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Opposing Amygdala and Ventral Striatum Connectivity During Emotion Identification

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Abstract

Lesion and electrophysiological studies in animals provide evidence of opposing functions for subcortical nuclei such as the amygdala and ventral striatum, but the implications of these findings for emotion identification in humans remain poorly described. Here we report a high-resolution fMRI study in a sample of 39 healthy subjects who performed a well-characterized emotion identification task. As expected, the amygdala responded to THREAT (angry or fearful) faces more than NON-THREAT (sad or happy) faces. A functional connectivity analysis of the time series from an anatomically defined amygdala seed revealed a strong anti-correlation between the amygdala and the ventral striatum /ventral pallidum, consistent with an opposing role for these regions in during emotion identification. A second functional connectivity analysis (psychophysiological interaction) investigating relative connectivity on THREAT vs. NON-THREAT trials demonstrated that the amygdala had increased connectivity with the orbitofrontal cortex during THREAT trials, whereas the ventral striatum demonstrated increased connectivity with the posterior hippocampus on NON-THREAT trials. These results indicate that activity in the amygdala and ventral striatum may be inversely related, and that both regions may provide opposing affective bias signals during emotion identification.

Keywords

emotion; amygdala; ventral striatum; fMRI; faces; connectivity

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INTRODUCTION

Identification of the emotional content of a human face is a fundamental and well-studied affective process (Adolphs et al., 1994; Adolphs et al., 1995; Ekman et al., 1969; Sackheim et al., 1978). Considerable evidence from human neuroimaging delineates a network of brain regions involved in face perception, including “core” regions such as the fusiform gyrus (FG) and the superior temporal sulcus (STS) as well as “extended” regions involved in affective processing including the amygdala, the orbitofrontal cortex (OFC), and the insula (Haxby et al., 2000; Vuilleumier & Pourtois, 2007). Convergent evidence suggests that the amygdala plays a unique role in the perception of threat-related signals (Fitzgerald et al., 2006; Gur et al., 2007; Loughhead et al., 2008; Phelps & LeDoux, 2005). Consistent with animal studies of fear conditioning (LeDoux, 2003), the amygdala responds to potentially threatening social signals (Zink et al., 2008), including angry and fearful faces (Breiter et al., 1996; Gur et al., 2002; Morris et al., 1996), perhaps in the context of a more general role as a detector of salience in the environment (Sergie et al., 2008).

Likewise, classical approach versus avoidance studies in animals posit separate dedicated brain systems for the processing of threat- and reward-related signals, and suggest that these two systems work in opposition (Olds, 1960; Olds & Olds, 1963). This opponent-process theory has been supported by electrophysiological experiments in animals, which suggest that reward and affiliation responses in the striatum (and the dopaminergic midbrain to which it is tightly linked) are opposed by aversive responses in the amygdala (Jhou et al., 2009; Rogan et al., 2005). The ventral striatum (VSTR) is a critical node in the reward system, having been associated with reward-related behaviors in both animals and humans (Knutson et al., 2001a; Milner, 1991; Olds and Milner, 1954; Satterthwaite et al., 2007). Previous studies have demonstrated that the VSTR responds to a variety of rewarding stimuli, including both non-social rewards and affiliative, social rewards (Aharon et al., 2001; Berns et al., 2001; Knutson et al., 2001; Glocker et al., 2009; Satterthwaite et al., 2007). The amygdala and VSTR have dense reciprocal connections demonstrated by fiber-tracing studies from animals (Russchen et al., 1985) and humans using diffusion tensor imaging (Kim & Whalen, 2009). However, there has been little research on how the amygdala and VSTR interact during emotion identification in humans.

Previous functional magnetic resonance imaging (fMRI) studies of emotion identification have largely relied upon standard blood oxygen level dependent (BOLD) contrasts, where activation in one condition (i.e., threatening faces) is contrasted with activity in another condition (Loughhead et al., 2008; Satterthwaite et al., 2009). While this method provides a measure of activity in a given region of interest (ROI), it does not allow examination of interactions among regions within an affective network. Functional connectivity (Fox & Raichle, 2007) is a promising technique to examine such interactions by assessing correlations among timeseries data of different regions. Functional connectivity has been useful for delineating large-scale brain networks involved in memory, attention, and executive function (Vincent et al., 2006; Vincent et al., 2008). Furthermore, Vincent and co-authors have demonstrated that fMRI functional connectivity overlaps with anatomic connectivity measured by retrograde staining of neurons in post-mortem tissue slices and other functional metrics such as electroencephalogram (EEG) coherence (Vincent et al., 2007). Nevertheless, few studies have examined the functional connectivity of affective networks implicated in emotion identification. Resting-state functional connectivity studies of the amygdala have demonstrated that its activity is highly correlated with other regions involved in affective processing and face perception, including the FG, temporal regions, and the OFC (Etkin et al., 2009; Roy et al., 2009). Roy et al (2009) also briefly noted negative correlations (often referred to as “anticorrelations”—see Fox et al. (2005)) between the amygdala and striatal regions involved in reward processing. However, there is little data

available regarding how amygdala functional connectivity is modulated by affiliative vs. aversive social signals during emotion identification. While two previous studies conducted psychophysiological interaction (PPI) analyses to investigate amygdala connectivity during affect identification, these studies focused on personality measures (Cremers et al., 2010) or modulation by pain (Yoshino et al., 2010). Thus, despite the longstanding theory of opposed systems of aversive and affiliative social processes, no prior study has directly examined this relationship in an affective task such as emotion identification.

