# Neocortical Modulation of the Amygdala Response to Fearful Stimuli

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**Background:** *The cortical circuitry involved in conscious cognitive processes and the subcortical circuitry involved in fear responses have been extensively studied with neuroimaging, but their interactions remain largely unexplored. A recent functional magnetic resonance imaging (fMRI) study demonstrated that the engagement of the right prefrontal cortex during the cognitive evaluation of angry and fearful facial expressions is associated with an attenuation of the response of the amygdala to these same stimuli, providing evidence for a functional neural network for emotional regulation.*

**Methods:** *In the current study, we have explored the generalizability of this functional network by using threatening and fearful non-face stimuli derived from the International Affective Picture System (IAPS), as well as the influence of this network on peripheral autonomic responses.*

**Results:** *Similar to the earlier findings with facial expressions, blood oxygen level dependent fMRI revealed that whereas perceptual processing of IAPS stimuli was associated with a bilateral amygdala response, cognitive evaluation of these same stimuli was associated with attenuation of this amygdala response and a correlated increase in response of the right prefrontal cortex and the anterior cingulate cortex. Moreover, this pattern was reflected in changes in skin conductance.*

**Conclusions:** *The current results further implicate the importance of neocortical regions, including the prefrontal and anterior cingulate cortices, in regulating emotional responses mediated by the amygdala through conscious evaluation and appraisal.* Biol Psychiatry 2003; 53:494–501 © *2003 Society of Biological Psychiatry*

**Key Words:** Emotion regulation, fear, prefrontal cortex, anterior cingulate cortex, amygdala, functional magnetic resonance imaging

## Introduction

The importance of cognition in the experience and regulation of emotions was originally explored by a core group of behavioral psychologists that included William James, Walter Cannon, Stanley Schacter, Jerome Singer, Stuart Valins, and Richard Lazarus. The collective work of these pioneers illustrated not only the importance of physiologic responses and subsequent feedback to the development of our emotions, but also how cognition and conscious evaluation of the conspiring events transform nonspecific bodily states into the experience of very specific emotions. Now, technological advances, especially noninvasive functional neuroimaging, have given us the tools to explore the brain mechanisms underlying both the unconscious physiologic responses to arousing stimuli and the conscious, cognitive modulation of these responses that gives each experience a distinct emotional label and allows us to modulate our unique emotional experiences.

The robust interconnections of the amygdala, which mediates the myriad physiologic and behavioral responses associated with distinct emotions, most notably fear, and of the prefrontal cortices, which are critical to various executive processes, are believed to play a major role in the integration of emotional and cognitive processes (Barbas 2000). Although the majority of the direct connections are found between the orbital prefrontal cortex (PFC) and the amygdala, other prefrontal regions, such as the ventral and dorsal prefrontal cortices, can potentially interact with the amygdala via reciprocal projections to the orbital PFC as well as via both thalamic and striatal circuits. Furthermore, whereas the orbital PFC has been most commonly implicated in "low-level" representation of reward or punishment values (O'Doherty et al 2001), the more lateral (i.e., ventral and dorsal) PFCs have been implicated in facilitating more complex adaptive behavioral responses to changes in reward or punishment values (Cools et al 2002). Therefore, the ability to modulate our own unique emotional experiences and responses likely depends on the interactions of the amygdala with these more lateral prefrontal cortices.

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The origins and terminations of the direct projections between the amygdala and prefrontal cortices, in either direction, also provide insight to the relative influence of each region over the other (Carmichael and Price 1995; McDonald et al 1996). Cortical projections to the amygdala originate primarily in the upper, feed-forward layers of the cortex and terminate on amygdala interneurons that are largely inhibitory. In contrast, amygdala projections terminate in the deeper, feedback layers of the PFC. Thus, the amygdala is situated to provide direct influence over prefrontal cortical output, whereas the latter is situated to modulate the response of the former through indirect inhibitory connections.

