

Limbic Activation and Psychophysiologic Responses to Aversive Visual Stimuli: Interaction with Cognitive Task

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We mapped regional brain activity and peripheral psychophysiologic responses, occurring in response to evocative emotional stimuli, and examined whether task instructions could modulate limbic activation. Ten subjects viewed pictures with neutral or aversive emotional content during simultaneous measurement of peripheral psychophysiology and brain activity with [15 O]water positron emission tomography (PET). Cognitive task was manipulated by having the subjects rate the pictures or perform a recognition memory task. Aversive pictures, relative to neutral pictures, increased cerebral activity in bilateral amygdala, thalamic/hypothalamic area, midbrain,

and left lateral prefrontal cortex, along with greater skin conductance responses (SCR). Voxel-by-voxel correlation coefficients between regional brain activity and SCR showed significant positive correlation peaks in the thalamus and right amygdala. Limbic activation was significantly greater during the rating condition compared to the recognition condition, suggesting that when task demands modify emotional responses, this modulation can occur at the level of limbic activity.

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Emotional responses are regulated by limbic regions of the brain, such as the amygdala, hypothalamus, limbic midbrain, and limbic cortex (anterior cingulate, orbitofrontal, temporal polar, medial temporal). The cytologi-

cal organization of various limbic structures and their inter-connectivity, suggest that these regions comprise a functional network (Alheid and Heimer 1988). Extracellular recording, electrical stimulation and lesion studies implicate the amygdala and related limbic structures in the expression or modulation of emotional responses (Adolphs et al. 1995; LeDoux 1986; McGaugh et al. 1996). Animal and human studies suggest that these same regions modulate autonomic components of emotional responses (Bechara et al. 1995; LaBar et al. 1995; Mangina and Beuzeron-Mangina 1996). Recent functional neuroimaging studies have demonstrated that the amygdala and cortico-limbic structures respond to fearful/aversive stimuli (Irwin et al. 1996; Reiman et al. 1997; Taylor et al. 1998; LaBar et al. 1998; Morris et al. 1999a), perception of facial expressions of fear and disgust (Breiter et al. 1996; Phillips et al. 1997; Whalen et al. 1998), perception of linguistic threat (Isen-

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berg et al. 1999) and of non verbal emotional vocalization (Morris et al. 1999b).

Emotional responses are highly variable and influenced by diverse factors such as arousal, temperament, prior expectation, context and task demands — factors which may affect a controlled experiment. For example, the skin conductance response (SCR) to a social scene will vary depending upon the narrative context in which the scene is viewed (Geen and Rakosky 1973; Lazarus 1984). In a study examining the effects of emotional stimulus content on memory, we noted that amygdaloid activation disappeared when the task changed from rating stimuli to recognizing them, suggesting an effect of task instruction on emotional processing (Taylor et al. 1998). Although our finding was confounded by an order effect, the modulation of emotional responses by cognitive states has been demonstrated in numerous behavioral studies (Folkman and Lazarus 1985; Smith et al. 1993). They were also consistent with observations by Lane and colleagues (1997) that reported a differential pattern of limbic activation when emotional responses were evoked during different cognitive task. Reiman and colleagues (1997) findings of different regional cerebral blood flow (rCBF) patterns associated with memory-generated vs. film-generated sadness, also support the notion of cognitive states modulating emotional responses. In this new study, we sought to investigate a hypothesis about one cognitive factor and how it might influence limbic activation.

The current [^{15}O]water positron emission tomography (PET) study was designed to identify components of the limbic brain (extended amygdala, thalamus, hypothalamus) associated with an emotional and psychophysiological response to aversive pictures. As converging validation, we also simultaneously recorded peripheral autonomic measures of emotional responses (Venables and Martin 1967) and applied a voxel-by-voxel correlation analysis in order to identify regions of the brain controlling these peripheral responses. To examine whether modification of task instructions would attenuate the activity in this network, we manipulated task instructions by having subjects either rate pictures in some scans or recognize pictures in other scans, predicting that when task instructions shifted from assessing emotional content to recognizing pictures, activation of central limbic regions would be attenuated.

METHODS

Subjects

Ten healthy female volunteers, were recruited from community advertisements (mean age = 26.1, range: 19–44). Subjects had no past or current history of

chronic medical or neurological illness. Absence of any Axis I psychiatric disorder was verified by a structured clinical interview (Spitzer et al. 1988). Because greater autonomic responses (Kring and Gordon 1998) and regional CBF differences (Gur et al. In press) have been documented in females, we studied only female subjects to maximize our ability to detect significant effects. All subjects gave written, informed consent after explanation of the experimental protocol, as approved by the local Institutional Review Board.

