The Application of Positron Emission Tomography to the Study of Normal and Pathologic Emotions

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This report reviews six studies in which positron emission tomography (PET) was used to investigate the neuroanatomic correlates of emotion, anxiety, and anxiety disorders. PET was used to study brain regions that participate in film- and recall-generated discrete emotions (happiness, sadness, and disgust), picture-generated positive and negative emotions, and normal anticipatory anxiety; participate in the predisposition to, elicitation of, and treatment of panic attacks; participate in social phobic anxiety; and participate in specific phobic anxiety. Results of these investigations suggest that thalamic and medial prefrontal regions may participate in aspects of normal emotion unrelated to its type, valence, or stimulus; that modality-specific sensory association areas and anterior temporal lobe regions appear to participate in the evaluation procedure that invests exteroceptive sensory information with emotional significance; that anterior insular regions appear to participate in the evaluation procedure that invests potentially distressing cognitive and interoceptive sensory information with negative emotional significance; and that anterior cingulate, cerebellar vermis, midbrain, and other brain regions appear to participate in the elaboration of normal and pathologic forms of anxiety. As a complement to other research strategies, PET promises to help determine how multiple brain regions and the mental operations to which they are related work in concert to produce emotions and how they conspire to produce emotional disorders. *(J Clin Psychiatry 1997;58[suppl 16]:4–12)*

This article reviews six studies in which my colleagues and I used positron emission tomography (PET) measurements of regional cerebral blood flow (CBF), a marker of local neuronal activity, to investigate regions of the brain that participate in emotion, anxiety, and anxiety disorders. Consideration is given to how these brain regions are related to different kinds of emotional stimuli, different types of emotion, emotional valence, and different forms of emotional pathology.

Our studies were designed to generate intense emotions and emotional syndromes in the laboratory setting, to acquire subjective and psychophysiologic measurements of the emotional state, and to control for nonspecific aspects of the emotion-generating task. Intravenous bolus injections of ^{15}O-water were used to make multiple 40- to 60-second scans during each imaging session, thereby permitting the acquisition of data during a brief and potentially uncomfortable behavioral state and the use of each individual as his or her own control. In all cases, the subjects were fully informed about the potential risks and discomfort involved in the study, provided their written consent, and were studied under guidelines approved by the human subjects committee of the responsible institution.

In most cases, brain mapping algorithms were used to normalize regional data for the variation in whole brain measurements, to transform each person's PET image into the coordinates of a standard brain atlas, to compute statistical maps of state-dependent increases in regional CBF, and to superimpose these maps onto an average of the subjects' magnetic resonance images (MRIs). These algorithms permitted us to distinguish subtle state-dependent CBF increases from noise, to compare data from different subjects, and to compare findings from different studies. (Indeed, our original brain mapping algorithm[1] was developed in direct response to the challenges presented by our study of panic disorder.) Procedures were recently developed, tested, and, when possible, used to address the potentially confounding effects of temporalis muscle activity, residual radiotracer activity in the internal carotid arteries, and partial-volume averaging (image blurring) on CBF measurements in the anterior temporal lobes.[2,3]

EXTERNALLY AND INTERNALLY GENERATED EMOTION

I begin with an earlier study in which we used PET measurements of regional CBF to investigate regions of the brain that are involved in normal human emotion, how these regions are related to the nature of the emotional stimulus, and how these regions are related to different types of emotion.[4,5] Twelve neurologically and psychiatrically healthy females were studied as they alternated between emotion-generating and emotionally neutral control tasks. For six scans, silent film clips[6] were used for the external generation of three subjectively, facially, and electrophysiologically well characterized target emotions (happiness, sadness, and disgust) and for the generation of three emotionally neutral conditions intended to control for potentially confounding features of the emotion-generating film task, such as visual stimulation and eye movements. For six additional scans, autobiographic scripts of recent experiences were used for the internal generation of the same three target emotions and for the generation of three emotionally neutral conditions intended to control for potentially confounding effects of the emotion-generating recall task, such as recall memory and visual imagery. During each scan, we acquired psychophysiologic measurements, including quantitative electroencephalographic measurements of brain activity, electromyographic measurements of facial muscle activity, electrooculographic measurements of eye movement, and measurements of heart rate and electrodermal activity. A hidden camera was used to record facial expressions,[7] but the quality of the videotapes turned out to be unsatisfactory for blind ratings of facial affect. Immediately following each scan, subjects rated their experience of seven emotions (happiness, sadness, disgust, interest, amusement, fear, and anger) on separate visual analogue scales. The sequence of scans was arranged to address potential order effects. In comparison to the control tasks, there were significant increases in subjective ratings of the relevant target emotion during the emotion-generating film tasks and recall tasks. The increases related to recall-generated emotions were slightly greater than those related to film-generated emotions.