The work of Damasio and colleagues has provided compelling evidence for the role of the PFC in regulating and integrating our emotional experiences. Collectively, their studies of patients with well-circumscribed brain lesions have substantiated the role of the amygdala in the perceptual and autonomic processing of emotional stimuli and that of the PFC in the appraisal and adaptive manipulation of these same stimuli (Bechara et al 1999; Damasio 1994). Functional neuroimaging studies of emotion processing and inhibitory control have also revealed an important modulatory role of the PFC, especially in the right hemisphere, on amygdala responses (Beauregard et al 2001; Nakamura et al 1999; Narumoto et al 2000).

In line with this evidence, Hariri et al (2000) have recently implicated the right PFC in modulating the response of the amygdala during cognitive evaluation of certain emotional stimuli. Using functional magnetic resonance imaging (fMRI), they found that whereas perceptual processing of angry and fearful facial expressions is associated with a strong bilateral amygdala response, linguistic evaluation (i.e., labeling) of these same stimuli is associated with an attenuated amygdala response and a correlated increase in the response of the right ventral PFC. In an ensuing study, they reported that this amygdala attenuation is associated with a corresponding attenuation of autonomic reactivity as measured by changes in skin conductance (Kapler et al, unpublished data). Thus, engagement of the right PFC appears to modulate the response of the amygdala, perhaps representing a system by which humans can control and direct their emotional responses through appraisal and evaluation of their experiences.

The purpose of the current fMRI study was to explore the generalizability of this functional network. Rather than the affective facial expressions used in the earlier study, we employed a small subset of complex visual scenes depicting fear, anger, or threat derived from the International Affective Picture System (IAPS), a standardized and well-characterized collection of visual images designed to evoke either neutral, positive, or negative emotional states (Lang et al 1997). In identifying the response patterns of the amygdala and PFC during both the perceptual and cognitive processing of IAPS stimuli, as well as autonomic changes via simultaneous skin conductance recordings, we sought to extend our understanding of the dynamic interplay between limbic and neocortical circuits that contribute to the functional network underlying our adaptive emotional behavior.

## Methods and Materials

### *Subjects*

Eleven healthy subjects (five male, six female, mean age = 32 years) gave written informed consent and participated in the study according to the guidelines of the National Institute of Mental Health Institutional Review Board. All subjects were free of neurologic, psychiatric, or substance abuse problems or history of other medical problems or medical treatment relevant to cerebral metabolism and blood flow. All subjects were strongly right-handed (Edinburgh Handedness Inventory $> 80$).

### *Stimuli*

Twelve different IAPS stimuli were used as targets, six representing threats of natural origin (i.e., dogs, sharks, snakes, spiders) and six threats of artificial origin (i.e., guns, car accidents, plane crashes, explosions). The mean ($\pm$ SEM) valence and arousal on a 9-point scale, where 1 represents maximum negative and 9 maximum positive valence or arousal, for all IAPS stimuli used were $3.13 \pm .20$ and $6.40 \pm .13$, respectively, based on previous data from large samples of healthy volunteers (Lang et al 1997). Simple geometric shapes (circles, vertical and horizontal ellipses) were used as control stimuli.

### *Experimental Paradigm*

The paradigm consisted of two experimental and one control condition. Both experimental conditions involved presentation of IAPS stimuli but differed in how subjects evaluate the stimuli (Figure 1). In the "match" condition, subjects were required to match one of two simultaneously presented IAPS stimuli with an identical target IAPS stimulus. "Match" is designed to evoke an amygdala response, as subjects tend to process stimuli based on perceptual characteristics but need not judge or interpret the type of threat represented. In the "label" condition, subjects were required to label the same target IAPS stimuli by selecting one of two simultaneously presented words. In contrast to the prior study by Hariri et al (2000), which used clearly identifiable facial expressions and affective labels such as "angry" and "afraid," we utilized the more abstract labels "Natural" and "Artificial." We felt that these labels were more easily applicable to the relatively complex and variable IAPS stimuli, which can represent multiple emotions, such as fear and anger. "Label" is designed to engage higher cognitive and linguistic processes subserved by neocortical regions, as subjects must interpret the origin of the displayed threat based on acquired knowledge and experience. As a

