Activation of Anterior Paralimbic Structures during Guilt-Related Script-Driven Imagery

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Background: *Several recent neuroimaging studies have examined the neuroanatomical correlates of normal emotional states, such as happiness, sadness, fear, anger, anxiety, and disgust; however, no previous study has examined the emotional state of guilt.*

Methods: *In the current study, we used positron emission tomography and the script-driven imagery paradigm to study regional cerebral blood flow (rCBF) during the transient emotional experience of guilt in eight healthy male participants. In the Guilt condition, participants recalled and imagined participating in a personal event involving the most guilt they had ever experienced. In the Neutral condition, participants recalled and imagined participating in an emotionally neutral personal event.*

Results: *In the Guilt versus Neutral comparison, rCBF increases occurred in anterior paralimbic regions of the brain: bilateral anterior temporal poles, anterior cingulate gyrus, and left anterior insular cortex/inferior frontal gyrus.*

Conclusions: *These results, along with those of previous studies, are consistent with the notion that anterior paralimbic regions of the brain mediate negative emotional states in healthy individuals.* Biol Psychiatry 2000;48: 43–50 © *2000 Society of Biological Psychiatry*

Key Words: PET, emotion, anterior cingulate, insula, paralimbic, guilt

Introduction

Several recent studies have examined the regions of the brain that are activated during the induction of positive and negative emotional states in healthy participants (e.g., Chua et al 1999; Fischer et al 1996; George et al 1995, 1996; Kimbrell et al 1999; Lane et al 1997a, 1997b; Paradiso et al 1997; Pardo et al 1993; Reiman et al 1997; Schneider et al 1995, 1997). These studies, which have included conditions of happiness, sadness, fear, anger, anxiety, and disgust, typically report increased activation in limbic and paralimbic regions of the brain, especially during negative emotional states. These findings are consistent with the notion that limbic and paralimbic regions of the brain mediate emotional states and the processing of information with affective significance (e.g., LeDoux 1992; Mesulam 1985). For example, George et al (1996) used positron emission tomography (PET) to study regional cerebral blood flow (rCBF) during transient sadness and happiness in healthy males and females. In separate scanning conditions, participants recalled neutral, sad, and happy events while they viewed affect-appropriate faces and attempted to experience the emotion corresponding to each facial expression. In the Sad versus Neutral comparison, participants exhibited blood flow increases in left insular cortex, and female participants showed additional blood flow increases in anterior cingulate gyrus.

Lane et al (1997b) used PET to examine rCBF during happiness, sadness, and disgust versus neutral states in healthy females. In separate scans, each of these states was induced via a film clip (Film Condition) and script-driven recall (Recall Condition). Within the Recall Condition only, rCBF increases during sadness occurred in insular cortex. Within the Film Condition only, rCBF increases during sadness occurred in bilateral amygdala. In both conditions combined, all three emotional states were associated with rCBF increases in anterior temporal poles.

Guilt is a negative emotion that has not been studied with neuroimaging techniques. Usually associated with the belief that one has harmed another person (Frijda 1994), guilt is a complex emotion, and situations that provoke guilt may also provoke other negative emotions. Furthermore, whether guilt is associated with a particular pattern of psychophysiological changes is not known (Levenson 1994). Despite these difficulties, the emotional state of guilt merits investigation because of its prevalence in healthy individuals and in patients with psychiatric disorders, such as depression and posttraumatic stress disorder (e.g., Berrios et al 1992; Henning and Frueh 1997).

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In the current study, we used PET and the script-driven imagery paradigm (Lang 1985; Lang et al 1983; Pitman et al 1987; Rauch et al 1996; Shin et al 1999) to study the neural correlates of transient emotional experiences of guilt in eight healthy male volunteers. In the script-driven imagery paradigm, participants are presented with audiotaped descriptions of personal events and are asked to recall and imagine those events and their related emotions as vividly as possible. During script-driven imagery, we measured participants' peripheral psychophysiologic responses (heart rate, skin conductance, and lateral frontalis electromyogram [EMG]), as well as rCBF. We sought to examine rCBF changes in the Guilt condition, relative to the Neutral condition. Given the results of previous studies of negative emotional states in both healthy individuals and patients with psychiatric disorders (e.g., George et al 1996; Lane et al 1997a, 1997b; Rauch et al 1994, 1995, 1996; Shin et al 1999), we predicted that rCBF increases in the Guilt versus Neutral comparison would occur in anterior paralimbic regions of the brain (i.e., orbitofrontal cortex, anterior cingulate gyrus, anterior insular cortex, anterior temporal poles) and amygdala. We had no specific predictions about rCBF decreases in the Guilt condition.