Which brain regions participate in the emotional response to a complex visual stimulus (in this case, silent film clips)? Film-generated emotion was distinguished from the emotionally neutral film tasks by significant, symmetrical CBF increases in the vicinity of occipitotemporal and anterior temporal cortex, amygdala, medial prefrontal cortex, thalamus, hypothalamus, midbrain, and lateral cerebellum.[4] The CBF increases in anterior temporal regions were unrelated to the potentially confounding effects of temporalis muscle activity or residual radiotracer activity in the internal carotid arteries.[2–4]

Which brain regions participate in the emotional response to a cognitive stimulus (in this case, the recollec-tion of recent experiences)? As with film-generated emotion, recall-generated emotion was distinguished from its own emotionally neutral condition by significant CBF increases in the vicinity of medial prefrontal cortex and thalamus; it was also associated with CBF increases in a region that includes anterior insular cortex, claustrum, and lateral putamen and in regions that appear to reflect the combined effects of temporalis muscle activity of partial volume averaging.[2,4] Post-hoc analyses revealed significantly increased CBF in the anterior insular region during recall-generated sadness and indicated that this increase was significantly greater than that associated with recall-generated happiness.[2,4,5]

How are the brain regions that participate in emotion related to the nature of the emotional stimulus? To address this question with greater statistical power, CBF increases related to film-generated emotion were directly compared with the CBF increases related to recall-generated emotion. Film-generated emotion was distinguished from recall-generated emotion by significantly greater, symmetrical CBF increases in the vicinity of occipitotemporoparietal cortex, anterior temporal cortex, amygdala, hippocampal formation, hypothalamus, and lateral cerebellum.[4] Although recall-generated emotion was not distinguished from film-generated emotion by significant increases in regional CBF, post-hoc analysis revealed that recall-generated sadness was distinguished from film-generated sadness by significantly greater CBF increases in the anterior insular region.[2,4,5]

Visual association areas in occipitotemporal cortex may be involved in the evaluation procedure that invests complex visual stimuli (or certain aspects of these visual stimuli) with emotional significance. Although the anterior temporal cortex, hippocampal formation, and amygdala have long been thought to participate in the generation of emotion,[8] our findings suggest that these heteromodal sensory association areas[9] are preferentially involved in the evaluation procedure that invests exteroceptive sensory stimuli with emotional significance. In contrast, findings from this study and others, noted below, suggest that the anterior insular region is preferentially involved in the evaluation procedure that invests potentially distressing thoughts or bodily sensations with negative emotional significance.

Finally, how are the implicated brain regions related to different types of emotion? (Some of our findings are summarized here; additional findings are described in our original report.[5]) Film- and recall-generated happiness, sadness, and disgust were all associated with increased CBF in the medial prefrontal and thalamic regions, suggesting that these regions participate in aspects of emotion that are unrelated to the nature of the emotional stimulus or the type of emotion.[5] Film-generated happiness, sadness, and disgust were associated with significantly increased CBF in the vicinity of occipitotemporal and ante-

rior temporal cortex, suggesting that these regions participate in aspects of externally generated emotion that are independent of the particular type of emotion.[5] As noted above, recall-generated sadness was associated with significantly increased CBF in the anterior insular region. Sadness and disgust, the two negative emotions, were each associated with significant CBF increases in the vicinity of the midbrain and cerebellar vermis[5]—increases that were also found in our studies of normal and pathologic forms of anxiety.[2,10] Our findings concerning the neuroanatomic correlates of discrete emotions should be interpreted with caution, since large increases in the ratings of each target emotion were associated with smaller increases in the ratings of other emotions.

POSITIVE AND NEGATIVE EMOTION

In a complementary study, we recently used PET measurements of regional CBF and the International Affective Picture System[11] to investigate regions of the brain that are involved in normal human emotion and to consider how these regions are related to emotional valence (i.e., the extent to which emotion is pleasant or unpleasant).[12] Twelve neurologically and psychiatrically healthy females received 12 scans as they alternated between watching homogenous sets of emotionally positive color pictures, emotionally negative color pictures, emotionally neutral color pictures, and a small eye-fixation cross-hair. During each scan, electromyography was used to record corrugator ("frowning") muscle activity (a measure of negative emotion[11]) and zygomatic ("smiling") muscle activity (a measure of positive emotion[11]), and electrodermal activity was used to provide a measure of physiologic arousal. Immediately following each scan, subjects rated their emotional valence and arousal using well-established rating scales.[12] The sequence of scans was arranged to address potential order effects.

