are perceived as aversive regardless of the cognitive context within which responses are given. By contrast, when the stimuli are emotionally ambiguous, the context within which to give behavioral responses may affect activity of the amygdala. More specifically, we hypothesized that negative social (i.e., avoid vs. approach) but not perceptual evaluation of neutral stimuli might trigger preferential responses of the amygdala during evaluation of their social ambiguity. Finally, given that the amygdala is part of a broader brain network for processing of emotional inputs, we also explored differential patterns of functional coupling between this brain area and interconnected regulatory regions of the prefrontal cortex during both forms of evaluation.

Methods and Materials

Subjects

Forty-three healthy subjects (24 men, mean age $\pm$ SD = 29.5 ± 7.1 ; mean IQ = 105.9 ± 8.9 [Wechsler Adult Intelligence Scale—Revised], mean handedness = $.9 \pm .2$ [Edinburgh Inventory]) (15) who had undergone extensive clinical evaluation were recruited for this study (Supplement 1). Inclusion criteria were the absence of 1) any current or past neurological or psychiatric disorder, 2) any medical condition, 3) any pharmacologic treatment that could influence cerebral metabolism or blood flow, 4) history of drug abuse. All subjects gave written informed consent after the procedure had been fully explained. The

protocol was approved by the National Institute of Mental Health Institutional Review Board.

Experimental Paradigm

The event-related fMRI paradigm consisted of two runs; each run presented angry, fearful, happy, and neutral facial expressions derived from a validated set of facial pictures (NimStim, <http://www.macbrain.org/resources.htm>)(16). The same stimuli were presented in each run with the same order. During one run, subjects were instructed to decide whether they would “approach” or “avoid” the actor in the picture (social judgment task). In the other run, subjects were asked to identify the sex of each actor (nonsocial sex discrimination task). The order of presentation of the two runs was counterbalanced across subjects. The total number of stimuli was 144: 30 angry, 39 fearful, 37 happy, and 38 neutral faces. The order of the stimuli was randomly distributed across the session (17). Each stimulus was presented for 500 msec, with the interstimulus interval (ISI) randomly jittered between 2 sec and 7 sec for a total run time of 6 min, 8 sec. A fixation crosshair was presented during the interstimulus interval. All stimuli were presented using a back-projection system. A fiber-optic response box was used to measure subject preference (and reaction time) for each stimulus—left button for approach/male response and right button for avoid/female response.

Image Acquisition

The BOLD fMRI was acquired on a GE Signa 3-T scanner while subjects performed the tasks (Supplement 1).

Data Analysis

Behavioral Data—A repeated-measures analysis of variance (ANOVA) with the four facial expressions and the two tasks as the within-effect factors was used to compare behavioral measures. Tukey test was used for post hoc comparisons.

fMRI Data—Whole-brain image analysis was completed using Statistical Parametric Mapping 5 (SPM5; <http://www.fil.ion.ucl.ac.uk/spm>). Images for each subject were realigned, spatially normalized into the Montreal Neurological Institute (MNI) template (12 parameter affine model), and spatially smoothed (10-mm Gaussian filter). The fMRI responses were modeled using a canonical hemodynamic response function and temporally filtered using a high-pass filter of 128 Hz to minimize scanner drift. For the social judgment run, vectors were created for angry, fearful, and neutral faces that subjects would choose to avoid. For the nonsocial sex discrimination run, vectors were created for the same angry, fearful, and neutral faces that subjects would choose to avoid during the social judgment run. This method allows for comparisons of responses to the same facial stimuli during the social judgment and nonsocial sex discrimination tasks runs. Timing of presentation of all other stimuli was also convolved with hemodynamic response functions (HRF) but not considered for further investigation in this main analysis. In particular, we did not further analyze happy faces because of the limited number of “avoid” responses for this facial expression. The residual movement was modeled as a regressor of no interest.