Methods and Materials

Participants

Participants were eight healthy, right-handed (Oldfield 1971) men with a mean age of 25.0 years (SD = 4.4) and mean education of 15.9 years (SD = 3.6). Participants had no history of psychiatric disorders (as determined by the Structured Clinical Interview for DSM-IIIR; Spitzer et al 1990), neurological disorders, head injury, or other major medical conditions. In addition, no participant was taking psychotropic or cardiovascular medication. The study was approved by the Subcommittee on Human Studies of the Massachusetts General Hospital, Boston, MA, and the Veterans Affairs Medical Center, Manchester, NH. Written informed consent was obtained from each participant.

Scripts

Prior to the PET scanning session, participants provided written descriptions of personal events: one involving the most guilt the participant had ever experienced, and two additional events involving no prominent emotion. These descriptions were then modified according to established procedures (Lang et al 1983; Pitman et al 1987, 1990; Rauch et al 1996; Shin et al 1999) and were written in the second person, present tense. Scripts were read and tape-recorded in a neutral male voice for playback in the PET scanner. All scripts were between 30 and 40 sec in duration.

Measures

PSYCHOPHYSIOLOGY. Participants' heart rate, skin conductance, and left lateral frontalis electromyograms (EMG) were measured via a Coulbourn Instruments (Allentown, PA) Modular Instrument System in the PET laboratory according to established procedures (Orr et al 1998; Pitman et al 1987, 1990).

Psychophysiologic measurements were recorded for 30 sec before each PET scan (baseline), and for 60 sec during each PET scan (imagery). Within the baseline and imagery periods (for each scan), readings were averaged. For each scan, the mean value of the baseline period was subtracted from the mean value of the imagery period, yielding "response" (i.e., change) scores.

SUBJECTIVE RATINGS. After each scan, participants rated the intensity of several emotions using separate visual analog scales (Pitman et al 1987, 1990; Rauch et al 1996; Shin et al 1999; 0 = absent; 10 = maximal). The rated emotions included guilt, shame, sadness, disgust, anger, fear, surprise, happiness, general arousal, competitive arousal, and sexual arousal. Participants also rated the overall valence (−5 to +5) of their emotional state during each scan.

State Induction/Imagery Procedure

Participants underwent PET scanning in two conditions: Guilt (one scan) and Neutral (two scans, with two different scripts). (Participants also underwent scanning in three other conditions [anger, competitive arousal, and sexual arousal] as part of a larger study; however, those other conditions are not relevant to the current results and are presented elsewhere; see Dougherty et al 1999; Rauch et al 1999.) During each scan, participants recalled and imagined the contents of a single script. The neutral scans always occurred first and last; the order of the remaining scans (one Guilt and three other scans not reported here) were completely counterbalanced in a Latin Square design.

Immediately before each scan, participants were instructed to close their eyes, listen carefully to the audiotaped script, and imagine the described event as vividly as possible, as if they were actually participating in the event again. The script started playing and the PET camera was turned on when there were 30 sec left in the script. At the end of the script, $^{15}O\text{-}CO_2$ administration began. During the next 60 sec, participants continued to recall and imagine the event while PET and peripheral psychophysiologic data were acquired. Then $^{15}O\text{-}CO_2$ administration and PET data acquisition were terminated, and participants were instructed to stop imagining the event and to relax. Thirty sec later, participants gave ratings of their emotional experiences during the preceding scan. PET scans were separated by at least 10 min in order to allow for radiation decay and a return to a baseline emotional state.

PET

PROCEDURES. The PET equipment and procedures have been described previously (Rauch et al 1996; Shin et al 1997, 1999). Briefly, PET data were gathered by a 15-slice, whole-body tomograph (Scanditronix PC 4096, General Electric, Milwaukee). The camera produced contiguous slices 6.5 mm apart, with axial resolution at 6.0 mm full-width half maximum (FWHM; axial field, 97.5 mm). Images were reconstructed using a measured attenuation correction and a Hanning-weighted reconstruction filter set to allow for 8-mm in-plane spatial resolution (FWHM).

After entering the scanner, each participant was fitted with a thermoplastic custom-molded face mask, an overlying face mask attached to a vacuum, and nasal cannulae which delivered the $^{15}O-CO_2$. The concentration of the $^{15}O-CO_2$ was 2960 MBq/L; the flow rate was 2 L/min. Each participant's head was aligned in the scanner relative to the canthomeatal line, and transmission measurements were made using an orbiting pin source.