Task Design

The experimental design consisted of two orthogonal factors (stimulus valence and task), each with two levels (negative and neutral, rating and recognizing, respectively). During the PET scans, subjects viewed pictures from one of two sets, selected from the standardized International Affective Picture System (IAPS) (Lang and Greenwald 1988) and supplemented from our own collection (approximately 30%). For the supplemental pictures, valence ratings obtained in a separate experiment were comparable to ratings from the IAPS (Taylor et al. unpublished data). We selected *negative* pictures which elicited emotional responses of fear/disgust, such as graphic pictures of facial mutilation, wounds, dead bodies, etc. *Neutral* pictures were selected which did not elicit strong emotions, positive or negative, such as people at rest, faces with neutral expressions, and benign scenes. Since processing of faces recruits specific brain regions (Dolan et al. 1996; Haxby et al. 1996), we matched the neutral and negative pictures with respect to the number of slides portraying faces and human figures.

The tasks consisted either of the subjects rating the pictures for aversive content (*rating*) or determining whether the pictures had been previously presented (*recognition*). In the *rating* phase, subjects received instructions to rate each picture verbally on a 5-point scale (5 = extremely disgusting and 1 = not at all disgusting), indicating the degree to which they found the image disgusting. Within the rating phase, all pictures were novel. In the *recognition* phase, subjects were instructed that some slides would be repeated from the previous blocks, and they were to verbally indicate whether or not they recognized the slide, using a 3-point scale: "1" for previously seen; "3" for uncertainty; and "5" for not previously seen. Approximately 50% of the slides in the recognition blocks were repeated from the rating phase. During the rating phase the subjects were not told that pictures would later be repeated in a recognition task. The pictures (35 mm slides) were presented on a back-projecting slide carousel (Kodak Model 570AF), on a screen suspended 40 cm from the subject, subtending 15 degrees of viewing angle. View-

ing duration was 5 sec for each slide, with no inter-stimulus interval.

Each subject saw 10 blocks of pictures and the stimuli presented in each block were either all negative slides or all neutral slides. The first two blocks consisted of the rating task, but without actual image acquisition, allowing the subjects to become comfortable with the scanner. Eight actual PET scans were acquired for each subject, beginning with the third block and continuing through the tenth and final block of pictures. The first two PET scans consisted of rating followed by four scans on the recognition task, and then two scans in the rating task.

Data Acquisition

Psychophysiological data were recorded using an MP-100 psychophysiological monitoring system (BioPac Systems, Santa Barbara, CA). Skin conductance was recorded using Ag/AgCl electrodes filled with isotonic NaCl unibase electrolyte, attached to the volar surface of the second phalanx of the first and third fingers of the left hand. Heart rate (HR) was monitored via EKG with an automated R-wave detector and filtered with a 60-Hz notch filter.

The subjects underwent PET scans in a Siemens CTI 931-08/12 scanner (CTI Inc., Knoxville, TN) which acquires 15 slices over an axial length of approximately 10 cm. Before emission scanning, subjects had a transmission scan measured by external $^{68}\text{Ge}/^{68}\text{Ga}$ ring sources. For each emission scan, subjects were given an intravenous (i.v.) bolus injection of 50 mCi of $^{15}\text{O}[\text{H}_2\text{O}]$. Data were collected in a single 60 sec frame beginning 5 sec after the arrival of the radioactivity in the brain. Lights were dimmed and ambient noise (from cooling fans) was minimal. Eight PET scans separated by 12 minutes were acquired for each subject. Stimuli presentation began 5 sec prior to image acquisition, and continued for the first 30 sec of each scan (uptake phase of the tracer), so as to maximize changes in the PET signals associated with the task of interest (Cherry et al. 1993). The second 30 sec of each scan always contained neutral stimuli, and subjects continued the task begun 35 sec prior.