Linear contrasts employing canonical HRF were thus used to estimate condition-specific BOLD activation for each individual and each scan. To evaluate responses during the social judgment task, we compared activity associated with processing of faces stimuli of each expression that subjects would choose to avoid with baseline activity (i.e., the interstimulus interval during which the subjects focused on crosshairs). Similarly, to evaluate responses for the same stimuli, that is, those that subjects would choose to avoid in the social judgment task, during the nonsocial sex discrimination task, we set up contrasts to compare activity

related to these stimuli and baseline activity. These individual contrast images (i.e., weighted sum of the beta images) were then used in second-level random effects models that account for both scan-to-scan and participant-to-participant variability to determine mean condition-specific regional responses. Furthermore, ANOVA was used to investigate the main effect of 1) task (i.e., social judgment vs. nonsocial sex discrimination tasks on cues that subjects would choose to avoid), 2) emotional expression, and 3) their interaction. Further analyses were conducted to analyze the effect of task on each expression type.

Furthermore, to compare brain activity associated with negative and positive social judgment of neutral faces, we performed a separate ANOVA (Supplement 1) to evaluate a task by judgment (i.e., avoid vs. approach) interaction on amygdala activity during processing of neutral expressions.

All analyses were constrained by a mask obtained by combining group activation maps for each run for angry, fearful, and neutral expressions ($p < .05$). Brodmann's areas (BAs) were assigned using the Talairach Daemon (<http://ric.uthscsa.edu/projects/talairachdaemon.html>) after converting the MNI coordinates of the local maxima in the activated clusters to Talairach coordinates (<http://www.mrc-cbu.cam.ac.uk/Imaging/Common/mnispace.shtml>).

Psychophysiological interaction (PPI) analysis was also performed to explore specifically modulation of amygdala functional connectivity during the social judgment task, particularly for the neutral faces stimuli that the subjects would choose to avoid and for the same stimuli during the nonsocial sex discrimination task. In particular, we focused PPI analysis on the cluster in the right amygdala that showed a significant task by emotion interaction (see Results for more details). The individual PPI contrasts for each subject (Supplement 1) were entered into an ANOVA to investigate the main effect of task (social judgment or nonsocial sex discrimination on faces that subjects would choose to avoid) on the functional connectivity of the amygdala during processing of neutral expressions.

For all analyses, a statistical threshold of $p < .005$, minimum cluster size (k) = 4 was used. All results were further family wise error (FWE) small volume corrected at $p < .05$ within a 10-mm radius sphere centered around the coordinates published in previous studies on emotion processing (5).

Results

Behavioral Data

Analysis of behavioral data indicated that there was an effect of emotional expression on the number of faces that subjects judged they would avoid [$F(3,126) = 165.1$; $p < .0001$]. Post hoc analysis showed no statistical difference between the number of fearful and angry faces that subjects judged they would avoid ($p > .6$). Furthermore, subjects judged that they would avoid a significantly lower number of neutral and happy compared with fearful and angry faces (both $ps < .00001$). Moreover, the number of neutral faces that subjects judged they would avoid was greater than those of happy faces associated with similar judgment ($p < .00001$; Figure 1).

Reaction time data showed an effect of task [$F(1,30) = 34.7$; $p < .00001$], of face expression [$F(3,90) = 10.1$; $p < .0001$], and an interaction between these factors [$F(3,90) = 9.0$; $p < .0001$]. Post hoc analysis indicated greater reaction times during the social judgment than the nonsocial sex discrimination task relative to faces that subjects judged they would avoid for all expressions (all $ps < .03$). Furthermore, greater reaction times for neutral compared with happy, fearful, and angry faces that subjects judged they would avoid was present only during the social judgment task (all $ps < .002$; Figure 1).