Here, we apply two types of functional connectivity analyses to a sample of 39 healthy people that completed an emotion identification task during BOLD imaging. Acquisition was optimized to resolve the amygdala and VSTR using 2mm isotropic voxels that were acquired in a ventrally-located oblique slab. We hypothesized that the BOLD signal in the amygdala and VSTR would vary in opposition to each other, and differentially interact with the “extended” face perception network involved in affective processing. This hypothesis generates three specific predictions. First, as shown by previous work, we predicted that the amygdala would respond preferentially to threatening (angry or fearful) faces, whereas the ventral striatum would respond to the affiliative aspect of non-threatening faces (as in Satterthwaite et al., 2009). Second, we predicted that functional connectivity across all timepoints (“overall functional connectivity;” (Fox et al., 2005) would reveal that the VSTR and other reward-related regions are anticorrelated with amygdalar activity throughout the task. Finally, we expected that the amygdala and VSTR would have opposed event-related connectivity during the task. Specifically, we expected that the amygdala would have more connectivity during identification of THREAT compared to NON-THREAT faces as measured using PPI (Friston et al., 1997). In contrast, we predicted that the VSTR would demonstrate greater connectivity during identification of NON-THREAT compared to THREAT faces. These predictions were generally supported, providing novel empirical evidence that brain systems governing threat and affiliation work in opposition during emotion identification.

METHODS

Subjects

We studied 44 right-handed participants, who were free from psychiatric or neurologic comorbidity as assessed by the Diagnostic Interview for Genetic Studies (Nurnberger et al., 1994). No subjects were taking psychoactive medication; all had a negative urine drug screen. After a complete description of the study, subjects provided written informed consent. Four subjects were excluded for excessive in-scanner motion and one subject was excluded due to scanner malfunction, resulting in a final sample of 39 subjects (53.8% male, mean age 35.6 years, SD=11.0). All study procedures were approved by the University of Pennsylvania Institutional Review Board.

Task

The emotion identification task is an extension of prior studies in our laboratory (Gur et al., 2002; Gur et al., 2007). It employs a fast event-related design with a jittered inter-stimulus interval (ISI). Subjects viewed 60 faces displaying neutral, happy, sad, angry, or fearful expressions, and were asked to label the emotion displayed (Figure 1A). Stimuli construction and validation are detailed elsewhere (Gur et al., 2002). Briefly, the stimuli were color photographs of actors (50% female) who volunteered to participate in a study on emotion. Actors were coached by professional directors to express a range of facial expressions. For the present task, a subset of intense expressions was selected based on high degree of accurate identification (80%) by raters. Prior research has demonstrated that this task is not confounded by variables such as arousal (Britton et al., 2006); construct validity

has been established in previous work (Carter et al., 2008; Gur et al., 2010; Mathersul et al., 2009). Each face was displayed for 5.5 seconds followed by a variable ISI of 0.5 to 18.5 seconds, during which a complex crosshair (matched the faces' perceptual qualities) was displayed. Total task duration was 10.5 minutes.

Prior experiments in our laboratory have examined fearful, angry, happy, and sad faces separately (Gur et al., 2002a; Gur et al., 2002b; Gur et al., 2007; Loughhead et al., 2008). However, we have noted that threatening faces (angry or fearful) provoke a different pattern of response compared to non-threatening faces (happy or sad) in limbic regions involved in emotion regulation (Loughhead et al., 2008). Subsequent studies have produced similar results, and we have therefore employed the threat versus non-threat distinction (Satterthwaite et al., 2009; Satterthwaite et al., 2010). This is supported by other demonstrations of robust amygdala activation to anger and fear (Stein et al., 2002; Hariri et al., 2000; Suslow et al., 2006; Scott et al., 2008; Ewbank et al., 2008; Beaver et al., 2008). Several studies outside of our group have also categorized angry and fearful faces as threatening (Hariri et al., 2000; Kret et al., 2011; Sripada et al., 2010; Suslow et al., 2006).