Data Analysis

Analysis of the PET data first employed a standardization process for each image that enabled averaging of image data both within and across subjects. Automated routines proportionally normalized images to the mean of global activity (arbitrarily set to 1000), and individual images within each subject were co-registered to the fourth scan to correct for head movement occurring between scans (usually less than 2 mm translation and less than 2 degrees rotation). A non-linear transformation was then applied to each image to standardize individual anatomy

according to a reference brain atlas (Minoshima et al. 1992, 1993, 1994). Standardized images were smoothed with a 3D Gaussian filter, yielding a final, effective FWHM of around 14 mm. Difference images were made by subtracting the scan obtained in one condition from that obtained in another condition. Mean differences were expressed as Z-scores, using the between-subjects variance (Friston et al. 1991; Worsley et al. 1992).

We performed analyses of negative versus neutral in each phase (rating and recognition) and analysis of the interaction of emotional content and task context, which we analyzed as a compound difference image, i.e., rating (negative minus neutral) minus recognition (negative minus neutral).

Planned or "A Priori" Analysis. We searched for significant activations on the basis of regional *a priori* hypotheses as well as an image-wide search unconstrained by regional predictions. For the *a priori* search region, we delimited a 120 cc volume of brain in the following areas: medial frontal cortex (including rostral anterior cingulate gyrus), bilateral amygdaloid area, hypothalamus, and thalamus. Within this volume, a significance threshold of $Z = 3.6$ yielded a false positive expectation of 0.05 (Worsley et al. 1992). We accepted $3.6 > Z > 3.09$ as trend-level activation ($p < .001$, uncorrected) in the region of interest, in order to permit comparisons with other published work. We also performed targeted volume of interest (VOI) analyses on bilateral amygdaloid complexes by placement of a 15.75 mm sphere at the stereotactic coordinates of the amygdala ($x, y, z = \pm 24, -4, -16$) in the Talairach and Tournoux atlas (Talairach and Tournoux 1988).

Since the diameter of the amygdala is closer to 10 mm, we selected a slightly larger region to capture the individual variation in amygdala size and location, not corrected for by our warping routines. From our first study (Taylor et al. 1998), we also tested a VOI in the lingual gyrus (13.5 mm sphere; $x, y, z = -12, -87, -7$). For our image-wide search, we reported activation foci that exceeded a corrected probability of $p < .05$, generally corresponding to a Z-score of around 4.4 for our image sets (Worsley et al. 1992). Six out of eighty individual scans were not analyzable due to technical difficulties (stimulus presentation or tracer injection), without affecting the total number of subjects or conditions analyzed.

Psychophysiological Correlation. To identify possible neural substrates of the peripheral SCR, we performed a voxel-by-voxel, within-subjects correlation analysis (Minoshima et al. 1995). For each voxel within each subject, we calculated a correlation coefficient between normalized pixel counts and the integrated SCR for that scan, for a total of eight observation pairs.

The estimated correlation coefficients were then transformed to Z-values using Fisher's Z-transformation.

tion. The transformed maps were averaged across subjects, which further assured a normal distribution of the final summed correlation Z-map and increased the sensitivity of the analysis. Based on the theory of Gaussian random fields (Worsley et al. 1992), we determined a statistical threshold for the final correlation map. Pixel-by-pixel correlation maps were analyzed with the same *a priori* defined ROIs, used in the analysis of activation peaks. This analysis has the advantage of providing good protection against outlier values leveraging correlation coefficients and causing false positives in a statistical parametric map.

Psychophysiological Data. The changes in skin conductance for each block of pictures were analyzed by analysis of variance of the peak conductance change as well as the conductance level integrated over the first 30 sec epoch of image presentation (relative to a 5 sec baseline prior to image presentation). Heart rate was calculated beat-to-beat and averaged over this interval. Analysis of psychophysiology data was performed offline with AcKnowledge software (BioPac Systems, Santa Barbara, CA). Statistical analysis outside of custom-written software was performed with StatView (Abacus Concepts, Berkeley, CA).

RESULTS

Behavioral and Psychophysiological Results

Our subjects experienced the negative pictures as significantly more disturbing than the neutral pictures ($t = 19.5$, $df = 9$, $p < .0001$) (Table 1). During the recognition phase, subjects demonstrated non-significantly greater accuracy in the classification of the negative pictures ($81 \pm 12\%$ correct \pm S.D. for neutral, and $88 \pm 6.0\%$ for negative pictures; $t = 1.7$, $df = 9$, $p = .12$).