Picture-generated positive emotion was distinguished from picture-generated neutral emotion by significantly increased CBF in a region that includes the thalamus, hypothalamus, and midbrain and in medial prefrontal cortex.[12] As with picture-generated positive emotion, picture-generated negative emotion was distinguished from picture-generated neutral emotion by significantly increased CBF in a region that includes the thalamus, hypothalamus, and midbrain and in medial prefrontal cortex.[12] In addition, picture-generated negative emotion was distinguished from both picture-generated neutral and positive emotions by significantly increased CBF in occipitotemporal cortex and lateral cerebellum and in a region that includes the left amygdala, hippocampal formation, and parahippocampal gyrus. Increases in blood flow in the vicinity of anterolateral temporal and inferolateral frontal regions appeared to be at least partly related to the combined effects of temporalis muscle activity and partial volume averaging.[12] We postulate that

relevant sensory association areas preferentially attend, evaluate, and prepare to respond to stimuli that are emotionally unpleasant and potentially threatening.[2]

NORMAL ANTICIPATORY ANXIETY

First in St. Louis[13] and subsequently in Arizona,[2] we used PET measurements of regional CBF to investigate regions of the brain that are involved in normal anticipatory anxiety. In St. Louis, eight neurologically and psychiatrically healthy subjects were studied before, during, and after the prospect of receiving an electric shock. (The shock was administered just after the completion of the second 1-minute scan; it was brief and well tolerated, thereby preserving the investigators' credibility with the subjects for the remainder of the study.) In addition, the subjects were studied during a fist-opening-and-closing task, another baseline task, and a tonic fist-clenching task in an attempt to address the effects of movement and muscle tension. Anticipation of shock was associated with large and significant increases in subjective ratings of anxiety, heart rate, and nonspecific fluctuations in electrodermal activity.[13]

Anticipatory anxiety was distinguished from each of the baseline conditions by significant increases in the vicinity of anterior temporal cortex.[13] However, subsequent studies in Montreal[14] and St. Louis[15] raised the possibility that these increases could be at least partly related to the combined effects of temporalis muscle activity and partial volume averaging. (In our initial PET studies, we did not acquire MRIs in any of the subjects, and we excluded data from outside the brain in order to normalize local brain measurements for the whole-brain variations.)

In Arizona, we repeated the study[2] in a larger subject group. MRIs were acquired in each subject (as was the case in our Arizona studies of emotion, social phobic, and specific phobic anxiety), and we developed, tested, and applied techniques that addressed the potentially confounding effects of temporalis muscle activity, internal carotid artery activity, and partial volume averaging on blood flow changes observed in the anterior temporal lobes.[2] Fourteen neurologically and psychiatrically healthy females were studied before, during, and after the prospect of receiving an electric shock. In addition, they were studied during a jaw-clenching task that produced robust increases in temporalis and masseter muscle activity, during another baseline task, and during a voluntary hyperventilation task that sought to address the potentially confounding effects of hyperventilation-induced hypocapnia on regional measurements. In each case, the subjects rested quietly in the supine position with their eyes closed, and electrodes were placed on both hands for administration of the electric shock. Anticipation shock was associated with large and significant increases in subjective ratings of anxiety and heart rate.[2]

We first investigated the relationship between the blood-flow increases related to jaw clenching, anticipatory anxiety, and (using data from another study[3]) residual radiotracer activity in the internal carotid arteries. Jaw clenching was associated with large, significant, bilateral blood-flow increases that extended medially from temporalis muscle into anterolateral temporal and inferolateral frontal areas because of partial volume averaging and extended superiorly into sensorimotor areas that participate in jaw movement.[2] Anticipatory anxiety was associated with significant bilateral blood-flow increases in the vicinity of temporalis muscle, anterolateral temporal areas, and inferolateral frontal areas that overlapped the increases associated with jaw clenching (but were smaller in magnitude and spatially less extensive); anticipatory anxiety was also associated with significantly increased CBF in the vicinity of anterior insular cortex.[2] Internal carotid artery activity extended into anteromedial temporal and posterior orbitofrontal regions but did not overlap the blood-flow increases observed during anticipatory anxiety.[2,3]