Similarly, the grouping of happy and sad together into a category of non-threat is suggested by our previous work (Loughhead et al., 2008; Satterthwaite et al., 2009; Satterthwaite et al., 2010) as well as prior accounts of social emotions, which suggest that sad and happy faces may prompt similar responses because they both are affiliative in nature (Eisenberg et al., 1989; Eisenberg and Miller, 1987; Killgore and Yurgelun-Todd, 2004). As per Bonanno et al. (2008): "the nonverbal expression of sadness is thought to serve important interpersonal functions. From a social-functional perspective expressions of emotion in mammals are evolutionary adaptations to social environments related to the creation and maintenance of social relationships....The facial expression of sadness is thought by some to support group behavior by evoking sympathy and helping responses in others" (page 799). Similarly, Kilgore and Yurgelun-Todd (2004) suggest that a "display of sadness can have a strong regulatory effect over social interactions by leading others to inhibit aggression and exhibit pro-social behavior." A sad face may be viewed as socially submissive or pliable within a social hierarchy; two recent studies demonstrate the rewarding value of social hierarchies (Fliessbach et al., 2008; Zink et al., 2008). Finally, sad faces have been found to activate the striatum in two other neuroimaging experiments (Beauregard et al. 1998; Fu et al., 2004).

This categorization of social stimuli on the basis of threat vs. non-threat finds a theoretical basis in the work of Gray (1990), who postulated the existence of opposing behavioral activation and inhibition systems that governed approach vs. avoidance behaviors in animals, with correlates to affiliation vs. anxiety in humans. This grouping of emotions is at odds with some accounts (Harmon-Jones & Segilman, 2001). However, given competing theoretical accounts, we believe that available data supports our use of threat and non-threat categories.

Interpretation of responses to neutral faces is confounded by the fact that they are ambiguously emotional (Blasi et al., 2009; Kline et al., 1992; Kohler et al., 2003). Therefore, neutral faces were treated as a covariate of no interest in all analyses. The four target emotions were each displayed during 12 trials, resulting in 24 THREAT and 24 NON-THREAT events modeled. No faces were displayed more than once.

Performance analysis

Mean percent correct and response time was calculated for THREAT and NON-THREAT trials. Accuracy was near ceiling for all participants; in order to satisfy assumptions of normality, an arc-sine transformation was applied to accuracy data. Differences in accuracy and response time among the conditions were evaluated with t-tests (2 tailed

fMRI Procedures

Participants were required to demonstrate understanding of the task instructions and the response device during a pre-scan practice session where they completed 10 practice trials. They also completed one trial of practice in the scanner prior to acquisition of fMRI data. Earplugs were used to muffle scanner noise and head fixation was aided by foam-rubber restraints mounted on the head coil. Stimuli were rear-projected to the center of the visual field using a PowerLite 7300 video projector (Epson America, Inc.; Long Beach, CA) and viewed through a head coil mounted mirror. Stimulus presentation was synchronized with image acquisition using the Presentation software package (Neurobehavioral Systems, Inc., Albany, CA). Responses were recorded with a non-ferromagnetic response device (fORP; Current Designs, Inc.; Philadelphia, PA).

Image Acquisition

BOLD fMRI was acquired with a Siemens Trio 3 Tesla (Erlangen, Germany) system with the following parameters: TR/TE=3000/32 ms, FOV=240 mm, matrix= 128×128 , slice thickness/gap=2/0mm (interleaved), 30 slices, effective voxel resolution of $1.875 \times 1.875 \times 2$ mm. Time-series acquisition began with a 12 sec. scan period that was discarded to ensure that the MR signal reached steady-state. Online geometric distortion correction (DiCo) addressed non-linear deformation of echo-planar images due to main magnetic field inhomogeneity and used a sequence based on those of Maxim Zaitsev (Zaitsev et al., 2004). A point-spread-function mapping method (Zeng & Constable, 2002) was implemented and acquired with a reference scan prior to collection of time series data. To reduce partial volume effects in orbitofrontal and medial temporal regions, images were acquired obliquely (approximately -7 degree axial/coronal from the AC-PC line). This resulted in coverage of the temporal lobe and inferior frontal lobes, with good resolution of the amygdala and VSTR (Figure 1B). Prior to time-series acquisition, a 5-minute magnetization-prepared, rapid acquisition gradient-echo T1-weighted image (MPRAGE, TR 1630ms, TE 3.87 ms, FOV 180×240 mm, matrix 192×256×160, effective voxel resolution of $1 \times 1 \times 1$ mm) was collected for anatomic overlays of functional data and to aid spatial normalization to standard atlas space.

Image analysis

fMRI data were preprocessed and analyzed using FEAT (fMRI Expert Analysis Tool) Version 5.9, part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). Images were slice-time corrected, motion corrected to the median image using a tri-linear interpolation with six degrees of freedom (Jenkinson et al., 2002), high pass filtered (100s), spatially smoothed (4mm FWHM, isotropic), and grand-mean scaled. BET was used to remove non-brain areas (Smith, 2002). The median functional and anatomical volumes were coregistered, and then transformed into the standard anatomical space (T1 NMI template, voxel dimensions of $2 \times 2 \times 2$ mm) using tri-linear interpolation. Subject level time-series statistical analysis was carried out using FILM (FMRIB's Improved General Linear Model) with local autocorrelation correction (Woolrich et al., 2001). All events were modeled in the GLM after convolution with a canonical hemodynamic response function; temporal derivatives of each condition were also included in the model. Six rigid body movement parameters were included as nuisance covariates. Mixed-effects analyses using FLAME (FMRIB's local analysis of mixed effects) were performed to conduct one-sample t-tests on subject-level whole-brain contrasts.