Changes in skin conductance confirmed the differential emotional response to the pictures. While there was no difference in baseline measures of skin conductance prior to stimuli presentation, the negative stimuli elicited a larger maximal increase in SCR as compared to neutral stimuli (Rating, negative vs. neutral: 1.03 ± 0.58 vs. 0.52 ± 0.36 ; Recognition, negative vs. neutral: 0.96 ± 0.80 vs. 0.81 ± 0.56 , $\mu\text{mho} \pm$ S.D.; Effect of valence: $F [1,9] = 9.76$, $p = .01$). There was a significant interaction of stimulus type by condition, such that the effect of negative pictures during rating was greater than the effect of negative pictures during recognition for conductance peak and integral ($F [1,9] = 10.21$, $p = .01$; $F [1,9] = 5.46$, $p = .04$, respectively). We found no effects — main or interaction — for stimulus type and phase on heart rate.

Neuroimaging Results

Activation Peaks. We examined the effects of negative versus neutral content of the stimuli during both the rating and recognition phases. During the rating phase, a significant activation focus in our area of interest centered on the limbic diencephalon, contiguous with the mid-thalamic nuclei and extended amygdala. A trend-level focus in the midbrain also appeared, just outside our area of interest, but continuous with the diencephalic focus (Figure 1). A volume of interest analysis with spherical VOIs placed at the stereotactic coordinates of the amygdala confirmed activation in the right and left amygdaloid regions ($t = 2.16$, $df = 9$, $p = .03$; $t = 2.21$, $df = 9$, $p = .03$, respectively) (see Figure 2).

In addition to the limbic activation, we also observed trend-level activation of the left middle frontal gyrus, as well as significant relative decreases in activity in the striate cortex. Trends to relative decrease were also noted in the lingual gyrus, orbital gyrus, and left cerebellum. During the recognition phase, negative emotional content produced significant activation in the

Table 1. Subjective and Psychophysiological Responses to Aversive Stimuli

Parameter	Rating		Recognition	
	Neutral	Negative	Neutral	Negative
Subject responses				
Ratings of disgust	1.0 \pm 0.02	3.6 \pm 0.46 ^a	—	—
Recognition accuracy			81 \pm 12%	88 \pm 6
Psychophysiological measurements				
Skin conductance				
Baseline	5.19 \pm 2.01	5.10 \pm 1.77	5.47 \pm 1.92	4.89 \pm 1
Max amplitude increase	0.52 \pm 0.36	1.03 \pm 0.58 ^{b,d}	0.81 \pm 0.56	0.96 \pm 0
Integrated conductance	10.06 \pm 11.59	23.44 \pm 16.55 ^{c,d}	16.99 \pm 15.7	23.1 \pm 2
Heart Rate	73.8 \pm 14.2	74.6 \pm 15.4	73.1 \pm 12.8	74.8 \pm 1

^aNegative greater than neutral, $p < .0001$.

^bNegative greater than neutral, $p < .005$.

^cNegative greater than neutral, $p < .05$.

^dEffect of negative = neutral during encoding greater than during recognition, $p < .04$.

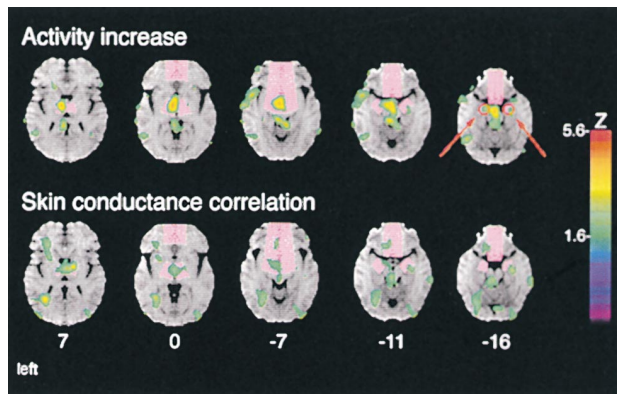


Figure 1. (A) Activity increase while viewing aversive stimuli occurs in limbic regions relative to viewing neutral pictures. The pink shading indicates the *a priori* search region; red arrows indicate the location of a spherical volume of interest for the amygdaloid complex. (B) Correlation map for activity and skin conductance, calculated on a voxel-by-voxel basis for all scan conditions, and Z-transformed. For this Figure as well as Figure 3, all Z-scores > 1.65 are displayed and superimposed upon a reference MRI scan. Numbers on the bottom row indicate mm above (or below) the bi-commissural line.

right middle frontal gyrus (Table 2). We did not note any trend level activations or decreases during this phase.