fMRI Data

Analysis of the imaging data during both social judgment and nonsocial sex discrimination tasks showed that processing of facial expressions that the subjects would choose to avoid were associated with activity in a distributed network with nodes in bilateral dorsolateral, ventrolateral, and medial prefrontal cortex, as well as bilateral amygdala. In particular, robust amygdala activity was present during sex discrimination of angry and fearful but not neutral faces. ANOVA on the same stimuli, that is, those the subjects would choose to avoid, revealed a significant main effect of task in lateral and medial regions of the prefrontal cortex bilaterally, as well as in the right amygdala (Figure 2A, Table 1), and a significant main effect of facial expression bilaterally in several prefrontal regions and in the amygdala (Figure 2B, Table 1). In particular, angry facial expressions showed greater responses in the amygdala relative to fearful faces, which in turn were associated with the lowest activity, irrespective of the task at hand. Moreover, an interaction between task and facial expression was identified in the prefrontal cortex bilaterally and in the right amygdala (Figures 2C and 3, Table 1). Specific contrasts indicated that the effect of task and its interaction with facial expression on amygdala activity was due to differential response during processing of neutral facial expressions. In particular, in comparison with the nonsocial sex discrimination task, there was greater right amygdala activity during the social judgment task while processing faces with neutral expressions only (Figure 4). No brain regions showed greater activity during the nonsocial sex discrimination relative to the social judgment task.

A separate ANOVA within SPM comparing the effect of negative (avoid) versus positive (approach) social judgment of neutral expressions showed a task-by-judgment interaction in the right amygdala (Table 2). Specific post hoc contrasts revealed that during the social judgment task, neutral faces judged to be avoided had greater right amygdala activity relative to those judged to be approached. Furthermore, faces judged to be avoided showed greater right amygdala activity during the social judgment relative to the sex discrimination task (Table 2). This latter effect was not found for faces judged to be approached.

Because analysis of BOLD responses showed specific modulation of amygdala activity by task during the evaluation of neutral expressions only, functional connectivity analyses were restricted to this effect. For these analyses, we used the right amygdala cluster that showed a significant task-by-emotion interaction as the seed region of interest. ANOVA indicated an effect of task, with relatively greater amygdala-subgenual cingulate ($x = 11$ years = 34 $z = -10$; BA32; $Z = 3.02$, $p = .001$; $k = 17$) functional connectivity during the nonsocial sex discrimination task and relatively greater amygdala-dorsolateral prefrontal cortex ($x = -55$ years = 30 $z = 17$; BA46; $z = 3.23$, $p = .001$; $k = 8$) functional connectivity during the social judgment task (Figure 5).

Discussion

We report specific modulation of amygdala activity and functional connectivity during explicit social decision making of emotionally ambiguous facial expressions. We found a significant interaction between task and expression on right amygdala activity. In particular, activity in this brain region was specifically modulated by differential processing of faces with ambiguous (i.e., neutral) expressions. Amygdala activity was greater during social judgment relative to sex discrimination of faces with relatively ambiguous expressions (i.e., neutral expressions) that the subjects would choose to avoid. No such effect was present during processing of faces with relatively unambiguous expressions (i.e., angry, fearful, happy). Furthermore, during the social judgment run, amygdala activity during evaluation of neutral faces judged to be avoided was also greater compared with neutral faces judged to be approached. We also found that functional connectivity of the amygdala with cortical

regions was differentially modulated by task during evaluation of ambiguous expressions. Social judgment relative to sex discrimination of ambiguous expressions that subjects would choose to avoid was associated with greater amygdala-dorsolateral prefrontal cortex functional connectivity, whereas greater amygdala-subgenual cingulate functional connectivity was present during sex discrimination of these same ambiguous expressions.

Consistent with this pattern, behavioral data revealed that the number of ambiguous cues (i.e., faces with neutral expression) judged to be avoided were intermediate to those representing relatively unambiguous cues (i.e., negative or positive emotional valence). Furthermore, although there was no effect of emotion on reaction time during sex discrimination of faces judged to be avoided during the social judgment run, subjects took longer to respond during the social judgment of neutral faces judged to be avoided relative to all other facial expressions with similar judgment. These behavioral data suggest increased processing of faces with neutral emotional expression associated with greater ambiguity during social decision making relative to unambiguous facial expressions. The absence of subjective reports of perceived ambiguity and/or emotional impact limits our ability to link conclusively our observed neurobiological and behavioral findings with these complex, social processes.