Although the procedure that corrects for the potentially confounding effects of temporalis muscle activity prevents us from investigating CBF increases in anterolateral temporal and inferolateral frontal regions, it improves our ability to detect CBF increases in the rest of the brain.[2] Using this procedure, normal anticipatory anxiety was associated with significantly increased CBF bilaterally in the vicinity of anterior insular, temporoparietal, and lateral prefrontal cortex, caudate, right anterior temporal cortex, thalamus and a region that includes anterior cingulate and medial prefrontal cortex, as well as with significant trends in the cerebellar vermis and midbrain.[2] Based on these findings, the blood-flow increases in anterior temporal cortex appear to partly reflect the combined effects of temporalis muscle activity and partial volume averaging (even though electromyography failed to indicate appreciable increases in temporalis muscle activity) and to partly reflect increased activity in anterior temporal cortex.[2]

We postulate that anterior insular regions serve as internal alarm centers; that anterior temporal regions serve as external alarm centers (perhaps in this case representing an attempt to monitor exteroceptive sensory stimuli); that the anterior cingulate/medial prefrontal region participates in the conscious experience of, attentional response to, or behavioral response to the anxiety-provoking situation; that the cerebellar vermis participates in the behavioral response to the anxiety-provoking situation (facial expressions of anxiety, muscle tension, readiness to respond, or restraint from fleeing the situation) or cognitive features of anxiety that remain to be elucidated; that the temporoparietal regions participate in spatial orientation or auditory vigilance to the threatening situation; that the lateral prefrontal regions participate in the process of deciding how to respond to the threatening situation; and that the thalamus and caudate participate in a basal ganglia-thalamic-frontal circuit that participates in the integrated expressions of anxiety.[2] Of course, these findings need to be replicated in an independent study, and our hypotheses need to be tested using potentially complementary research strategies.

In this study, we considered the brain regions that participate in normal anticipatory anxiety—normal because it is tolerable, does not interfere with the individual's ability to cope with the anxiety-provoking situation, and even mobilizes the person to respond to the threatening situation. In the three studies described below, we considered the brain regions that participate in pathologic forms of anxiety—anxiety disorders that are associated with intolerable distress and typically interfere with the individual's ability to cope with the anxiety-provoking situation (although it was endured by subjects during the course of the PET study). Among other questions, we wished to consider the neural processes that participate in both pathologic and normal forms of anxiety and the processes that distinguish pathologic from normal forms of anxiety.

PANIC DISORDER

Several years ago, we used PET and lactate infusion to investigate regions of the brain that are involved in the predisposition to, elicitation of, and prevention of panic attacks in patients with panic disorder.[10,16–20] Lactate infusion precipitates a panic attack in many patients with panic disorder but rarely does so in normal controls.[16] When antipanic treatments block naturally occurring panic attacks, they also block the attacks induced by lactate.[16] PET was used to study patients with panic disorder and normal controls before and during lactate infusion. Many of the patients were treated with alprazolam for several weeks and then restudied.

We initially compared CBF measurements acquired in the nonpanic state prior to lactate infusion. Patients who were predisposed to lactate-induced panic had an abnormal asymmetry (right > left) in a preselected region-of-interest in the posterior parahippocampal gyrus.[17] We then extended our analysis of the parahippocampal region to larger subject groups. In the nonpanic state prior to infusion, patients who were predisposed to lactate-induced panic had an abnormal asymmetry (right > left) of parahippocampal CBF, blood volume, and oxygen metabolism; they also had abnormally increased oxygen metabolism in the whole brain.[18] The asymmetry appeared to reflect increased measurements in the right rather than decreased measurements in the left. It was unchanged during lactate-induced panic[10] and was not corrected by alprazolam treatment (Drevets W, Reiman EM, McLeod A, et al. Unpublished data).

Since brain-mapping algorithms have not yet been established for between-group comparisons—algorithms

that adjust individual images for their shape as well as their size and orientation—we are not yet sure whether the abnormality is centered in the preselected posterior parahippocampal region-of-interest or extends into this region from a neighboring structure (e.g., medial occipitotemporal cortex or midbrain), and we cannot yet address the possibility of additional abnormalities in unexplored regions.[16] Using a brain-mapping algorithm not yet established for between-group comparisons (one that adjusts brain images for their size and orientation, but not their shape), we found that patients with panic disorder who were predisposed to lactate-induced panic had abnormally increased CBF in a right-sided region that included the posterior parahippocampal gyrus, occipitotemporal cortex, and midbrain; patients with panic disorder who were not predisposed to lactate-induced panic had abnormally increased CBF in the same region bilaterally.