Interaction Effects. We examined the interaction between task and emotional valence by subtracting the effects of rating (negative minus neutral) from the effects recognition (negative minus neutral). We confirmed our prediction in the thalamic/hypothalamic region ($-1, 3, -4$; $Z = 3.95$) and the right amygdala ($24, -8, -14$; $Z = 3.85$), both of which had greater activation for the aversive stimuli during the rating phase compared to the recognition phase. The VOI analysis confirmed this result in the right amygdala ($t = 2.95$, $df = 9$, $p < .01$).

Our prior study had identified an interaction in the lingual gyrus, such that the effect of aversive stimuli was

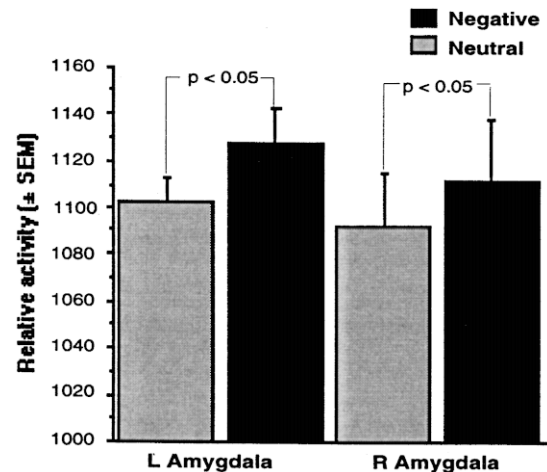


Figure 2. Activation of right and left amygdala during rating of pictures, normalized to mean of 1000 for gray-matter pixels. Activity calculated for spherical volume of interest of approximately 11 mm centered on amygdala coordinates derived from the Talairach and Tournoux (1988) atlas.

greater during the recognition phase. As Figure 3 indicates, a confluent area of activation from the lingual gyrus through the striate cortex confirmed this prediction, with a significant focus in the striate cortex ($1, -82, 11$; $Z = -4.49$), and a trend level focus near the interaction reported in our first study ($-10, -82, -9$; $Z = -3.52$). Placement of the *a priori* VOI derived from this study showed a trend toward interaction ($t = 1.64$, $df = 9$, $p = .07$).

Correlations. We examined voxel-by-voxel correlations between cerebral activity and the integrated SCR response. Within *a priori* defined regions, we found significant positive correlations between activity and skin conductance in the right thalamus ($15, -6, 14$, $Z = 3.6$) and trend level activations in the limbic diencephalon and midbrain area. As Figure 1 demonstrates, the correlation peaks overlapped the activation regions. There were no significant correlation peaks outside *a priori* de-

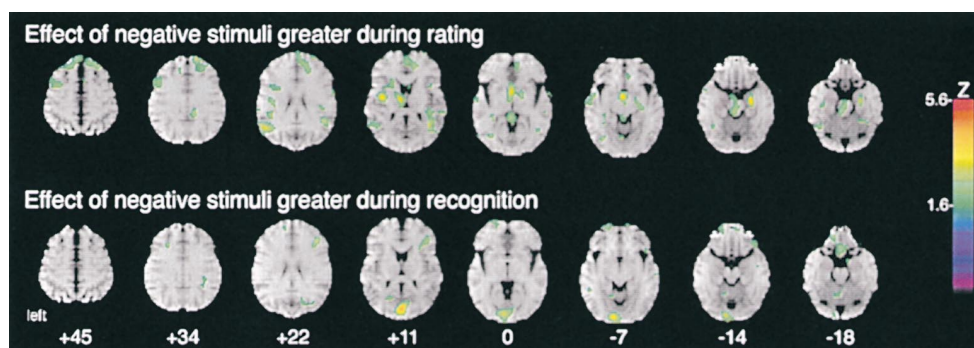


Figure 3. Effects of picture content interact with task. The top row shows the effects of negative emotional content (negative minus neutral) greater during rating than during recognition (the difference of two difference images). The bottom row demonstrates where the effect of negative content is greater during recognition, relative to rating.