The neurobiological and behavioral effects we observed suggest that the amygdala is recruited when processing ambiguous social stimuli, particularly when they are negatively evaluated. This interpretation is consistent with previous results in animal models, as well as in humans, demonstrating increased amygdala activity in response to ambiguous or uncertain behavioral situations and unpredictable stimuli. For example, electrophysiologic studies in rats (18,19) have shown that the amygdala is implicated in association processes related to danger and fear. In addition, imaging studies in humans (20) using fear-conditioning paradigms have indicated an association between the amygdala and ambiguity in stimulus contingencies. Herry *et al.* (21) investigated the effect of temporal unpredictability on brain physiology in both mice and humans. They reported that mice exposed to temporally unpredictable neutral sound pulses showed increased expression of the immediate-early gene *c-fos* and reduced rapid habituation of neuronal activity in amygdala. In humans, exposure to similar stimuli evoked sustained neuronal activity in this brain region and anxiety-like behavior (21). Finally, using a gambling paradigm, another study (22) showed that activity in the amygdala correlated positively with the level of ambiguity in choices. Our results are consistent with these earlier studies and suggest that the amygdala is involved in the processing of ambiguous stimuli (6). In particular, together with other data suggesting that the amygdala is specifically involved in the attribution of social relevance to environmental stimuli (23,24), our results further indicate that activity in this brain region may be elicited when ambiguity characterizes social interactions. In other words, within complex social hierarchies, such as those that define human societies, it is critical to determine whether unfamiliar individuals should be avoided or approached, and to adopt appropriate behavioral strategies associated with this social preference. Different considerations and qualities contribute to such social evaluations. Among these, facial expressions are of particular relevance (25,26). More specifically, individuals may use other people's facial expressions to make predictions about their putative social behavior and generate appropriate interactive strategies. This evaluative process may be of particular relevance during putatively unpleasant interactions associated with danger or threat. For example, individuals may preferentially avoid people with facial expressions characterized by negative emotional valence such as anger. However, although it may be easy to attribute specific social significance to such explicit facial expressions, this is not always possible for others. In fact, faces are often characterized by ambiguous emotional expressions that may not be unequivocally interpretable. The difficulty in attributing emotional and thus social significance to a facial expression may in turn lead to uncertainty and heightened vigilance

(6,12), as well as to anxiety and activity of error systems, and thus to increased amygdala activity. This interpretation is consistent with those offered in previous imaging studies in humans using facial stimuli. For example, Whalen *et al.* (27) found greater amygdala activity associated with fearful relative to angry faces. These authors suggest that this effect might be due to greater ambiguity of the former facial expression. In our study, the amygdala was associated with the opposite pattern of activity relative to that shown by Whalen *et al.* (27) when comparing angry and fearful faces. Several factors may be associated with these discrepancies, including the task requirement (e.g., passive viewing vs. decision making processes of different degrees), block versus event-related designs, and the type of stimuli used. Alternatively, the interpretation of our results and those by Whalen *et al.* may be similar in that preferential amygdala activity may be associated with stimuli with ambiguous information. In our study, stimulus ambiguity is inherent in the task requirement, that is, approach or avoid a stimulus with unclear socially relevant information.

Our data may also suggest that amygdala response during processing of faces with different valence have different origins. In fact, no difference in amygdala activity was found between tasks while fearful and angry facial expressions were processed, suggesting that basic perceptual characteristics of stimuli may be relevant in driving amygdala response. In this respect, these results are consistent with those found by Whalen *et al.* (28), which indicate that the size of sclera reflecting fearful or happy expressions modulate activity in the amygdala. By contrast, our results showing differential activity of amygdala across tasks while processing neutral expressions may suggest that the psychological ambiguity is more relevant in modulating amygdala activity while stimuli with unclear socially relevant information are processed.

It is also possible that the degree of perceived aversion to a stimulus may have modulated amygdala activity during the processing of the stimuli used in this study. However, it is important to note that processing of angry and fearful faces that subjects judged they would avoid did not show differential activity between the social judgment and the nonsocial sex discrimination tasks. In contrast, there was greater amygdala activity for neutral stimuli during the social judgment task compared with the nonsocial sex discrimination task. These results suggest that the subjective perception of neutral and possibly emotionally ambiguous stimuli as aversive may modulate amygdala activity. Consistent with this contention, during the social judgment task of our study, we also found that neutral facial expressions associated with judgment of avoidance showed greater amygdala activity relative to those judged to be approached.