Next, we considered the increases in regional CBF associated with lactate infusion. Lactate-induced panic was associated with significantly increased blood flow bilaterally in the vicinity of anterior temporal cortex, a region that includes anterior insular cortex, and the superior colliculi (midbrain structures) and in the left anterior cerebellar vermis, claustrum, or lateral putamen.[10] In retrospect, the blood-flow increases observed in the vicinity of anterior temporal cortex, although slightly more medial than those observed during normal anticipatory anxiety, could be at least partly related to the combined effects of temporalis muscle activity and partial volume averaging.[14,15] Lactate infusion was not associated with significant increases in regional CBF in the nonpanicking patients and control subjects.[10]

Although lactate infusion was associated with significantly increased whole brain CBF in nonpanicking patients and controls, it was not associated with increased CBF in the panicking patients.[19] The lactate-induced increase in whole brain CBF may reflect the effects of hemodilution or the development of a central acidosis.[19] The absence of a lactate-induced increase in whole brain CBF may reflect the effects of hyperventilation or a potential reduction in the permeability-surface area product for water (PSw).[19] (PSw, a measure of blood-brain barrier permeability to small molecules such as water, is an end-organ product of the central adrenergic system and is increased by antidepressants shown to block panic attacks.[16])

Finally, we considered the effects of alprazolam treatment on parahippocampal and whole brain measurements. As noted above, alprazolam treatment did not correct the regional abnormality (Drevets et al. Unpublished data). As previously shown with acute benzodiazepine administration, continuation treatment with alprazolam was associated with a significant reduction in whole brain CBF (Drevets et al. Unpublished data).

Our findings led us to propose the following model to account for the predisposition to, elicitation of, and medi-

cation and nonmedication treatment of panic attacks in patients with panic disorder.[20] We postulate that a regional abnormality, present in the nonpanic state, is involved in the predisposition to panic attacks. We postulate that this regional abnormality responds to a normally innocuous triggering event by sending a message to alarm centers that are involved in the elaboration of a panic attack. The normally innocuous triggering event may include an increase in central adrenergic activity, a decrease in central nervous system pH, certain somatic sensations, or some other process that remains to be determined. The alarm centers may reside in anterior insular and possibly anterior temporal regions.[2] We suggest that the regional abnormality distinguishes panic disorder from normal forms of anxiety; we also suggest that the same alarm centers participate in the elaboration of panic attacks and normal anticipatory anxiety—a false alarm in one case, a survival-enhancing alarm in the other. Finally, we postulate that antipanic medications exert their effects by interfering with the normally innocuous triggering event (e.g., by decreasing central adrenergic activity) and that cognitive-behavioral therapy exerts its effects downstream by increasing resistance to false alarms. (Until our hypotheses are tested, I am mindful of H. L. Mencken's admonition that "for every complex problem, there is a solution that is simple, neat, and wrong.")

SOCIAL PHOBIC ANXIETY

More recently, we used PET measurements of regional CBF to investigate regions of the brain that are involved in social phobic anxiety.[2] Seven patients with social phobia of the generalized type were studied before, during, and after the elicitation of social phobic anxiety. During all three scans, the patients sang the alphabet song out loud with their eyes closed. During the first and third scans, they understood that there were no observers in the scanning room. During the second scan, they understood that there were several observers in the scanning room monitoring the patients' performance. In addition, the patients were studied during a jaw-clenching task, a voluntary hyperventilation task, and a nonspeaking baseline condition. The public-speaking condition was distinguished from the private-speaking condition by significantly higher subjective ratings of anxiety and heart rate; in turn, the private-speaking condition was distinguished from the nonspeaking baseline condition by significantly higher subjective ratings of anxiety and heart rate.

The public- and private-singing conditions were each distinguished from the nonspeaking baseline condition by significantly increased CBF in the vicinity of auditory areas in the superior temporal gyrus, sensorimotor areas, anterior insular cortex, a region that includes posterior cingulate gyrus and precuneus, caudate, thalamus, cerebellar vermis, and midbrain.[2] Some of these regions appear to

participate in the singing task itself; some appear to participate in monitoring the patient's own performance; and some appear to participate in the social phobic anxiety that was present during both speaking conditions.

