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STRUCTURAL AND FUNCTIONAL IMAGING OF ANXIETY AND STRESS DISORDERS

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GENERAL PRINCIPLES

Neuroimaging research has emerged as a powerful force in shaping neurobiological models of psychiatric disorders. In this chapter, neuroimaging findings pertaining to anxiety and stress disorders are reviewed. This review necessarily extends previous ones that we have written, together with our colleagues, on this same and related topics (97,98,103).

Anxiety and Stress Disorders

Whereas anxiety disorders comprise a discrete category within the current version of the *Diagnostic and Statistical Manual* (2), the concept of stress disorders is less well defined. Although growing evidence suggests that stress may play a role across a variety of psychiatric disorders (such as major depression), posttraumatic stress disorder (PTSD) and acute stress disorder remain the only conditions for which exposure to traumatic stress is explicitly acknowledged as an etiologic factor and a criterion for diagnosis. In this chapter, we survey the imaging data pertinent to models of PTSD and other anxiety disorders, including obsessive-compulsive disorder (OCD), specific phobias (SpP), social phobia (SoP; also called social anxiety disorder) and panic disorder (PD).

In general, patients with anxiety disorders suffer either exaggerated fear responses to relatively innocuous stimuli (e.g., phobias) or spontaneous fear responses in the absence of true threat (e.g., PD). Thus, it is important to consider the mediating neuroanatomy of normal threat assessment and the fear response. In fact, contemporary models focus on these systems as candidate neural substrates for the anxiety disorders.

Relevant Neuroanatomy

The limbic system plays an important role in mediating human emotional states, including anxiety. Anterior paralimbic cortex (i.e., posterior medial orbitofrontal, anterior temporal, anterior cingulate, and insular cortex) links cortical regions subserving higher level cognition and sensory processing with deep limbic structures, such as the amygdala and the hippocampus (81).

Modern models of threat assessment and the normal fear response have focused on the role of the amygdala (1,75). The amygdala is positioned to receive input regarding the environment both directly and, thus, rapidly from the thalamus as well as from sensory cortex. The amygdala appears to serve several related functions, including preliminary threat assessment; facilitation of fight-or-flight responses; facilitation of additional information acquisition; and enhancement of arousal and plasticity, so the organism can learn from the current experience to guide responses optimally in future similar situations.

Conversely, several brain areas provide important feedback to the amygdala (1,75): medial frontal cortex (e.g., anterior cingulate and orbitofrontal cortex) may provide critical ''top-down'' governance over the amygdala, thus enabling attenuation of the fear response once danger has passed or when the meaning of a potentially threatening stimulus has changed; the hippocampus provides information about the context of a situation (based on information retrieved from explicit memory stores); and corticostriatothalamic circuits mediate ''gating'' at the level of the thalamus and thereby regulate the flow of incoming information that reaches the amygdala.

Finally, neuromodulators influence the activity within each of these various brain areas, as well as the interactions

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among the nodes of the entire system outlined earlier. Ascending projections from the raphe nuclei (serotonin) and the locus ceruleus (norepinephrine), as well as widespread local γ-aminobutyric acid–ergic (GABAergic) neurons, are perhaps most relevant to the physiology of anxiety (30,65, 114). These transmitter systems likely serve as the principal substrates for contemporary anxiolytic medications, including serotonergic reuptake inhibitors, monoamine oxidase inhibitors, other antidepressant medications, and benzodiazepines.

Neuroimaging Methods

Morphometric magnetic resonance imaging (mMRI) methods can be used to test hypotheses regarding abnormalities in the size or shape of particular brain structures. Functional imaging methods include positron emission tomography (PET) with tracers that measure blood flow (e.g., oxygen-15–labeled carbon dioxide) or glucose metabolism (i.e., fluorine-18–labeled fluorodeoxyglucose [FDG]), single photon emission tomography (SPECT) with tracers that measure correlates of blood flow (e.g., technetium-99–labeled hexamethylpropylene amine oxime [TcHMPAO]), and functional MRI (fMRI) to measure blood oxygenation level–dependent (BOLD) signal changes. Each of these techniques yields maps that reflect regional brain activity.