Several studies have linked the right hemisphere of the brain with emotion processing (29). In our study, it is likely that more processing may have been required for neutral facial expressions during the social judgment task when an explicit choice needed to be made on whether to approach or avoid, relative to the simple “sex discrimination” task, as these stimuli do not have adequate socially relevant information. Therefore, greater right amygdala activity during the former task relative to the latter may fit models postulating right hemisphere dominance during emotion processing. Furthermore, our lateralized findings may also be a reflection of stimulus novelty and detection supported by the right amygdala, versus sustained attention supported by the left amygdala (30).

Evaluative processes associated with social ambiguity of neutral expressions may be invoked as a possible explanation for our data on differential modulation of the functional relationship between the amygdala and other brain regions—namely, the prefrontal cortex and the subgenual cingulate. We find that social judgment of faces stimuli with neutral expression that subjects would choose to avoid elicited greater amygdala-dorsolateral prefrontal cortex functional coupling. In contrast, there was greater amygdala-subgenual

cingulate functional coupling during their nonsocial sex discrimination. Both dorsolateral prefrontal and subgenual cingulate cortices have been implicated in emotional processing, and their functional connections with the amygdala have been shown to predict complex emotional behaviors such as temperamental anxiety (3,4,31). In particular, the subgenual cingulate has been linked with appraisal (32), and there is evidence for bottom-up flow of information related to the saliency of environmental stimuli from amygdala to this brain region (3,32,33). By contrast, the dorsolateral prefrontal cortex is critically involved in conscious goal-oriented tasks such as coordinating responses in motor output regions (34) as well as in emotion regulation (32) and regulation of one's feelings (5,35). Importantly, there is also evidence that dorsolateral prefrontal areas are functionally coupled with the amygdala through other cortical nodes during emotion processing (3). On the basis of this prior evidence, our results suggest involvement of the amygdala-subgenual cingulate functional pathway in bottom-up processes associated with perception of social cues from neutral facial expressions. Further, in line with other studies suggesting a role of dorsolateral prefrontal areas in enhancing emotional responses (5,35), our results may implicate top-down regulatory mechanisms through which dorsolateral prefrontal control centers potentiate amygdala activity during social judgment of ambiguous facial expressions that the subjects would choose to avoid. By contrast, because the functional connectivity analysis does not provide information regarding directionality of effects, it is also equally possible that the amygdala might recruit the dorsolateral prefrontal cortex during the social judgment of those stimuli and that the subgenual cingulate might dampen amygdala signal during the nonsocial sex discrimination task. However, irrespective of these possible interpretations, these data suggest disparate functional coupling of the amygdala with prefrontal and cingulate regions during evaluation of neutral facial expressions as a function of the task at hand.

Medial, dorsolateral, and ventrolateral prefrontal regions also showed greater activity regardless of the emotional expression during the social judgment task than during the nonsocial sex discrimination tasks. All these prefrontal areas have been previously associated with emotion regulation and social cognition (35). In particular, studies in monkeys suggest that abnormal social behavior vis-à-vis grooming, huddling, and spatial relationships result from lesions in ventral regions of prefrontal cortex (36). In addition, human brain imaging link social cognition, especially communicating intentions and mentalizing, with activity in dorsomedial prefrontal and cingulate cortices (37,38). Activity in the ventromedial prefrontal cortex is possibly related to processing affective ambiguity (39). Furthermore, activity in dorsolateral prefrontal cortex has been linked to emotion regulation (5). Therefore, it is possible that heightened activity in these brain regions observed during social judgment of faces that subjects would choose to avoid may be due to greater regulatory or cognitive control associated with explicit processing of social stimuli.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. LeDoux JE. Emotion circuits in the brain. *Annu Rev Neurosci* 2000;23:155–184. [PubMed: 10845062]