We conducted three analyses of the BOLD data to examine different aspects of the task, including: 1) a t-test contrasting THREAT vs. NON-THREAT; 2) a functional connectivity analysis of inter-regional correlations within the BOLD signal in the amygdala across all trials (i.e. overall connectivity); and 3) an analysis examining differential connectivity

between THREAT and NON-THREAT trials using the psychophysiological interaction (PPI) (Friston et al., 1997).

THREAT vs. NON-THREAT

The THREAT vs. NON-THREAT contrast was composed of the component emotion trials of (anger + fear) vs. (happy + sad). The *a priori* ROIs for this contrast were the bilateral amygdala and the bilateral VSTR. These regions were defined using the Harvard-Oxford Subcortical Atlas; the amygdala ROI was thresholded at $p > 0.75$ (2.19 cm^3), and the VSTR ROI was constructed by thresholding the nucleus accumbens (NAc) at $p > 0.25$ (2.09 cm^3). As discussed below, no significant difference between THREAT and NON-THREAT response was seen in the VSTR ROI. Therefore, in order to investigate potential heterogeneity of VSTR response to individual emotions, we extracted signal change for each emotion from left and right VSTR ROIs. These values were submitted to two 5×1 repeated measures ANOVA implemented in STATA (College Station, Texas). We followed the *a priori* analyses with an exploratory voxelwise analysis of THREAT vs. NON-THREAT to identify significant effects outside of the *a priori* ROIs. For all analyses (see below also), we corrected for multiple comparisons using Monte Carlo simulations implemented with AFNI AlphaSim at a cluster height threshold of $Z > 3.09$ and a probability of spatial extent $p < 0.05$. The peak voxel of identified clusters were labeled according to anatomical regions using the Harvard-Oxford Cortical and Subcortical Atlas. For display purposes, all figures were smoothed and rendered using MANGO (J. L. Lancaster and J. Martinez; University of Texas, San Antonio). Coordinates are reported in Montreal Neurological Institute (MNI) coordinate space.

Overall Functional Connectivity Analysis

For the overall connectivity analysis, we extracted the timecourse across all trials from a structurally defined seed region in the bilateral amygdala (as above). To remove confounding sources of correlation, we included three regressors in addition to six motion parameters in the model: mean whole brain signal, mean signal within the cerebrospinal fluid (CSF), and mean signal within white matter (Fox et al., 2005). Visual inspection revealed residual motion artifact manifested as edge effects; these were masked at the group level. Timecourses for each of these confound regressors were extracted from masks defined on an individual subject basis using FSL's automated segmentation tool (FAST). This analysis identified a large, confluent ventral cluster that was positively correlated with the amygdala; local maxima are reported accordingly. Clusters of negative correlation were also identified. Preprocessing, group level analyses, voxelwise thresholding, and display of connectivity maps utilized methods described above. For clarity, clusters > 100 voxels are reported for this analysis.

PPI

In order to investigate how the amygdala and VSTR might provide affective bias signals during emotion identification, we performed a second functional connectivity analysis where differential connectivity between THREAT and NON-THREAT trials was evaluated using the PPI method (Friston et al., 1997). In the PPI analysis model, there were three regressors: 1) the structurally-defined amygdala or VSTR timecourse as above (physiologic regressor); 2) an event-related variable where THREAT trials were coded as +1, and NON-THREAT trials were coded as -1 (psychological regressor); and 3) the interaction term between these physiological and psychological variables (PPI regressor). In order to ascertain whether significant results from this analysis were driven by positive or negative changes in coupling among regions, we constructed two separate first level models using either THREAT or NON-THREAT as the psychological regressor, and extracted connectivity values from clusters that displayed differential THREAT vs. NON-THREAT connectivity. In each PPI

model, trial types that were not part of the psychological regressor were included as covariates of no interest. To constrain multiple comparisons, we evaluated the PPI analyses within a liberal mask of task-active voxels (at $z > 1.64$, uncorrected). Preprocessing, group level analyses, thresholding, and display are otherwise as described above.