A total of 15 measurements were made within each data acquisition run: the first three (10 sec each) occurred immediately prior to $^{15}O-CO_2$ administration, and the final 12 (5 sec each) occurred during $^{15}O-CO_2$ administration. After reconstruction, measurements 4–15 were summed to form images of cerebral blood flow. Terminal count rates were between 100,000 and 200,000 events/sec.

The PET images were corrected for interscan head movement and were transformed to the standard coordinate system of Talairach and Tournoux (1988). The images were smoothed and scaled using a two-dimensional Gaussian filter of 20-mm width (FWHM).

DATA ANALYSIS. Statistical analysis of the PET data was conducted using the SPM95 software package (Wellcome Department of Cognitive Neurology, London) which follows the theory of statistical parametric mapping (Friston et al 1991, 1995). At each voxel the PET data were normalized by the global mean and fit to a linear statistical model by the method of least squares. The analysis of variance considered Scan Condition as the main effect and Participants as a block effect. Planned contrasts at each voxel were conducted; this method fits a linear statistical model, voxel-by-voxel, to the data. Hypotheses were tested as contrasts in which linear compounds of the model parameters were evaluated using t statistics. Data from both conditions (Guilt and Neutral) were used to compute the contrast error term.

Regions containing foci of activation with Z scores greater than 3.09 are reported. For our a priori regions of interest, a Z score threshold of 3.09 ($p < .001$, one-tailed, uncorrected for multiple comparisons) was selected, because we had strong and directional a priori predictions about rCBF increases in limbic and paralimbic regions of the brain in the Guilt versus Neutral comparison. These predictions were based on the results of previous neuroimaging studies of other normal emotional states (e.g., George et al 1995, 1996; Lane et al 1997a, 1997b; Pardo et al 1993; Reiman et al 1997). For the sake of completeness and in order to obviate bias, we also report other (nonpredicted) regions that exhibited rCBF increases with Z scores greater than 3.09, although we advise the reader to use caution in interpreting them given their post-hoc nature.

Results

Psychophysiology and Ratings

Psychophysiologic responses were not significantly different in the Guilt condition than in the Neutral condition. Mean heart rate response scores for the Guilt and Neutral conditions were −0.17 (SD = 3.15) and −1.57 (SD = 3.28), respectively [$F(1,7) = 1.42$, $p = .27$]. Mean skin conductance response scores for the Guilt and Neutral conditions were −0.19 (SD = 0.43) and −0.11 (SD = 0.25), respectively [$F(1,7) = .44$, $p = .53$]. Mean EMG response scores for the Guilt and Neutral conditions were 0.41 (SD = 0.89) and 0.09 (SD = 0.60), respectively [$F(1,7) = .72$, $p = .43$].

Subjective ratings of emotional state during the Guilt and Neutral conditions are presented in Table 1. Ratings of guilt were significantly higher in the Guilt condition than in the Neutral condition [$F(1,7) = 317.59$, $p = .0001$]. Ratings of valence were significantly more negative in the Guilt condition than in the Neutral condition [$F(1,7) = 61.83$, $p = .0001$], but ratings of arousal did not significantly differ between the two conditions [$F(1,7) = 0.93$, $p = .37$]. Ratings of shame, sadness, disgust, anger, and fear were also higher in the Guilt condition than in the Neutral condition; however, within the Guilt condition, ratings of guilt were the highest of all ratings, and they were significantly higher than ratings of all other emotions, except for sadness and shame (guilt vs. sadness [$F(1,7) = 3.21$, $p = .12$]; guilt vs. shame [$F(1,7) = 3.32$, $p = .11$]).

Table 1. Subjective Ratings of Emotional State during the Guilt and Neutral Conditions

Rating scale	Guilt condition	Neutral condition	p value
Guilt	8.8	0.0	.0001
	(1.4)	(0.0)	
Valence	−3.9	0.8	.0001
	(1.7)	(1.0)	
Arousal	2.1	0.9	.37
	(3.0)	(1.2)	
Shame	7.4	0.0	.0002
	(2.8)	(0.0)	
Sadness	6.6	0.0	.001
	(3.5)	(0.0)	
Disgust	6.5	0.0	.0001
	(1.7)	(0.0)	
Anger	4.5	0.0	.005
	(3.2)	(0.0)	
Fear	2.6	0.0	.02
	(2.5)	(0.0)	
Surprise	2.3	0.06	.14
	(3.6)	(0.2)	
Happiness	0.0	2.3	.01
	(0.0)	(1.9)	
Competitive arousal	0.0	0.4	.35
	(0.0)	(1.1)	
Sexual arousal	0.0	0.0	—
	(0.0)	(0.0)	

Means of subjective ratings are reported. The rating scale was −5 to +5 for valence and 0 to +10 for all other measures. Standard deviations are given in parentheses.