After the potentially confounding effects of temporalis muscle activity and radiotracer activity in the internal carotid arteries were addressed, the public-speaking condition was distinguished from the private-speaking condition by significantly increased CBF in the vicinity of auditory, motor mouth, and other sensorimotor areas; in a region that includes the supplementary motor area and midcingulate cortex; in a region that includes posterior cingulate gyrus and precuneus; and in lateral prefrontal cortex, anterior temporal cortex, thalamus, and midbrain.[2] Significant trends in the vicinity of a region that includes anterior cingulate and medial prefrontal cortex, hippocampus, amygdala, hypothalamus, and cerebellar vermis were also noted. Some of the brain regions thus implicated in social phobic anxiety appear to participate in vigilance to the sound of the patient's own voice; some appear to participate in effortful vocalization; and others appear to participate in the mental operations that are common to several forms of anxiety.

Once a brain-mapping algorithm has been established for between-group comparisons, we will be able to address the possibility that the patients have one or more abnormalities in the nonspeaking, nonanxious baseline state—abnormalities that could predispose them to become anxious in social phobic situations. Although the size of our study sample is small, we will also consider the brain regions that are selectively affected by several weeks of treatment with the investigational medication brofaromine, a reversible inhibitor of monoamine oxidase A.

SPECIFIC PHOBIC ANXIETY

Finally, we studied a form of anxiety that could be elicited repeatedly. (Although not considered here, the acquisition of multiple images in the same subject during the same experimental and baseline state might permit us to characterize state-dependent changes in regional CBF in each individual person, thereby localizing these changes with greater precision.) Four patients with a snake phobia each had 16 scans over two imaging sessions as they alternated between exposure to a live 4-foot-long python and a stuffed stocking, similar to the snake in size and shape, which controlled for visual stimulation.[2] The snake and stuffed stocking were coiled around the horizontal bar of a periscopic, ceiling-mounted trapeze, which hung above the supine patient. To minimize psychophysiologic habituation, the horizontal bar was lowered closer to the patient's body and repositioned closer to the patient's face after each even-numbered scan. Patients who wished to be treated after the scanning sessions improved dramatically following additional exposures to the same snake. (By the end of the treatment, they could even wear the snake around their necks!)

By using the 64 images acquired in the four patients and removing the large blood-flow increases extending from temporalis muscle into anterolateral temporal cortex, snake phobic anxiety was associated with significant CBF increases in the vicinity of occipital visual association areas, a region that includes anterior cingulate and medial prefrontal cortex, anterior insular cortex, motor cortex, supplementary motor area, thalamus, caudate, midbrain, cerebellar vermis, and lateral cerebellum, as well as with significant trends in the hippocampal formation and parahippocampal gyrus.[2] The visual association areas may participate in vigilance to and evaluation of the emotionally threatening visual stimulus. The anterior cingulate/medial prefrontal region (also implicated in our Arizona studies of anticipatory anxiety and social phobic anxiety) may participate in the conscious experience of emotion, the attentional or behavioral response to the anxiety-provoking situation, the inhibition of excessive emotion, or the process of monitoring the individual's emotional state in order to make a personally relevant decision. The anterior insular region may serve as an internal alarm center, alerting the individual to potentially distressing interoceptive stimuli, such as the sensation of a pounding heart. The motor areas, supplementary motor area, and cerebellar regions may participate in the patients' readiness to flee from the threatening situation or their restraint from doing so. The thalamus and caudate may participate in a basal ganglia-thalamic-frontal circuit involved in the integrated behavioral or cognitive response to the frightening situation. The parahippocampal and hippocampal regions may serve as external alarm centers, alerting the individual to the threatening exteroceptive sensory stimulus or may provide the spatial context for the frightening situation. Failure to detect CBF increases in the vicinity of the amygdala may reflect limitations in statistical power, an attenuation of these increases by the combined effects of reduced residual radiotracer activity in the internal carotid arteries and partial volume averaging, or an insignificant increase in local neuronal activity. By excluding the large blood-flow increases centered in temporalis muscle and extending into neighboring brain regions, we were unable to explore CBF increases in anterolateral temporal cortex.

OVERVIEW

Our studies of normal and pathologic emotions touched on several common themes, which I will discuss in this section along with their possible implications.

Limbic areas (i.e., hippocampal formation and amygdala) and paralimbic areas (i.e., anterior temporal cortex and the parahippocampal gyrus) in the anterior temporal lobe have long been postulated to participate in emotion.[8,9] On the basis of our findings, we suggest that these regions

are preferentially involved in the emotional response to exteroceptive sensory stimuli and are less involved in the emotional response to cognitive (and perhaps interoceptive sensory) stimuli. We postulate that these regions, which receive projections from multimodal sensory association areas,[9] participate in the evaluation procedure that invests simple and complex exteroceptive sensory stimuli with emotional significance. Among other things, we suggest that these regions (and other sensory association areas) serve as external alarm centers, alerting the individual about outside dangers.