Tests to Rule Out Artifactual Anticorrelations

There has been increasing awareness that functional connectivity analyses using the whole brain signal as a confound regressor may produce spurious clusters of anticorrelation (Murphy et al., 2009). Given this concern, we used the steps outlined by Fox et al. (2009) to minimize the risk of artifactual anticorrelations. First, rather than mean-centering the data as a post-processing step, which is more prone to artifactual anticorrelations, we included the global signal as a covariate in the general linear model. Second, in order to obviate the mathematical necessity of negative correlations, we created a modified whole-brain mask that excluded voxels that were either strongly positively or negatively correlated with the amygdala ($Z > 1$ on the group-level map). The remaining uncorrelated voxels formed the new mask for the global signal regressor, and the overall connectivity analysis was re-run. Third, in order to demonstrate that the VSTR anticorrelation is qualitatively present regardless of the inclusion of the global signal regressor, we examined the overall amygdala functional connectivity map without the inclusion of any confound regressors (global signal, white matter, or CSF). As removing these confound regressors significantly weakens the power of the analysis, we examined this map for anticorrelations in the VSTR at a threshold of $p = 0.05$, uncorrected.

RESULTS

Performance

Behavioral results are displayed in Table 1. As expected from previous studies using variants of this task (Gur et al. 2007), subjects identified NON-THREAT (mean accuracy 92.5%, SD 8.5%) faces somewhat more accurately ($t[42] = 2.54$, $\text{corr } p = 0.03$) than THREAT faces (mean accuracy 90%, SD 9.6%). Subjects also responded slightly faster ($t[42] = 3.86$, $\text{corr } p < 0.005$) to NON-THREAT (mean RT 1694 ms, SD 280 ms) than to THREAT trials (mean RT 1713 ms, SD 352 ms).

THREAT vs. NON-THREAT

As predicted, the left amygdala (and right amygdala below threshold) displayed a significant response to THREAT > NON-THREAT: ($Z_{\text{max}} = 3.42$, 10 voxels, coordinates: -22, -10, -14; Figure 2 and Supplementary Figure 1). However, there was no significant differential activation of the VSTR to THREAT versus NON-THREAT; the subsequent 5×1 repeated measures ANOVA likewise did not reveal significant differences between VSTR responses to individual emotions (left: $f[4,38] = 1.10$, $p = 0.36$; right: $f[4,38] = 1.29$, $p = 0.28$). The voxelwise analysis revealed other significant clusters that responded to THREAT > NON-THREAT, including the orbitofrontal cortex, STS, and inferior frontal gyrus (see Table 2). NON-THREAT > THREAT was found to activate the ventromedial prefrontal cortex.

Overall Functional Connectivity

The overall connectivity analysis using the bilateral structural amygdala seed revealed that amygdala activity was strongly correlated with a network of other fronto-limbic regions (see Table 3). The high-resolution acquisition slab allowed fine-grained visualization of amygdala connectivity to the OFC, anterior STS, hippocampus, and FG (Figure 3). Furthermore, as predicted, there were several regions of strong anti-correlation with amygdala activity, including a bilateral cluster in the ventral pallidum and ventral striatum

(VP/VSTR), bilateral ventral tegmental area (VTA), and the medial prefrontal cortex (MPFC).

PPI

The amygdala PPI analysis supported our prediction that the amygdala would have enhanced functional connectivity with other regions in the extended face perception network during THREAT compared to NON-THREAT trials (Figure 4). There was increased connectivity during THREAT > NON-THREAT between the amygdala and the right OFC ($Z_{\max} = 4.51$, 12 voxels, coordinates: 50, 20, -12); a left OFC cluster showed a similar sub-threshold effect. Connectivity for THREAT and NON-THREAT trials extracted from separate first level models revealed that this result was driven by a combination of increased amygdala-OFC connectivity during THREAT trials and below-baseline connectivity during NON-THREAT trials. Notably, there were no regions that exhibited more connectivity with the amygdala on NON-THREAT > THREAT trials.

In order to investigate our hypothesis that the VSTR may oppose the amygdala in affective processing, we conducted a second PPI analysis using the anatomically defined VSTR as the seed region. Consistent with the interpretation that the VSTR may act in opposition to the amygdala, the PPI revealed increased connectivity between the VSTR and right hippocampus / perihippocampal gyrus on NON-THREAT > THREAT trials ($Z_{\max} = 3.46$, 11 voxels, coordinates: 30, 60, -16). This finding resulted from a combination of increased VSTR-hippocampal connectivity on NON-THREAT trials and below-baseline connectivity on THREAT trials (Figure 4). Two clusters that were contiguous at a lower threshold in white matter near the right dorsal thalamus ($Z_{\max} = 4.02$, 20 voxels, coordinates: -22, -26, 14;) and putamen ($Z_{\max} = 3.84$, 13 voxels, coordinates: -24, -9, 18) also displayed NON-THREAT > THREAT connectivity. Importantly, there were no clusters of THREAT > NON-THREAT connectivity using the VSTR seed.

Tests to Rule-Out Artifactual Anticorrelations

When the global signal was extracted from a mask of voxels that were not correlated with the amygdala, VSTR anticorrelation remained robustly present (Supplementary Figure 2). Furthermore, even without the global signal, white matter, or CSF regressors included, the VSTR anticorrelation was still qualitatively present at a lower threshold.