Table 2. Regions with Blood Flow Changes in the Guilt vs. Neutral Condition

Region	Z score	Coordinates
rCBF Increases		
Paralimbic regions of interest		
Temporal poles	4.82	+44, +4, −24
	4.59	+46, +12, −28
	4.40	−44, +20, −20
Anterior cingulate gyrus (32)	3.57	+12, +34, +24
Anterior insular cortex/ inferior frontal gyrus	3.69	−44, +16, −4
Other regions		
Mid-cingulate	3.29	−14, −10, +44
Cerebellum	3.25	+20, −50, −24
Precentral gyrus	3.19	−32, −14, +44
rCBF decreases		
Posterior insular cortex	3.49	−38, −12, +12
Visual association cortex (19)	4.42	−6, −80, +40
Precuneus	3.63	+10, −72, +48
Fusiform gyrus	3.72	−38, −44, −12
Precentral gyrus	3.17	+52, −8, +12

For each focus of activation, Z scores and coordinates are given. Coordinates are expressed in millimeters: $x > 0$ is right of the midsagittal plane, $y > 0$ is anterior to the anterior commissure, and $z > 0$ is superior to the anterior commissure–posterior commissure plane. Numbers in parentheses immediately following region names refer to approximate Brodmann areas. rCBF, regional cerebral blood flow.

PET Results

In the Guilt versus Neutral comparison, rCBF increases occurred in three of our paralimbic regions of interest: bilateral anterior temporal poles, anterior cingulate gyrus, and left anterior insular cortex/inferior frontal cortex (see Table 2 and Figure 1). No rCBF increases (or decreases) were observed in amygdala. rCBF increases occurred in the following other areas: mid-cingulate gyrus, cerebellum, and left precentral gyrus. rCBF decreases occurred in left posterior insular cortex, visual association cortex, right precuneus, left fusiform gyrus, and right precentral gyrus.

Discussion

Relative to the Neutral condition, the Guilt condition was associated with rCBF increases in three of our paralimbic regions of interest: bilateral anterior temporal poles, anterior cingulate gyrus, and left anterior insular cortex/inferior frontal cortex. rCBF decreases occurred in more posterior portions of left insular cortex. These findings are generally consistent with those of previous studies of normal emotional states.

Studies of nonhuman primates have revealed direct connections from anterior temporal poles to the amygdala (Aggleton et al 1980). In addition, electrical stimulation of anterior temporal poles can elicit autonomic responses in monkeys and cats (Anand and Dua 1956; Kaada et al 1949) and reports of fear and nervousness in humans (Mullan and Penfield 1959). Activation in anterior temporal poles has been reported in other studies of normal emotion (e.g., Lane et al 1997a, 1997b; Kimbrell et al 1999; Reiman et al 1997), as well as in studies of patients with anxiety disorders (Rauch et al 1995, 1996; Shin et al 1999). In two previous studies of anxiety, rCBF increases in temporal poles were attributed to extracranial artifacts of jaw muscle contraction (Drevets et al 1992; Benkelfat et al 1995); however, the temporopolar activations reported in the current study were clearly within brain. Although activation in anterior temporal poles has largely been associated with negative emotional states, at least one study has reported these types of activations during film- and recall-generated happiness (Lane et al 1997b). Thus, the anterior temporal poles may be involved in information processing of emotional material, possibly regardless of valence.