In contrast, a region in the vicinity of anterior insular cortex (another paralimbic area[8,9]) appears to be preferentially involved in the emotional response to potentially distressing cognitive stimuli, interoceptive sensory stimuli, and body sensations. Perhaps this region has received less attention than limbic areas in studies that investigate the neural substrates of emotion in laboratory animals because it is difficult to elicit an emotional response in the absence of an exteroceptive sensory stimulus. (Try as one may, it is difficult to ask a laboratory rat to recall and relive a sad experience!) We have now observed CBF increases in a region that includes anterior insular cortex, claustrum, and lateral putamen during recall-generated sadness,[5] normal anticipatory anxiety,[2] lactate-induced panic,[10] the perception of temperature and pain,[21] and the luteal phase of the normal menstrual cycle.[22] On the basis of these and other studies, we postulate that the anterior insular region participates in the evaluation procedure that invests potentially distressing thoughts and body sensations with negative emotional significance. Among other things, this region may serve as an internal alarm center, alerting the individual about potential dangers inside the body.

The thalamus appears to participate in aspects of emotion that are unrelated to the type of emotion, emotional valence, or the nature of the emotional stimulus.[4,5,12] Limitations in anatomic localization and spatial resolution prevent us from relating the increases in thalamic CBF to particular thalamic nuclei, particular basal ganglia-thalamic-frontal circuits, or particular aspects of emotion, anxiety, and anxiety syndromes. On the basis of Cannon and Bard's classic studies of sham rage,[8] we postulate that the increases observed in anterior thalamus participate in some fashion in the integrated expression of emotion.

Like the thalamus, medial prefrontal cortex (Brodmann's area 9) appears to participate in aspects of emotion that are unrelated to the type of emotion, emotional valence, or the nature of the emotional stimulus.[4,5,12] We postulate that this region participates in the conscious experience of emotion, inhibition of potentially excessive emotion, or the process of monitoring one's own emotional state in order to make personally relevant decisions. Kihlstrom suggests that "the difference that makes for consciousness" is the connection between per-

ceptual or cognitive processes and an integrated representation of the self that resides in working memory.[23] If, like dorsolateral prefrontal cortex,[24] the medial prefrontal region is involved in working memory, it may participate in the conscious experience of emotion. The medial prefrontal cortex may have a role in the inhibition of excessive expressions of emotion for the following reasons: medial prefrontal lesions prolong the time it takes to extinguish conditioned fear in laboratory rats[25]; medial prefrontal lesions can be associated with socially inappropriate expressions of emotion in brain-injured patients[26]; and medial prefrontal activity was found to be inversely related to amygdala activity in patients with major depressive disorder.[27] Finally, studies of Phineas Gage and other patients with medial prefrontal damage suggest that this region monitors the person's emotional state in order to make personally relevant decisions.[26] (Our studies suggest that the behavioral changes observed in these patients may be related to lesions in a medial prefrontal region dorsal to the ventromedial prefrontal region highlighted by Damasio and colleagues.[26])

In addition to these regions, we find that modality-specific sensory association areas, a region including anterior cingulate and medial prefrontal cortex (ventral to the medial prefrontal region noted above), the caudate, the cerebellar vermis, and a midbrain region participate in normal and pathologic forms of anxiety.[2] As noted above, we postulate that the anterior cingulate/medial prefrontal region participates in the conscious experience of, attentional response to, or behavioral response to emotionally distressing circumstances, such as anxiety and pain, that the cerebellar vermis participates in the behavioral response to the distressing situation (i.e., facial expressions of anxiety, muscle tension, readiness to respond, or restraint from fleeing the situation) or cognitive aspects of anxiety that remain to be determined, and that thalamic and caudate regions are components in a basal ganglia-thalamic-frontal circuit[28] that somehow participates in the integrated expression of anxiety.