Table 2. Negative Pictures Minus Neutral Pictures During Each Phase

Region ^a	Rating phase		Recognition phase	
	(x, y, z)	Z-score	(x, y, z)	Z-score
		Relative increase		
L middle frontal g (44/9)	-51, 10, 27	4.12	39, 28, 18	4.83
R middle frontal g (46)				
Diencephalon	-6, -6, 0	4.50		
Midbrain	1, -8, -14	4.13		
		Relative decrease		
Striate cortex	1, -82, 11	-6.24		
L lingual g (18)	-12, -82, -7	-4.20		
Orbital g (11)	1, 23, -18	-4.09		
L cerebellum	-35, -60, -29	-4.04		

This and table 2 list maxima/minima of foci of significant difference. Activation foci are shown with Z-scores > 3.5 , for regions with a priori hypotheses, and $Z > 4.0$, for regions without a priori hypotheses. The x, y and z coordinates derive from the Talairach and Tournoux atlas (Talairach and Tournoux 1988): right/left, anterior/posterior and superior/inferior, respectively. The numbers in parentheses refer to topographic regions based on the Brodman area labels from the atlas.

finer regions (significance threshold of $p < .05$ corrected for multiple comparisons).

Since we had no significant effect of negative content on heart rate, we did not analyze correlation maps. Furthermore, heart rate decreased across the course of the scanning session, so that session effects on cerebral activity would seriously confound any observed correlations. We did not observe a session effect for SCR.

DISCUSSION

Aversive emotional content activated a network of limbic regions including thalamus, extended amygdala, and hypothalamus in our subjects. The subjective reports and the skin conductance data further confirmed that the activation reflected the emotional response to the aversive pictures. Significantly lower activity in the right amygdala and limbic diencephalon was observed when the cognitive task was altered, confirming our prediction that limbic activation would be modulated by a change in cognitive processing. Similar modulation of activity in limbic cortex (anterior cingulate cortex) was reported by Lane and colleagues (1997), when subjects switched from assessing the emotional impact to judging non-affective qualities of a picture. Directing attention to personal experience (self monitoring) employed, could explain the different limbic region that got activated in this study (anterior cingulate cortex vs. amygdaloid region).

Modulation of limbic activity observed in these studies may reflect mechanisms to suppress or modify emotional responses during the cognitive task. While "suppression" of emotions could conceivably occur without a change in the underlying limbic activity, our findings suggest an active process that directly reduces limbic responses. It is important to note, however, that some of

the observed difference could have been due to the repetition of some slides during the recognition phase and additional studies will be needed to separate the effects of modulation and the effects of repetition (see discussion below). Additional work will be required to determine if this modulation originates in another structure, active but not apparent in our study, which projects to the amygdaloid complex and diencephalon, such as the entorhinal cortex/hippocampal formation (LeDoux 1993; Phillips and LeDoux 1992), or anterior cingulate cortex (Lane et al. 1997). Alternatively, modulation could occur within one of the activated regions, such as the extended amygdala.

We found prefrontal activation during rating and recognition of emotional stimuli which lateralized with the task. The activation trend in left middle frontal region during rating corresponded very closely to a focus from our first study. In a combined analysis of both data sets (18 subjects), we found a significant activation focus ($Z = 4.7$) in this region during the rating phase for the aversive visual stimuli. Left middle frontal gyrus activation by emotional content during the perception of the stimuli may reflect the appraisal process (rating the pictures) for the aversive stimuli, or alternatively, the finding may represent a component of affect regulation by the lateral prefrontal cortex (Stuss and Benson 1986). Although experiments with surface EEG have suggested that aversive stimuli elicit right prefrontal cortical activity (Davidson 1998; Kalin et al. 1998; Tomarken et al. 1992), differences in methodology (blood flow versus brain electrical activity) or duration of emotional state (persistent vs. transient) could account for our somewhat different findings. During the recognition phase, subjects did activate the right middle frontal gyrus. The right prefrontal cortex has been repeatedly associated with recognition/retrieval from episodic memory (Tulving et al. 1994) and activation by

aversive relative to neutral pictures may reflect the process of picture recognition. Since these prefrontal regions exhibited a different lateralized pattern similar in each task, they may be candidates for regions which modulate activity in the extended amygdala as discussed above.

Alternative interpretations of the decreased limbic activation during recognition have to be considered as well. Previous reports have noted desensitization in the amygdala across an experimental session (Breiter et al. 1996; Taylor et al. 1998). Our counterbalanced, ABBA design would have protected against the effects of desensitization over the experimental session, and we found no session effect when the first and the last "rating" scans were compared. It is possible that the repetition of some of the pictures during the recognition task might have caused habituation in the amygdala weakening the activation signal. It is not likely however, that this could explain all of the findings, since 50 % of the pictures viewed during each recognition scan were still novel to the subject, and we also selected aversive pictures with particularly strong negative content to avoid desensitizing subjects. Furthermore, skin conductance increases that were present during the recognition of the negative pictures argue against general desensitization. Additional studies, e.g., presenting previously seen pictures during the rating phase, will be able to fully assess the potential contribution of habituation to the observed modulation.