2. Pezawas L, Verchinski BA, Mattay VS, Callicott JH, Kolachana BS, Straub RE, et al. The brain-derived neurotrophic factor Val66met polymorphism and variation in human cortical morphology. *J Neurosci* 2004;24:10099–10102. [PubMed: 15537879]
3. Stein JL, Wiedholz LM, Bassett DS, Weinberger DR, Zink CF, Mattay VS, et al. A validated network of effective amygdala connectivity. *Neuroimage* 2007;36:736–745. [PubMed: 17475514]
4. Williams LM, Das P, Liddell BJ, Kemp AH, Rennie CJ, Gordon E. Mode of functional connectivity in amygdala pathways dissociates level of awareness for signals of fear. *J Neurosci* 2006;26:9264–9271. [PubMed: 16957082]
5. Ochsner KN, Knierim K, Ludlow DH, Hanelin J, Ramachandran T, Glover G, et al. Reflecting upon feelings: An fMRI study of neural systems supporting the attribution of emotion to self and other. *J Cogn Neurosci* 2004;16:1746–1772. [PubMed: 15701226]
6. Whalen PJ. Fear, vigilance, and ambiguity: Initial neuroimaging studies of the human amygdala. *Curr Dir Psychol Sci* 1998;7:177–188.
7. Adolphs R, Tranel D, Damasio AR. The human amygdala in social judgment. *Nature* 1998;393:470–474. [PubMed: 9624002]
8. Winston JS, Strange BA, O'Doherty J, Dolan RJ. Automatic and intentional brain responses during evaluation of trustworthiness of faces. *Nat Neurosci* 2002;5:277–283. [PubMed: 11850635]
9. Wright P, Liu Y. Neutral faces activate the amygdala during identity matching. *Neuroimage* 2006;29:628–636. [PubMed: 16143545]
10. Schwartz CE, Wright CI, Shin LM, Kagan J, Whalen PJ, McMullin KG, et al. Differential amygdalar response to novel versus newly familiar neutral faces: A functional MRI probe developed for studying inhibited temperament. *Biol Psychiatry* 2003;53:854–862. [PubMed: 12742672]
11. Adams RB Jr, Gordon HL, Baird AA, Ambady N, Kleck RE. Effects of gaze on amygdala sensitivity to anger and fear faces. *Science* 2003;300:1536. [PubMed: 12791983]
12. Rosen JB, Donley MP. Animal studies of amygdala function in fear and uncertainty: Relevance to human research. *Biol Psychol* 2006;73:49–60. [PubMed: 16500019]
13. Whalen PJ. The uncertainty of it all. *Trends Cogn Sci* 2007;11:499–500. [PubMed: 18024182]
14. Hariri AR, Tessitore A, Mattay VS, Fera F, Weinberger DR. The amygdala response to emotional stimuli: A comparison of faces and scenes. *Neuroimage* 2002;17:317–323. [PubMed: 12482086]
15. Oldfield RC. The assessment and analysis of handedness: The Edinburgh inventory. *Neuropsychologia* 1971;9:97–113. [PubMed: 5146491]
16. Tottenham N, Tanaka J, Leon AC, McCarry T, Nurse M, Hare TA, et al. The NimStim set of facial expressions: Judgments from untrained research participants. *Psychiatry Res* 2009;168:242–249. [PubMed: 19564050]
17. Friston KJ, Zarahn E, Josephs O, Henson RN, Dale AM. Stochastic designs in event-related fMRI. *Neuroimage* 1999;10:607–619. [PubMed: 10547338]
18. Quirk GJ, Armony JL, LeDoux JE. Fear conditioning enhances different temporal components of tone-evoked spike trains in auditory cortex and lateral amygdala. *Neuron* 1997;19:613–624. [PubMed: 9331352]
19. Quirk GJ, Repa C, LeDoux JE. Fear conditioning enhances short-latency auditory responses of lateral amygdala neurons: Parallel recordings in the freely behaving rat. *Neuron* 1995;15:1029–1039. [PubMed: 7576647]
20. LaBar KS, Gatenby JC, Gore JC, LeDoux JE, Phelps EA. Human amygdala activation during conditioned fear acquisition and extinction: A mixed-trial fMRI study. *Neuron* 1998;20:937–945. [PubMed: 9620698]
21. Herry C, Bach DR, Esposito F, Di Salle F, Perrig WJ, Scheffler K, et al. Processing of temporal unpredictability in human and animal amygdala. *J Neurosci* 2007;27:5958–5966. [PubMed: 17537966]
22. Hsu M, Bhatt M, Adolphs R, Tranel D, Camerer CF. Neural systems responding to degrees of uncertainty in human decision-making. *Science* 2005;310:1680–1683. [PubMed: 16339445]
23. Amaral DG. The primate amygdala and the neurobiology of social behavior: Implications for understanding social anxiety. *Biol Psychiatry* 2002;51:11–17. [PubMed: 11801227]