DISCUSSION

This study used high resolution fMRI to investigate the opposing role of subcortical nuclei during emotion identification. We found that the amygdala responds preferentially to threatening (fearful or angry) faces and has increased connectivity during threat trials with the OFC. When connectivity across all trials was examined, we found that the amygdala was strongly anticorrelated with the bilateral VP/VSTR. Furthermore, the VSTR demonstrated greater connectivity with the posterior hippocampus on non-threat trials compared to threat trials. Taken together, these results suggest that evaluation of social stimuli may be governed in part by functionally opposed subcortical nuclei.

Amygdala responds to threat and provides bias signals in an affective network

As expected, we found that the amygdala responded preferentially to threatening (fearful or angry) faces. The amygdala has a well-established role in the detection of social threats (Amaral, 2003; LeDoux, 2003). This literature is consistent in its findings across modalities and designs, including lesion studies in both animals (Amaral, 2003; Rosovold et al., 1954) and humans (Adolphs et al., 1994; Adolphs et al., 2005; Anderson & Phelps, 2001;

Vuilleumier et al., 2004), electrophysiological studies in primates (Gothard et al., 2007), and neuroimaging studies in humans (Morris et al., 1996; Phelps et al., 2001).

While the amygdala can function as a multi-modal threat detector (Isenberg et al., 1999; Phelps et al., 2001), it appears to play a particularly prominent role in the detection of social threat during face perception (Vuilleumier & Pourtois, 2007). Haxby and co-authors (Haxby et al., 2000; Haxby et al., 2002) define a “core” network of regions involved in processing the visual properties of faces, including the FG (Kanwisher, et al., 1997) and STS (Pelphrey et al., 2005). Beyond these core regions, additional regions form an “extended” network (including the amygdala, OFC, and insula) that responds to the affective content of emotional faces (Haxby et al., 2000). Studies in non-human primates demonstrate that the amygdala has ample anatomic connections to these regions and others including the hippocampus (Amaral & Price, 1984; Amaral et al., 2003; Russchen et al., 1985). These findings have subsequently been confirmed in humans using diffusion tensor imaging (Kim & Whalen, 2009). With high-resolution fMRI functional connectivity, our results provide a detailed corroboration of these findings, with the strongest connectivity seen between the amygdala and the FG, STS, OFC, and hippocampus.

During emotion identification of threat-related expressions, we found that the amygdala has enhanced connectivity with the right OFC (and left OFC at a sub-threshold level). Although threat-related modulation of the face perception network by the amygdala has been suggested (Haxby et al., 2000), this increase has not been demonstrated previously. Prior studies have examined how threat modulates dorsal cortical regions outside of the face perception network (Williams et al., 2006) or thalamocortical networks (Das et al., 2005). Similarly, one prior study examined interactions within the core and extended network, but only contrasted emotional and neutral faces, rather than types of emotional faces (Fairhall & Ishai, 2007).

VSTR is anticorrelated with and may oppose the amygdala

In addition to examining the regions that were positively correlated with the amygdala, we explored regions that exhibited negative functional connectivity with the amygdala. In particular, we investigated whether regions involved in social affiliation including the VSTR would display a negative correlation with the amygdala, consistent with an oppositional role in affective processing. We found bilateral clusters in the VP/VSTR that were strongly anticorrelated with the amygdala. Notably, several of the other regions that displayed a significant anticorrelation are also associated with reward, including the VTA and the MPFC (Dreher et al., 2005; Knutson et al., 2001b; Knutson & Wimmer, 2007; Olds & Milner, 1954).

The VP/VSTR cluster spanned several specific nuclei, including the NAc, the ventral caudate, and the ventral pallidum. While the role of the NAc and caudate in reward and affiliation is well established, recent evidence suggests that the VP also may play an important role in motivational processes (Napier & Mickiewicz, 2010): the VP activates in response to monetary rewards (Pessiglione et al., 2007), cues for drug rewards (Childress et al., 2008), and also is over-active in patients with Parkinson’s Disease who gamble compulsively (Cilia et al., 2008). Using a PPI analysis with the bilateral anatomic VSTR as a seed, we found that the VSTR displays increased connectivity with the right posterior hippocampus on NON-THREAT compared to THREAT trials. This result is consistent with previous research indicates that the posterior hippocampus responds to viewing of affective faces (Britton et al., 2006) as well as encoding of subsequently remembered faces (Nelson et al., 2003). Overall, this data indicates that VSTR may oppose the aversive, threat-related signals of the amygdala in response to non-threatening, affiliative social stimuli.