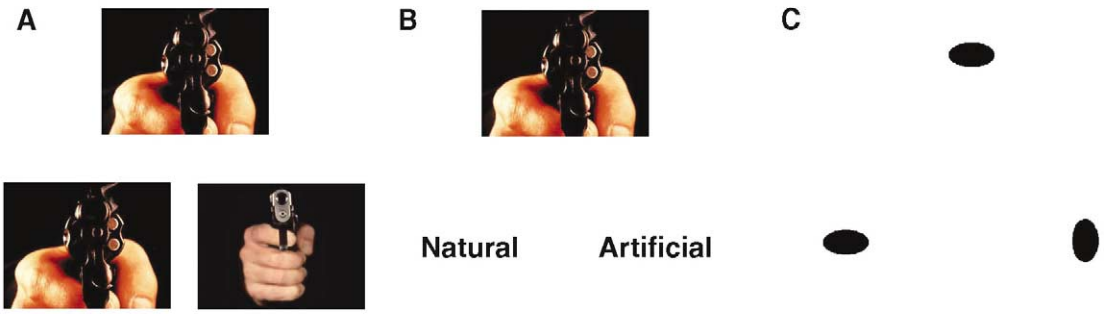


Figure 1. Experimental paradigm. Subjects performed three tasks while undergoing functional magnetic resonance imaging. Each experimental condition presented threatening or fearful International Affective Picture System stimuli, but differed in how the subjects evaluated the stimuli. **(A)** In the first condition ("match"), subjects viewed a target picture and had to select which one of two pictures was identical to the target. **(B)** In the second condition ("label"), subjects viewed the same target pictures but had to judge which of two linguistic labels, "Natural" or "Artificial," best described the content of the pictures. **(C)** As a sensorimotor control, the subjects viewed a target oval shape and chose which of two ovals matched the target.

sensorimotor control task, subjects were required to choose which of two geometric shapes matched a simultaneously presented target shape. This control task was designed to eliminate common sensorimotor responses only and not to control for level of difficulty or arousal, or to exactly mirror the perceptual characteristics of each experimental task. In fact, the experimental tasks are designed to explore both difficulty, as represented by cognitive processes and PFC engagement, as well as arousal, as represented by amygdala engagement and skin conductance load (SCL) responses. Thus, we employed a relatively simple control to allow for such exploration.

The fMRI paradigm consisted of nine experimental blocks: two blocks each of "match" and "label" interleaved with five control blocks, each lasting for 32 sec, for a total scan time of 4:48 min. Each block began with a brief (2-sec) instruction statement: "Match Pictures," "Label Pictures," or "Match Forms." Each experimental block consisted of six target images, three of each threat origin (natural or artificial). All images were presented sequentially, with no interstimulus interval, for a period of 5 sec and in a randomized fashion for all conditions. The order of the paradigm was counterbalanced across subjects. During imaging, subjects responded by pressing one of two buttons with their dominant hand, allowing for the determination of accuracy and reaction time.

## *Physiologic Responses*

To ascertain the relationship between changes in amygdala response and autonomic reactivity, we measured SCL (Dawson et al 2000) during the acquisition of functional scans in six (three male, three female) of the 11 subjects. We did not have access to fMRI compatible skin conductance recording equipment in the other five subjects. Skin conductance load was recorded from the palmar surface of the middle phalanx of the index and middle digits of the left hand using Ag/AgCl electrodes. Digitized (24-bit) signals were acquired using a radio frequency shielded cable, processed through a remote preamplifier, and recorded at 20 Hz on a personal computer (Contact Precision Instruments Inc., Cambridge, MA). Mean percent changes in SCL from adjacent blocks of the sensorimotor control task were determined for both "match" and "label" conditions. By calculating task-specific mean percent change in SCL from adjacent control blocks, we sought to minimize the influence of signal drift and task-independent phenomenon over the course of the scan.