How do pathologic and normal forms of anxiety differ, how are they alike, and how do therapeutic interventions exert their beneficial effects? As indicated in our model of panic disorder, we propose that one or more regional abnormalities participate in the predisposition to pathologic forms of anxiety. We suggest that these abnormalities respond to a normally innocuous triggering event (e.g., a neurochemical change, a hormonal change, or a particular interoceptive or exteroceptive sensory stimulus) by sending a message to a common pathway that participates in pathologic and normal forms of anxiety; by sending a message to additional neuronal systems that participate in the vigilance to, monitoring of, and readiness to respond to the threatening situation; and by sending a message to neuronal systems that attempt to inhibit or compensate for potentially excessive emotion. We postulate that such fea-

tures as an anxiety disorder's natural history, sex distribution, and treatment may have more to do with alterations in the normally innocuous processes that participate in the initiation and elaboration of anxiety than they have to do with the regional abnormalities themselves. Although it remains possible that treatments exert their therapeutic effects by correcting the underlying abnormality, it appears at least as likely that they compensate for the abnormality by affecting other processes.[20]

While the long lists of brain regions implicated in normal and pathologic forms of anxiety may appear daunting—at the least, difficult to remember—they make an important point. The phrenologist's view that complex behaviors like emotion can be localized to a single brain center should be rejected. Instead, we should consider how the multiple mental operations and the spatially distributed brain processes that subserve them work in concert to produce a multifaceted emotional response.[2]

LIMITATIONS

In this article, I considered the CBF increases observed in our own PET studies of emotion, anxiety, and anxiety disorders. I have not discussed findings from the elegant PET studies of emotion,[29–31] anxiety,[14,32] and anxiety disorders[32–45] performed in other laboratories; I have not discussed how PET may help characterize the neurochemical processes that underlie the observed changes in neuronal activity. I have not considered the potentially complementary role of other imaging techniques, such as structural MRI,[46] magnetic resonance spectroscopy,[47–49] and functional magnetic resonance imaging[50–52]; and I have not considered how PET complements other research strategies (e.g., neural tract tracing, lesion, stimulation, unit recording, cognitive, developmental, pharmacologic challenge, treatment, and other kinds of brain imaging studies) that can be performed in laboratory animals, patients with selective brain injuries, patients with psychiatric disorders, and normal volunteers.[53] I have not described potentially important hemispheric asymmetries,[54] for which we have modified our brain-mapping algorithms to directly compare regional CBF changes in one hemisphere with those in the other. Finally, I have not considered potentially important decreases in regional CBF, some of which may be related to selective inattention to less relevant sensory modalities, emotional repression, and the disinhibition of normally repressed emotions.

Reductions in cerebral activity may play an important role in the generation of emotion. Confirming the original discovery by Goltz more than 100 years ago, Cannon and Bard found that the cerebral cortex is unnecessary for the expression of emotions such as fear and rage.[8] Surgical removal of the cerebral cortex above the level of the hypothalamus and caudoventral thalamus caused cats and dogs to exhibit what the investigators called "sham rage," an unprovoked and integrated emotional response with behavioral, autonomic, and endocrine components.[8] Their findings suggest that the cerebral cortex serves to inhibit unbridled expressions of emotion. It remains to be determined which cortical structures participate in emotional inhibition; which structures, if any, need to be "turned off" for the disinhibition of emotion; and how the deactivation of such structures may lead efferent pathways to participate in the generation of emotion.

PET studies have several limitations that prevent the complete characterization of the neuronal pathways that are causally related to the dissectable components of emotion and anxiety. Limitations in anatomic standardization (necessary for comparing data between subjects) and spatial resolution make it difficult to specify the structures (e.g., particular thalamic nuclei and insular cortex versus claustrum) responsible for the observed increases in regional CBF. Limitations in temporal resolution prevent us from characterizing the sequence in which the implicated regions are activated. Although PET studies provide information about the brain regions that are selectively affected during an emotional response, lesion studies are required to determine whether the implicated regions are necessary or sufficient for particular aspects of the response. Since increases in regional CBF appear to reflect the activity of terminal neuronal fields (including those from local interneurons and afferent projections arising from other sites), lesion studies may be necessary to specify the neuronal projections responsible for these increases. Finally, in some cases, failure to detect significant increases in regional CBF may be related to limitations in the contrast resolution, spatial resolution, and statistical power of PET; changes in the pattern rather than the overall level of neuronal activity; and heterogeneity in different subjects' responses to a particular emotion-eliciting situation. For all of these reasons, negative findings should be interpreted with caution; positive findings should be interpreted in the form of testable hypotheses and replicated; and PET should be used in a manner that complements other research strategies.

CONCLUSION

When used in conjunction with other research strategies, PET promises to help determine how multiple mental operations and the spatially distributed brain processes that subserve them work in concert to produce multifaceted emotions and how they conspire to produce emotional disorders.

Drug name: alprazolam (Xanax).

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