We have also found evidence of an interaction between the emotional activation and visual recognition in the striate cortex and lingual gyrus, replicating prior findings of greater activation for the recognition phase, compared to the rating phase. The lingual gyrus carries out early cortical elaboration of visual stimuli, and therefore would have been recruited for the perception of the complex visual stimuli (Livingstone and Hubel 1988; Van Essen et al. 1992). We have suggested that interaction in the lingual gyrus represents an enhanced processing of emotionally-laden stimuli during recognition (Taylor et al. 1998). Others have also reported differential activity in the visual cortex in response to emotionally salient stimuli (Kosslyn et al. 1996; Lang et al. 1998; Paradiso et al. 1997; Reiman et al. 1997).

Although in our earlier study we did not find differential activation of these regions during the rating phase, in our current study we noted a relative *decrease* of activity in the striate cortex and lingual gyrus during rating. Taken together, these findings add to a growing body of data showing that early visual processing is subjected to significant modulatory influences, particularly with respect to selective processing (Corbetta 1993; Watanabe et al. 1998).

Limbic regions, such as the amygdaloid nuclei, send projections to the early visual cortex (Amaral and Price 1984) and may be one source of modulation observed in

the visual cortex. It is also possible that the instructions to attend to a subjective internal state ("how disgusting the image is") during the rating phase diverted the subject's attention from external stimuli, thereby decreasing primary visual processing. The interaction pattern in lingual gyrus and striatal cortex could also have been contributed to by differences in visual processing between the tasks. While our slides were matched with respect to the number of pictures portraying faces and human figures, they were not matched on visual complexity, luminescence, or color scheme, which could have contributed to the larger activation in these regions. On the other hand, recognition of negative pictures was easier than recognition of neutral pictures, as our subjects reported that they recognized the negative pictures more readily. With easier recognition, one would generally expect less activation in these regions for negative stimuli (Grasby et al. 1994).

The correlation maps for cerebral activity and peripheral skin conductance provide direct evidence linking negative emotional responses, peripheral autonomic changes and specific CNS structures. Correlations occurred in the same diencephalic regions where we observed increased activity in response to the emotional pictures. The thalamic focus of correlation appeared in the region of the anterior nucleus of the thalamus, which exchanges projections with the anterior cingulate cortex; however, activity from medial thalamic nuclei, which exchange projections with the amygdala, might also have contributed to the correlation map in Figure 1. The closely proximate lateral hypothalamus, may have also contributed to the observed correlations (Jansen et al. 1995). While we cannot adequately resolve individual thalamic nuclei with this PET methodology, a focus centered over a limbic nucleus reinforces the face validity of the results. Mangina and Beuzeron-Mangina (1996) found that direct stimulation of the human amygdala elicited ipsilateral SCRs, however the difference between direct stimulation and the more "physiologic" method used in our study could account for the differences in laterality. Others reported that amygdaloid lesions abolish conditioning of the SCR by emotional stimuli, while sparing the skin conductance component of the orienting response (Bechara et al. 1995). While links between the emotional response and the SCR, and between limbic structures and emotional response, have been established, the current findings provide direct neuroimaging evidence linking emotions and the peripheral autonomic response with central structures in humans.

Our results suggest a number of interesting directions for future investigation. The current study included female subjects only, thus studies with males will have to confirm the generalizability of these results. We observed activation in both amygdalae, but the task specific interaction and the correlation with the

SCR were observed predominantly on the right. Others have noted laterality (Mangina and Beuzeron-Mangina 1996) or differential activation in right vs. left amygdala (Morris 1996; Morris et al. 1998). Whereas it is possible that this merely reflects the low experimental power, it is also possible that activation thresholds or the time course differ for right and left amygdalae, or that they play differential roles in the modulation of emotions. There is a need to further define the role of left middle frontal gyrus in the perception of emotional stimuli, and the right middle frontal gyrus involvement in recognition. With that in mind, we believe that our current findings provide strong evidence for task specific activation of an emotional network within limbic regions, and direct evidence of limbic diencephalon involvement in the peripheral SCR to emotional stimuli.

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