## *Image Acquisition*

Each subject was scanned using a GE Signa 3T scanner with a real-time functional imaging upgrade (General Electric Medical Systems, Milwaukee, WI). An automated shim procedure was applied to minimize possible magnetic field inhomogeneities. Functional image planes were prescribed using a T2-weighted sagittal scout. Functional images were acquired with a gradient echo, echo-planar imaging (EPI) sequence, and covered 24 axial slices (4 mm thick, 1 mm gap) that began at the cerebral vertex and encompassed the entire cerebrum and the majority of the cerebellum (time to repetition/time to echo = 2000/28 msec, field of view = 24 cm, matrix = 64 × 64). All scanning parameters were selected to optimize the quality of the blood oxygen level dependent (BOLD) signal while maintaining a sufficient number of slices to acquire whole-brain data. Before the collection of fMRI data for each subject, we acquired a reference EPI scan that we visually inspected for artifacts (i.e., ghosting) as well as good signal across the entire volume of acquisition, including the medial temporal lobes. The fMRI data from all 11 subjects included in this study were cleared of such problems.

## *Data Analysis*

Whole-brain image analysis was completed using the general linear model in SPM99 (Friston et al 1995). For each scan, images for each subject were realigned to the first volume in the time series to correct for head motion. All 11 data sets met our criteria for high quality and scan stability, as demonstrated by small ($<2$ mm in all three planes) motion correction, and were included in

Table 1. Significant BOLD fMRI Responses for All Comparisons and Correlation Analyses

| | Talairach Coordinates (x, y, z) | Cluster Size (no. of voxels) | *Z* Score |
|---|---|---|---|
| Main Effects of Task | | | |
| "Match" vs. control | | | |
| Amygdala | 26, −5, −12 | 6 | 2.49 |
| | −22, −5, −12 | 4 | 2.79 |
| Ventral prefrontal cortex (BA 47) | ±45, 18, −5 | 60/35 | 2.55/2.22 |
| Broca's area (BA 44/45) | −45, 23, 17 | 77 | 3.00 |
| Fusiform/parahippocampal gyri | ±23, 48, −10 | 155/109 | 10.74/6.93 |
| "Label" vs. control | | | |
| Ventral prefrontal cortex (BA 47) | ±45, 18, −5 | 69/85 | 3.61/2.93 |
| Broca's area (BA 44/45) | −45, 23, 17 | 102 | 5.30 |
| Anterior cingulate cortex (BA 32) | 0, 24, 40 | 11 | 3.51 |
| Fusiform/parahippocampal gyri | ±23, 48, −10 | 106/69 | 9.70/3.09 |
| Direct Comparisons | | | |
| "Match" > "Label" | | | |
| Amygdala | ±26, −8, −12 | 9/7 | 2.29/2.27 |
| Fusiform/parahippocampal gyri | 38, −41, −11 | 41 | 2.92 |
| "Label" > "Match" | | | |
| Ventral prefrontal cortex (BA 47) | −38, 22, −5 | 19 | 2.45 |
| | 38, 18, −5 | 16 | 2.83 |
| Broca's area (BA 44/45) | −49, 22, 22 | 27 | 2.51 |
| Anterior cingulate cortex (BA 32) | 0, 24, 40 | 51 | 3.61 |
| Correlation Analyses | | | |
| Positively correlated (with response of left amygdala) | | | |
| Amygdala | 24, −6, −16 | 6 | 4.70 |
| Broca's area (BA 44/45) | −40, 18, 12 | 15 | 5.40 |
| Fusiform/parahippocampal gyri | −24, −70, −12 | 14 | 5.46 |
| | 32, −52, −12 | 16 | 5.45 |
| Negatively Correlated (with response of left amygdala) | | | |
| Ventral prefrontal cortex (BA 47) | 34, 44, 4 | 18 | 4.70 |
| Anterior cingulate cortex (BA 32) | 0, 30, 28 | 12 | 3.32 |