The cingulate gyrus is a large structure that appears to have different functional subdivisions (Devinsky et al 1995; Vogt et al 1992, 1995). The activation reported in the present study is located in a region of the anterior cingulate gyrus (approximately Brodmann area 32) that lies just superior to the genu of the corpus callosum, approximately 24 mm above the anterior commissure–posterior commissure (AC–PC) plane. This region may correspond to superior portions of the affective division of the anterior cingulate gyrus (ACad), which lies inferior to the dorsal region of the anterior cingulate that is thought to principally mediate cognitive processes (e.g., Bush et al 1998; Pardo et al 1990; see Vogt et al 1992, 1995), and superior to the portion of the anterior cingulate that is thought to mediate visceral functions (Vogt et al 1992, 1995). Activations in this vicinity (roughly 10–24 mm above the AC–PC plane) have also been reported in studies involving procaine-induced fear (Ketter et al 1996; Servan-Schreiber et al 1998), the recollection of traumatic events in trauma-exposed healthy individuals (Shin et al 1999), the performance of the emotional Stroop task (Whalen et al 1998a), the prediction of treatment response in depression (Mayberg et al 1997), and symptom provocation in patients with obsessive-compulsive disorder (Rauch et al 1994).

In the current study, the Guilt condition was associated with rCBF increases in anterior insular cortex/inferior frontal gyrus and rCBF decreases in more posterior regions of insular cortex. Anterior and posterior portions of insular cortex appear to differ considerably in terms of cellular organization, connections with other brain regions, and function (Mesulam and Mufson 1982a, 1982b; Mufson and Mesulam 1982). Anterior insular cortex contains agranular and dysgranular cells, shares extensive connections with other anterior paralimbic regions and the amygdala (Aggleton et al 1980), and is involved in olfactory, gustatory, and autonomic function (Mesulam