Opposing affective bias signals from subcortical nuclei

The idea that neural systems governing threatening and affiliative social stimuli exist in opposition to each other has existed for almost 50 years, stemming originally from approach vs. avoidance behavioral research in rats (Olds, 1960; Olds & Olds, 1963). Lesion studies in rats and in non-human primates have reinforced this notion: lesions of the amygdala can result in a decrease in aggressive and fear-related behaviors, and a significant increase in affiliative, pro-social behaviors (Amaral, 2003; Rosvold et al., 1954). Such behaviors range from increased sociability to frank hypersexuality; these behaviors have led others to posit that the threat-detection systems of the amygdala may counterbalance and check the reward system that drives such affiliative behaviors (Amaral, 2003; Bauman et al., 2004). Studies of humans with amygdala lesions also demonstrate a diminished ability to recognize signals of social threat such as a fearful face (Adolphs et al., 1995; Adolphs et al., 1998). Blinded interviews with a patient who had suffered a bilateral amygdala lesion revealed a lack of emotion in recounting past traumas and a surprising predominance of affiliative responses, consistent with a system of social reward-seeking no longer opposed by aversive learning (Tranel et al., 2006). These lesion studies have been supported by electrophysiological studies in animals, which demonstrate opposing signals for threat and safety in the amygdala and striatum (Rogan et al., 2005). This is anatomically plausible, given data from fiber-tracing studies from animals (Russchen et al., 1985) and humans using DTI (Kim & Whalen, 2009), which show dense reciprocal connections between the amygdala and the VSTR.

However, there have been no prior studies in humans that investigated opposing functional connectivity during a social task. Roy et al. (2009) reported (but did not focus upon) anticorrelations between the amygdala and striatum. Our group has also observed anticorrelations between these two regions across multiple tasks; given the reproducibility of such findings across data sets, we suspect that the negative correlation between the amygdala and VSTR reflects properties of intrinsic brain organization, rather than a response to specific task demands. This is consistent with our finding that the anticorrelation between the amygdala and VP/VSTR does not appear to be modulated by trial type in the PPI analysis. Due to increasing concern regarding artificial anticorrelations in functional connectivity analyses (Murphy et al., 2009), we conducted several analyses recommended by Fox et al. (2009) confirming that these clusters of negative correlation between the amygdala and VP/VSTR were not an artifact of image processing. The current study supplements this literature to suggest that one function of these anatomically connected but functionally anticorrelated regions is to provide opposing affective bias signals during emotional processing. This result accords with work that suggests that amygdala may send similar bias signals to enhance sensory processing during affective vision (Keil et al., 2009; Sabatinelli et al., 2009).

Limitations and Summary

Several limitations of this study should be acknowledged. First, our grouping of stimuli into THREAT and NON-THREAT, while suggested by earlier work, may obscure relevant differences between emotions. For example, an angry face represents a direct threat indicated by gaze, but a fearful face indicates a more ambiguous environmental threat. Second, the VSTR cluster did not show a NON-THREAT > THREAT response; while other studies using these stimuli and a different design have demonstrated such effects (Satterthwaite et al., 2009), they have been relatively subtle and may be susceptible to type II error. Future tasks may require more immediately rewarding stimuli (monetary rewards, attractive faces) to demonstrate VSTR activation. Third, while the anticorrelation between the amygdala and the VSTR is highly supportive of an opposing affective process, this study does not allow us to rule out other possibilities or roles for these systems. As suggested by other investigators (Krishnan & Nestler, 2008), the view that the amygdala represents

negative valence and the VSTR represents positive valence is likely simplistic; both the VSTR (Zink et al., 2003; Zink et al., 2004; Zink et al., 2006) and amygdala (Zald, 2003; Sergerie et al., 2008) also have been shown to respond to salience as well as valence. Future work is needed to disambiguate the amygdala response to threat and salience. Fourth, while the slab acquisition allowed high-resolution coverage of ventral brain regions, it prohibited sampling of dorsal brain regions are also known to be involved in emotion identification (Vuilleumier & Pourtois, 2007). Finally, as in other studies of emotion identification, small differences in behavioral performance may have influenced the imaging results.

Notwithstanding these limitations, this study demonstrates that subcortical nuclei such as the amygdala and VSTR may play opposing roles in affective processing. While the amygdala demonstrates increased activity and connectivity during threat identification, the VSTR is anticorrelated with the amygdala across all trials and displays greater connectivity while identifying non-threatening faces. These results link previously disparate literatures regarding aversive and affiliative processing, and extend to humans previous findings from electrophysiological studies in animals (Rogan et al., 2005). We hope in future studies to examine the anticorrelated relationship between the VSTR and amygdala under different task demands, and investigate how these opposing bias signals may influence learning and motivation over time. Understanding the reciprocal signaling of threat and reward systems is pivotal for elucidating social communication and behavior. These results may have implications for understanding neuropsychiatric disorders, which are defined in part by an imbalance between aversive and reward-related learning, especially depression (Pizzagalli et al., 2009) and negative symptoms in schizophrenia (Wolf, 2006).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Research Highlights

- The amygdala responds during the identification of threatening emotions.
- The amygdala is anticorrelated across all time points with brain regions involved in reward including the ventral striatum, ventral tegmental area, and medial prefrontal cortex.
- The amygdala displays differential connectivity with the orbitofrontal cortex under threat, whereas the ventral striatum has more connectivity with the posterior hippocampus during non-threat emotion identification.
- Taken together, these findings suggest that subcortical nuclei may in part oppose each other during emotion identification.