Coordinates represent voxels in each region with the most significant magnitude and spatial extent ($p < .05$, corrected across a small volume of interest). BOLD, blood oxygen level dependent; fMRI, functional magnetic resonance imaging; BA, Brodmann's area.

subsequent analyses. These realigned images were then spatially normalized into a standard stereotactic space (Montreal Neurologic Institute template) using a 12-parameter affine model. Finally, these normalized images were smoothed to minimize noise and residual differences in gyral anatomy with a Gaussian filter, set at 8 mm full-width at half-maximum, producing an effective spatial resolution of 12.5 × 12.7 × 11.4 mm. Voxel-wise signal intensities were ratio normalized to the whole-brain global mean.

These preprocessed data sets were analyzed using second-level random effects models that account for both scan-to-scan and subject-to-subject variability. This approach allows for a more critical and stringent exploration of BOLD responses than traditional fixed-effects models that only account for scan-to-scan variability. For each subject and scan, predetermined condition effects at each voxel were calculated using a *t* statistic, producing a statistical image for each contrast: 1) "match" > control; and 2) "label" > control. These individual contrast images were then used to determine task-specific regional responses using one-sample (main effects of task) and paired *t* tests (direct comparisons). A statistical threshold of $p < .05$, corrected for multiple comparisons across a small volume of interest, was used to identify significant voxels for all comparisons.

A correlation analysis was used to quantitatively evaluate task-specific interactions between the response of the amygdala and neocortical regions (Hariri et al 2000). For this, the BOLD signal for the entire time-course was extracted from the maximally activated voxel of the amygdala, resulting from the contrast of "match" > control, and used as a covariate of interest in a separate analysis to determine condition-specific regressions over the entire time-course at every voxel, generating a statistical parametric map for regions of either positive or negative correlation (Elliott and Dolan 1998; Friston et al 1997). A statistical threshold of $p < .05$, corrected for multiple comparisons, was used to identify significant correlations.

Behavioral and physiologic data were analyzed using repeated-measures analysis of variance and post hoc comparisons using Fisher's Paired Least Significant Difference test.

## Results

### *BOLD fMRI Responses*

Table 1 provides a summary of significant BOLD responses for all comparisons and correlation analyses. In comparison with the control condition, there was a strong

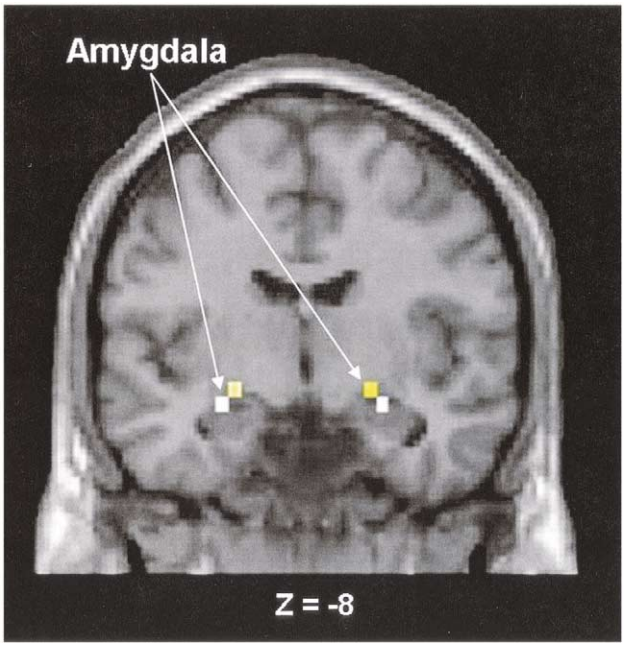


Figure 2. Statistical parametric map illustrating relatively increased activity ($p < .05$, corrected) in bilateral amygdala during the perceptual processing of fearful and threatening scenes ("match" > "label"). See Table 1 for complete regional Talairach coordinates and associated statistics.