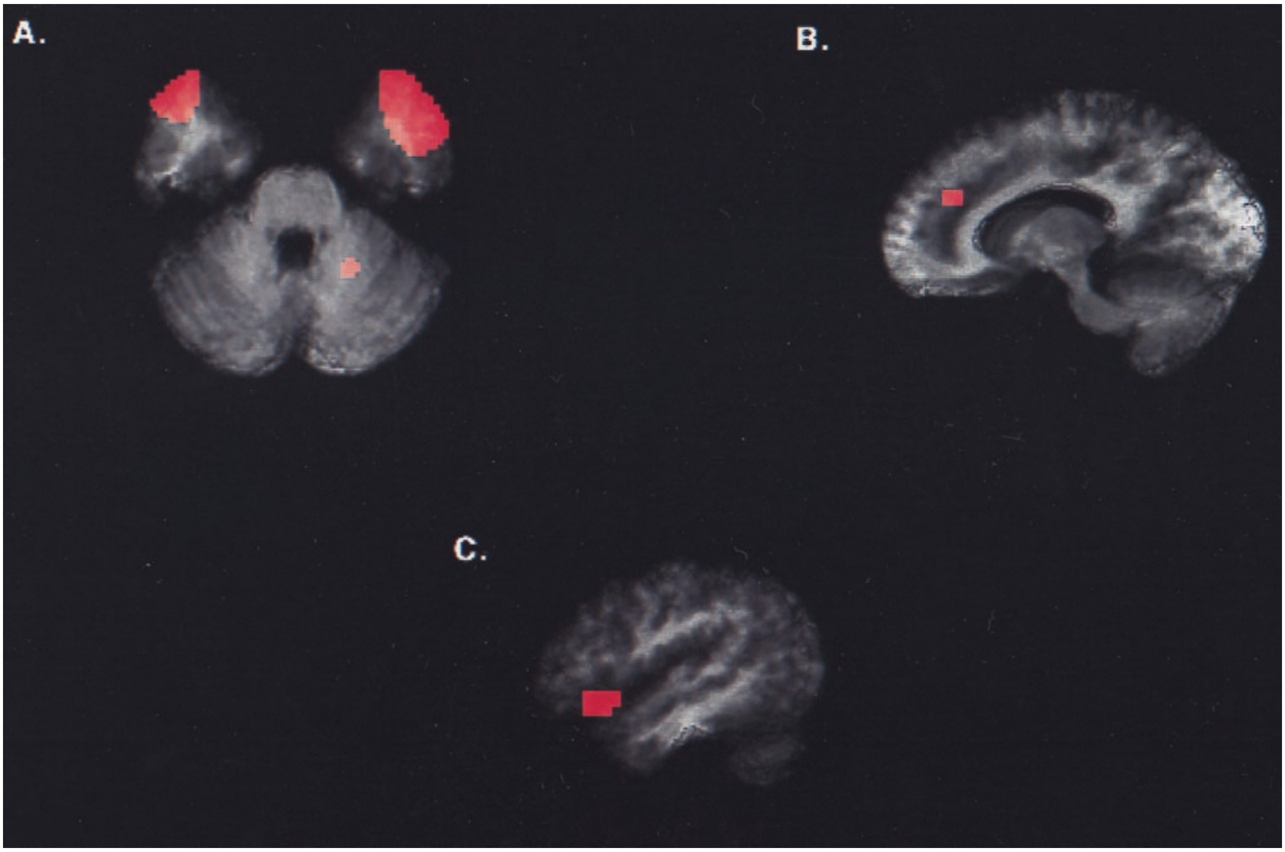

Figure 1. Regional cerebral blood flow increases in the Guilt versus Neutral comparison were observed in **(A)** anterior temporal poles (horizontal view), **(B)** anterior cingulate gyrus (sagittal view), and **(C)** left anterior insular cortex/inferior frontal gyrus (sagittal view).

and Mufson 1982b; Small et al 1999). Electrical stimulation of anterior insular cortex is associated with reports of fear in humans (Mullan and Penfield 1959), and activation of anterior insular cortex has occurred during symptom provocation in patients with phobias (Rauch et al 1995), the recollection of negative events in healthy individuals (George et al 1996; Shin et al 1999), procaine-induced fear (Ketter et al 1996; Servan-Schreiber et al 1998), the perception of facial expressions of disgust (Phillips et al 1997), imagery of aversive stimuli (Kosslyn et al 1996), and aversive gustatory stimulation (Zald et al 1998). In contrast, posterior insular cortex contains granular cells, shares connections with superior temporal, parietal, premotor, and somatosensory cortex, and is involved in the processing of auditory and somatosensory information (Coghill et al 1994; Francis et al 1999; Mesulam and Mufson 1982a, 1982b; Mufson and Mesulam 1982; Schneider et al 1993). Activation in anterior insular cortex during the emotional state of guilt is consistent with theory and data regarding the role that this region may play in the processing of emotional information. Deactivation in more posterior regions of insular cortex during the Guilt condition was unexpected, but could reflect a reallocation of blood flow toward more anterior regions of insular cortex during a negative emotional state.

No activation occurred in the amygdala or orbitofrontal cortex during the Guilt condition in this study. Indeed, the amygdala may be more involved in fear and the processing of fear-related stimuli (e.g., LaBar et al 1998; Morris et al 1996; Rauch et al 1996; Whalen et al 1998b). In addition, in healthy individuals, the amygdala may be more responsive during conditions involving the perception of emotional stimuli than the recollection and imagery of those stimuli (Reiman et al 1997; Whalen 1998). Furthermore, the limited spatial and temporal resolution of PET may have hindered our ability to detect activation in the amygdala. The absence of activation in orbitofrontal cortex in this study was somewhat surprising, given previous reports of orbitofrontal activation during negative emotional states in healthy humans (e.g., Fischer et al 1996; Paradiso et al 1997; Pardo et al 1993; Zald et al 1998).

Possible limitations of this study include the modest sample size, the lack of behavioral measures, and the dependence on self-report data. In addition, one might argue that the absence of significant peripheral psychophysiologic changes between the Guilt and Neutral conditions was a limitation. To our knowledge, however, there is no evidence that the emotional state of guilt is accompanied by such changes. Furthermore, although great care was taken to match the conditions as closely as possible on a number of different variables (such as script length, tense, voice), the conditions may have differed in more subtle ways. For example, although the Guilt condition was indeed marked by high subjective ratings of guilt, it was also accompanied by moderate ratings of related emotions, especially shame and sadness. Anxiety, which has been associated with paralimbic activation (e.g., Chua et al 1999; Cottraux et al 1996; Kimbrell et al 1999; Rauch et al 1994, 1995, 1996; Shin et al 1997, 1999), also may have occurred in the Guilt condition, although the lack of peripheral psychophysiologic changes during the Guilt condition may not be consistent with this possibility. In short, activations in the Guilt versus Neutral comparison may have reflected changes in other related emotions as well. Finally, PET studies in general are limited by errors in precise neuroanatomical localization that can arise from constraints set by the spatial resolution of PET, unavoidable head movement, or stereotaxic transformation. In addition, normalizing whole-brain blood flow prevented us from detecting any absolute blood flow changes between conditions.

In conclusion, the Guilt condition was associated with rCBF increases in bilateral anterior temporal poles, anterior cingulate gyrus, and left anterior insular cortex/inferior frontal cortex and rCBF decreases in more posterior portions of left insular cortex. The results of this and other similar studies are consistent with the notion that anterior paralimbic regions of the brain mediate negative emotional states in healthy individuals and are involved in the processing of information with affective significance.

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