Figure 1.

A. Emotion identification task. Subjects performed an emotion identification task in which they identified the facial affect displayed. Five emotional labels were available, including two non-threatening affects (happy and sad), two threatening affects (angry and fearful), as well as neutral. Faces were displayed for 5.5 seconds and separated by a variable interval (500ms-18.5 seconds) during which a complex crosshair was displayed. Each emotion was displayed 12 times; there were 24 THREAT and NON-THREAT trials each. **B.** Image acquisition. To allow for high resolution sampling of limbic regions involved in affective processing, we acquired data in an oblique slab that provided excellent detail of the amygdala and ventral striatum.

Figure 2.

A. THREAT vs. NON-THREAT contrast. As expected, the left amygdala responds to THREAT > NON-THREAT. A subthreshold effect was present in the right amygdala as well. **B.** Extracted signal change (versus baseline) from the significant cluster in the left amygdala for each individual emotion.

Figure 3.

Amygdala functional connectivity. Activity in a structurally defined bilateral amygdala seed demonstrates robust correlation with a network of limbic regions, including the hippocampus, anterior superior temporal sulcus (STS), orbitofrontal cortex (OFC), and fusiform gyrus. The amygdala was strongly anticorrelated with reward-related regions including the ventral pallidum / ventral striatum (VP/VSTR), ventral tegmental area (VTA), and medial prefrontal cortex (MPFC).

Figure 4. Psychophysiological interaction (PPI) analyses. The amygdala demonstrated increased connectivity on THREAT trials with the right orbitofrontal cortex (OFC); a subthreshold effect was also seen in the left OFC. The ventral striatum demonstrated increased connectivity during NON-THREAT trials with the right posterior hippocampus.

Table 1

Task Performance

Trial Type	Mean Percent Correct (SD)	Mean Response Time (SD)
THREAT	90.0 (10.0) %	2339 (285) ms
Angry	90.2 (11.2) %	2403 (423) ms
Fearful	89.7 (11.2) %	2600 (471) ms
NON-THREAT	93.1 (8.7) %	2502 (357) ms
Happy	98.2 (3.4) %	2339 (298) ms
Sad	88.2 (15.9) %	2615 (396) ms

Table 2

Exploratory Voxelwise Analysis of THREAT vs. NON-THREAT

Cluster	Hem	Max Z	Voxels	Peak (x, y, z)
<i>THREAT > NON-THREAT</i>				
Fusiform gyrus	B	7.18	4,157	10, -78, -10
OFC / Insula / IFG	L	7.01	3,098	-50, 28, 2
Superior temporal gyrus	L	5.60	747	-56, -44, -2
OFC / Insula	R	4.94	661	34, 22, -2
<i>NON-THREAT > THREAT</i>				
Ventromedial PFC	B	5.30	2,019	4, 56, 0

B=bilateral

R=right

L=left

Table 3

Overall functional connectivity with bilateral amygdala

Cluster	Hem	Max Z	Voxels	Peak (x, y, z)
<i>Positive Correlations</i>				
Large ventral cluster	B	10.6	17,519	26, -4, -18
Local Maxima:				
Amygdala	R	10.6		26, -4, -18
Amygdala	L	9.59		-22, -6, -16
Parahippocampal gyrus	L	7.51		-20, -28, -16
Temporal pole	R	4.61		56, 10, -22
Fusiform gyrus	R	3.93		26, -82, -18
Lateral occipital cortex	R	3.46		36, -86, -8
Fusiform gyrus	L	3.45		-32, -72, -6
Lateral occipital cortex	R	3.33		46, -72, -8
Fusiform gyrus	L	3.29		-30, -66, -18
Subcallosal cortex	B	3.29		0, 18, 4
Medial OFC	L	3.21		-10, 56, -10
Lateral occipital cortex	L	3.21		-48, -66, -14
Insula	L	3.18		-32, -14, 12
<i>Negative Correlations</i>				
Medial prefrontal cortex	B	6.09	825	2, 42, 12
Frontal pole	R	5.57	499	30, 58, 12
VP/VSTR	R	5.52	298	14, 8, -2
Frontal pole	L	4.92	276	-30, 50, 4
VP/VSTR	L	5.44	227	-18, 0, -4
Inferior frontal gyrus	R	4.66	145	54, 28, -8
Ventral Tegmental Area	B	5.60	128	-4, -16, -8
Inferior temporal gyrus	R	6.08	109	52, -22, -32

B=bilateral

R=right

L=left