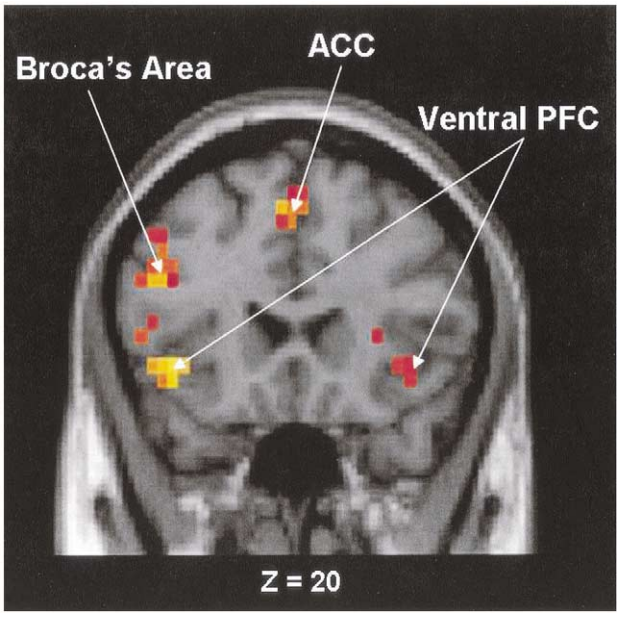


Figure 3. Statistical parametric map illustrating relatively increased activity ($p < .05$, corrected) in bilateral ventral prefrontal cortex (PFC), anterior cingulate cortex (ACC), and Broca's area (Brodmann's area 45) during the linguistic evaluation of fearful and threatening scenes ("label" > "match"). See Table 1 for complete regional Talairach coordinates and associated statistics.

bilateral amygdala response during "match" that was absent during "label." An opposite pattern was observed in bilateral ventral PFC (Brodmann's area [BA] 44/45, 47), with a larger response during "label" than "match." There was a strong response in the anterior cingulate cortex (ACC) (BA 32) during "label" that was absent during "match." These task-specific regional response patterns were further reflected in direct comparisons of the two tasks (Figures 2 and 3). In addition, although both "match" and "label" were associated with significant responses in bilateral ventral temporal cortex, including the fusiform and parahippocampal gyri as well as Broca's area (BA 44/45), the responses of the former regions were greater during "match" and those of the latter region during "label" (Figure 3).

Correlation analyses between regions exhibiting task-specific responses revealed significant positive correlations between the response of the left amygdala, which had the most robust response during "match," and that of the right amygdala as well as those of the bilateral fusiform gyri and Broca's area. Significant negative correlations were identified between the response of the left amygdala and those of the right ventral PFC as well as the ACC.

### *Behavior and Physiology*

There was no difference in mean accuracy between tasks, with subjects performing at ceiling (100%) for both "match" and "label." In contrast, there was a significant difference in mean reaction time [$F(1,20) = 41.98$, $p < .0001$], with subjects responding faster during "match" (1851.13 msec ± 34.29 SEM) than "label" (2644.120 msec ± 117.36 SEM).

There was no main effect of task on mean percent change in SCL in our small sample [$F(1,10) = .19$, $p = .67$]. Nevertheless, there was a larger SCL increase (mean percent change ± SEM) from adjacent sensorimotor control blocks during "match" (1.06 ± .6%, $p = .08$) than during "label" (.56 ± 1.0%, $p = .60$).

## Discussion

Consistent with the previous study by Hariri et al (2000) using angry and fearful facial expressions, perceptual processing ("match") of threatening and fearful scenes was associated with a strong bilateral amygdala response, whereas cognitive evaluation ("label") of these same stimuli was associated with an attenuation of this response and a correlated increase in the response of the right ventral PFC. In addition, there was an increase in the response of the ACC during "label." This pattern of task-specific regional engagement was reflected in comparisons of both tasks with the sensorimotor control as well as in direct task comparisons. Correlation analyses

further confirmed this functional pattern by illustrating that the response of the amygdala was inversely correlated with those of the right ventral PFC and ACC.