24. Adolphs R. Is the human amygdala specialized for processing social information? *Ann NY Acad Sci* 2003;985:326–340. [PubMed: 12724168]
25. Darwin, C. *The Expression of the Emotions in Man and Animals*. Oxford University Press; New York: 1998.
26. Ekman, P.; Friesen, W. *Pictures of Facial Affect*. Consulting Psychologists; Palo Alto, CA: 1976.
27. Whalen PJ, Shin LM, McInerney SC, Fischer H, Wright CI, Rauch SL. A functional MRI study of human amygdala responses to facial expressions of fear versus anger. *Emotion* 2001;1:70–83. [PubMed: 12894812]
28. Whalen PJ, Kagan J, Cook RG, Davis FC, Kim H, Polis S, et al. Human amygdala responsivity to masked fearful eye whites. *Science* 2004;306:2061. [PubMed: 15604401]
29. Demaree HA, Everhart DE, Youngstrom EA, Harrison DW. Brain lateralization of emotional processing: Historical roots and a future incorporating “dominance”. *Behav Cogn Neurosci Rev* 2005;4:3–20. [PubMed: 15886400]
30. Wright CI, Fischer H, Whalen PJ, McInerney SC, Shin LM, Rauch SL. Differential prefrontal cortex and amygdala habituation to repeatedly presented emotional stimuli. *Neuroreport* 2001;12:379–383. [PubMed: 11209954]
31. Pezawas L, Meyer-Lindenberg A, Drabant EM, Verchinski BA, Munoz KE, Kolachana BS, et al. 5-HTTLPR polymorphism impacts human cingulate-amygdala interactions: A genetic susceptibility mechanism for depression. *Nat Neurosci* 2005;8:828–834. [PubMed: 15880108]
32. Phillips ML, Drevets WC, Rauch SL, Lane R. Neurobiology of emotion perception I: The neural basis of normal emotion perception. *Biol Psychiatry* 2003;54:504–514. [PubMed: 12946879]
33. Amaral DG, Price JL. Amygdalocortical projections in the monkey (*Macaca fascicularis*). *J Comp Neurol* 1984;230:465–496. [PubMed: 6520247]
34. Koehler E, Ody C, Kouneiher F. The architecture of cognitive control in the human prefrontal cortex. *Science* 2003;302:1181–1185. [PubMed: 14615530]
35. Ochsner KN, Gross JJ. The cognitive control of emotion. *Trends Cogn Sci* 2005;9:242–249. [PubMed: 15866151]
36. Raleigh MJ, Steklis HD. Effect of orbitofrontal and temporal neocortical lesions of the affiliative behavior of vervet monkeys (*Cercopithecus aethiops Sabaeus*). *Exp Neurol* 1981;73:378–389. [PubMed: 7262243]
37. Frith CD. The social brain? *Philos Trans R Soc Lond B Biol Sci* 2007;362:671–678. [PubMed: 17255010]
38. Amodio DM, Frith CD. Meeting of minds: The medial frontal cortex and social cognition. *Nat Rev Neurosci* 2006;7:268–277. [PubMed: 16552413]
39. Simmons A, Stein MB, Matthews SC, Feinstein JS, Paulus MP. Affective Ambiguity for a group recruits ventromedial prefrontal cortex. *Neuroimage* 2006;29:655–661. [PubMed: 16125977]

Figure 1. Plots showing the number of faces associated with judgment of avoidance (as % of total) during the social judgment task (left), as well as reaction time (milliseconds) during the social judgment and nonsocial sex discrimination tasks (right). See text for statistics.

Figure 2. Rendered images and coronal sections illustrating statistical parametric maps of prefrontal and amygdala activation associated with **(A)** main effect of task, **(B)** main effect of expression, and **(C)** interaction between task and expression.