A similar ACC response was not reported in the prior study by Hariri et al (2000), but technical parameters did not allow for coverage of this anterior region during functional imaging; however, the engagement of the ACC during "label" is not surprising and most likely reflects this region's regulatory or modulatory influence on the amygdala occurring either in series with or parallel to those of the PFC. Given the highly interconnected nature of the ACC with both limbic and prefrontal structures (Barbas and Pandya 1989), this brain region is ideally situated to mediate top-down regulation of the amygdala during cognitive evaluation of fearful stimuli. Several studies using modalities such as electroencephalogram, positron emission tomography, and fMRI have implicated the ACC in both normal and dysfunctional emotional self-control (Allman et al 2001) as well as tasks requiring executive control and evaluation of both stimuli and behavioral responses (Paus 2001).

Skin conductance load data in a small subset of subjects revealed a corresponding trend in autonomic reactivity to the observed BOLD fMRI response of the amygdala, with a larger increase from baseline during "match" in comparison with "label." This suggests that changes in the response and interaction of the amygdala and neocortical regions, such as the right ventral PFC and ACC, influence physiologic processes critical to the fear response. Kapler et al (unpublished data) have previously described similar and statistically significant task-specific SCL changes in response to facial expressions.

In addition to the negative correlations observed between the response of the amygdala to that of both the right ventral PFC and ACC, we observed several interesting positive correlations. The positive correlation between the response of the left and right amygdala suggests that these distinct collections of nuclei work in concert, possibly through direct reciprocal connections via the anterior commissure and/or symmetrical thalamic inputs, to produce an orchestrated behavioral response to fearful and threatening stimuli. The positive correlation observed between the amygdala and fusiform/parahippocampal gyri likely reflects excitatory feedback from the amygdala to these object-specific processing regions, in an effort to improve recognition and refine behavioral responses (Morris et al 1998); however, this relationship may also reflect a common, but not physiologically linked, increase in activity in both regions as a response to the presentation of different numbers of visual stimuli (three vs. one) during the "match" and "label" tasks. Finally, and perhaps most interestingly, we observed a positive correlation between the response of the left amygdala and that of Broca's area. This may reflect the relative cognitive demands or load associated with processing IAPS stimuli such as the verbal translation of visual information.

More specifically, the meaning of the stimuli represented in the IAPS, which in comparison with facial expressions are more complex in structure, are generated through experience and acquired knowledge. For example, unlike facial expressions of fear and anger, an individual is not inherently fearful of a pointed weapon but only becomes so after negative exposure, either direct or indirect, to the stimulus. The processing of stimuli with such acquired rather than intrinsic significance may then be more dependent on interactions of cognitive and linguistic systems, such as Broca's area, with limbic circuitry. The positive correlation we observed between the amygdala and Broca's area may reflect such a relationship and form of affective processing.

Additionally, the nonaffective, abstract labels ("natural" and "artificial") employed in this study during the linguistic evaluation of IAPS stimuli likely engage left hemisphere lateralized language processing regions, such as Broca's area, to a greater extent than the affective labels ("angry" or "afraid") used during the evaluation of facial expressions in the prior study of Hariri et al (2000). Such linguistic processing differences may also contribute to the observed positive correlation between the amygdala and Broca's area. As previous studies (Nagae and Moscovitch 2002; Windmann et al 2002) have implicated a critical role for the right hemisphere in processing affective words, it will be of interest to directly compare the use of nonaffective and affective labels during the linguistic evaluation of emotional stimuli on the functional interactions of the amygdala with both the left and right PFC.

A potential experimental confound in our current study is the difference in the number of stimuli presented during the affective tasks. Thus, the increased response of the amygdala observed during "match" relative to "label" may simply reflect the greater number of affective stimuli (three scenes vs. one) viewed by the subjects during each task. In fact, we did observe a greater response in object-processing areas, such as the fusiform and parahippocampal gyri, during "match" in comparison with "label." These relative regional response differences, as mentioned previously, may reflect the augmentation of the response of these regions through excitatory feedback from the amygdala (Morris et al 1998). Moreover, several functional imaging studies have revealed amygdala responses during the passive viewing of single emotional stimuli, including both facial expressions and IAPS stimuli (Davis and Whalen 2001). Amygdala responses have also been observed during "masked" presentations of such

emotional stimuli, where subjects are not even consciously aware of their appearance (Whalen et al 1998).

To directly explore the potential contribution of the number of emotional stimuli on the response of the amygdala, we had an independent cohort of eight healthy male volunteers undergo fMRI during two perceptual processing tasks involving the presentation of either one or three IAPS stimuli. Subjects either matched one of two IAPS stimuli with a simultaneously presented target (identical to the current "match" task) or determined whether a single IAPS stimulus represented an "Indoor" or "Outdoor" scene. We have found that such discrimination during the latter task involves relatively simple perceptual processing and is associated with a robust amygdala response (Hariri et al, unpublished data). The IAPS stimuli employed were identical to those of the current study, and the order of the tasks was counterbalanced across subjects. Most importantly, analysis of the fMRI data revealed that there was no difference in the response of the amygdala during the perceptual processing of either one or three IAPS stimuli. Therefore, we feel it unlikely that the task-specific changes we report in the response of the amygdala simply reflect the number of stimuli presented during each task. Rather, we believe that there is compelling evidence (see below) to suggest that these changes reveal critical and dynamic interactions of the amygdala and neocortex that underlie the active, conscious regulation of our emotional responses.

Functional MRI studies involving the appraisal and evaluation of emotional stimuli (Nakamura et al 1999; Narumoto et al 2000) or self-regulation of emotional responses (Beauregard et al 2001) have also implicated similar regions of the right ventral PFC and ACC in such emotional modulation. The engagement of the right ventral PFC has also been associated with response inhibition (Garavan et al 1999; Konishi et al 1999b) as well as set shifting during the Wisconsin Card Sorting Test (Konishi et al 1999a). Whereas our findings, along with the former studies, implicate these neocortical regions in modulating emotional behavior specifically, the findings of the latter studies suggest a more extensive and generalized role for these regions in multiple forms of behavioral inhibition.

Importantly, animal models have revealed a similar inhibitory role for the PFC during emotional behaviors. For example, prefrontal lesions interfere with the extinction of conditioned fear responses (Quirk et al 2000) and reversal learning (Baxter et al 2000; Schoenbaum et al 2000). Furthermore, direct stimulation of prefrontal inputs inhibits both neuronal firing in (Rosenkranz and Grace 1999, 2001, 2002) as well as emotional behaviors initiated by the amygdala (al Maskati and Zbrozyna 1989; Zbrozyna and Westwood 1991). In addition, input-specific, long-term depression in the lateral amygdala can be induced during theta frequency stimulation, representative of cortical inputs (Heinbockel and Pape 2000), and long-term potentiation in the PFC is associated with maintenance of fear extinction (Herry and Garcia 2002). Finally, in an opposite pattern, amygdala activity during conditioned freezing behavior in mice has been shown to suppress spontaneous prefrontal neuronal activity (Garcia et al 1999).

Collectively, our current findings along with those of earlier investigators highlight the importance of neocortical networks, specifically the right ventral PFC and ACC, in modulating the response of the amygdala and, in turn, the autonomic nervous system. Such dynamic interactions provide a system by which humans can control and direct their emotional responses through conscious appraisal and evaluation of their experiences. Likewise, imbalances or breakdowns in these interactions may contribute to disorders of emotional behavior such as anxiety, panic, phobia, and posttraumatic stress disorder.

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