Figure 3.

Plots showing parameter estimates for each facial expression in the two tasks in a right amygdala cluster exhibiting a significant task by expression interaction ($x = 26, y = -8, z = 16$).

Figure 4.

Center view: coronal section with an overlay of the statistical parametric map that shows greater amygdala activation during evaluation of neutral faces associated with judgment of avoidance during the social judgment task than during the nonsocial sex discrimination task. Top and bottom views: rendered images illustrating regions of the dorsolateral, ventrolateral, and medial prefrontal cortex showing greater activity during the same comparison.

Figure 5. Rendered images of functional connectivity maps related to processing of neutral faces that received judgment of avoidance. **(A)** Region of dorsolateral prefrontal cortex that shows greater functional connectivity with the amygdala during the social judgment task than during the nonsocial sex discrimination task and **(B)** region of subgenual cingulate cortex that shows greater functional connectivity with the amygdala during the nonsocial sex discrimination task than during the social judgment task.

Table 1

Summary of Significant Task-Specific Regional Brain Activations

Brain Region	BA	Coordinates				
		x	y	z	k	Z
Main Effect of Task						
Left superior frontal gyrus	8	0	21	50	80	5.05
Right inferior frontal gyrus	44	52	12	18	109	4.49
Left inferior frontal gyrus	47	-34	25	-14	52	3.58
Left inferior frontal gyrus	9	-45	16	22	39	3.36
Left middle frontal gyrus	10	-34	48	7	6	3.20
Right inferior frontal gyrus	47	49	22	-5	22	3.05
Right amygdala		19	-5	-21	5	2.77
Main Effect of Emotion						
Right amygdala		22	-1	-17		2.83
Right cingulate gyrus	32	8	24	40	114	5.19
Right inferior frontal gyrus	9	49	9	32	44	3.82
Left amygdala		-19	-5	-17	17	3.75
Left inferior frontal gyrus	10	-34	52	16	10	3.66
Left middle frontal gyrus	9	-56	20	36	7	3.30
Task by Emotion Interaction						
Left superior frontal gyrus	8	-4	21	50	52	4.60
Right inferior frontal gyrus	44	51	11	13	83	4.07
Right amygdala/ parahippocampus	34	15	14	-4	47	3.79
Right inferior frontal gyrus	47	34	22	-10	37	3.37
Right amygdala		26	-8	-16	4	2.81
Neutral Faces: Social Judgment > Sex Discrimination						
Left superior frontal gyrus	8	-4	21	50	73	5.02
Right inferior frontal gyrus	44	52	12	18	108	4.53
Left inferior frontal gyrus	47	-30	25	-14	49	3.63
Right inferior frontal gyrus	47	34	22	-10	40	3.45

Brain Region	BA	Coordinates			k	Z
		x	y	z		
Left inferior frontal gyrus	9	-45	12	22	6	2.96
Right amygdala		22	-5	-17	5	2.87

BA, Brodmann's area.

Table 2

List of Brain Regions Showing a Significant Task by Judgment (i.e., Avoid vs. Approach) Interaction During Processing of Neutral Expressions

Brain Region	BA	Coordinates				k	Z
		x	y	z			
Neutral Faces: Task × Social Judgment Interaction							
Right amygdala		22	-8	-16	23	3.74	
Right superior frontal gyrus	9	34	49	30	17	3.15	
Neutral Faces: Avoided > Approached							
Left medial frontal gyrus	6	-1	-11	65	8	3.25	
Left medial frontal gyrus	6	-8	-4	51	12	2.97	
Right amygdala		22	-8	-21	5	2.67	
Neutral Faces Judged to Be Avoided: Social Judgment > Sex Discrimination							
Left superior frontal gyrus	8	-4	21	50	71	4.90	
Right inferior frontal gyrus	44	51	11	13	104	4.20	
Right inferior frontal gyrus	47	38	22	-14	51	3.91	
Left inferior frontal gyrus	47	-26	21	-18	45	3.71	
Right putamen/globus pallidus		11	4	0	33	3.70	
Right amygdala		22	-5	-17	11	3.28	
Left inferior frontal gyrus	9	-45	12	22	13	3.18	