Functional imaging methods can be applied in the context of various experimental paradigms. In *neutral state paradigms,* subjects are studied during a nominal ''resting'' state or while they perform a nonspecific continuous task. Thus, between-group comparisons are made to test hypotheses regarding group differences in regional brain activity, without particular attention to state variables. In *treatment paradigms,* subjects are scanned in the context of a treatment protocol. In pre/posttreatment studies, subjects are scanned both before and after a trial. Then, within-group comparisons are made to test hypotheses regarding changes in brain activity profiles associated with symptomatic improvement. Alternatively, correlational analyses can be performed to identify pretreatment brain activity characteristics that predict good or poor treatment response. In *symptom provocation paradigms,* subjects are scanned during a symptomatic state (after having their symptoms intentionally induced) as well as during control conditions. Within-group comparisons can be made to test hypotheses regarding the mediating anatomy of the symptomatic state; group-by-condition interactions can be sought to distinguish responses in patient versus control groups. Behavioral and pharmacologic challenges can be used to induce symptoms. In some cases, when symptomatic states occur spontaneously, experiments are designed to capture these events without the need for provocation or induction *per se.* In *cognitive activation paradigms,* subjects are studied while they perform specially designed cognitive-behavioral tasks. This approach is intended to increase sensitivity by employing tasks that specifically activate brain systems of interest. Again, group-by-condition interactions are sought to test the functional responsivity or integrity of specific brain systems in patients versus control subjects.

Imaging studies of neurochemistry have employed PET and SPECT methods in conjunction with radiolabeled high-affinity ligands. In this way, regional receptor number and or affinity can be characterized *in vivo* (i.e., receptor-characterization studies). Other approaches include the use of magnetic resonance spectroscopy (MRS) to measure the regional relative concentration of select ''MRS-visible'' compounds. For instance, MRS can be used to measure the compound *N*-acetylaspartate (NAA), which is a purported marker of healthy neuronal density.

These various neuroimaging techniques should be viewed as complementary. Convergent findings across paradigms and laboratories yield the most cohesive and compelling models of pathophysiology.

RELEVANT NEUROIMAGING FINDINGS IN HEALTHY SUBJECTS

Anxiety and Other Negative Emotional States

Behaviorally Induced Fear and Anxiety

Fischer and colleagues used PET to study regional cerebral blood flow (rCBF) in bank officials while they viewed security camera videotape of a robbery that they had experienced previously (46). Watching the robbery video was associated with rCBF increases in orbitofrontal cortex, visual cortex, and posterior cingulate gyrus; rCBF decreases occurred in Broca's area, left angular gyrus, operculum, and secondary somatosensory cortex. Paradiso et al. studied rCBF in healthy elderly subjects who viewed emotionally evocative film clips; a fear/disgust versus neutral comparison revealed activation in orbitofrontal cortex, among other areas (93). Similarly, Kimbrell et al. studied induced emotional states in healthy adults (67); relative to a neutral condition, an anxiety condition was associated with rCBF increases in left anterior cingulate and left temporal pole, whereas rCBF decreases were found in nonparalimbic frontal cortical regions. Liotti et al. used PET and autobiographic memory scripts to examine the neural correlates of anxiety and sadness in healthy women (77); relative to a neutral condition, an anxiety condition was associated with rCBF increases in insular, orbitofrontal, and anterior temporal cortex and rCBF decreases in parahippocampal gyri.

Pharmacologically Induced Fear and Anxiety

Benkelfat et al. examined rCBF changes associated with the administration of cholecystokinin tetrapeptide versus saline in healthy persons (10). Administration of cholecystokinin

tetrapeptide was accompanied by increased heart rate and panic symptoms and rCBF increases in right cerebellar vermis, left anterior cingulate gyrus, bilateral claustrum-insula-amygdala, and bilateral temporal poles. However, further analyses suggested that the apparent temporal pole activations were attributable to extracranial artifacts of jaw muscle contraction. Ketter et al. used PET to study rCBF changes during procaine versus saline administration in healthy persons (66). In the procaine versus saline contrast, rCBF increases occurred in amygdala and anterior paralimbic structures, including anterior cingulate gyrus, insular cortex, and orbitofrontal cortex. Blood flow in left amygdala was positively correlated with fear intensity and was negatively correlated with euphoria intensity. Similar results were reported by Servan-Schreiber et al. (126).

Other Negative Emotions

Several studies examining rCBF associated with behaviorally induced sadness in healthy subjects have implicated both anterior paralimbic and nonparalimbic frontal cortical areas (4,54,55,77,94). Some studies of behaviorally induced sadness have also found rCBF changes within the amygdala (71, 120,121). Of note, studies of other behaviorally induced negative emotions, including anger (39,67) and guilt (127), have likewise found activation of anterior paralimbic cortical territories.

Processing Unpleasant, Arousing, or Threat-Related Stimuli

In functional imaging studies of responses to unpleasant pictures (73), several studies have found amygdala activation when contrasted with a neutral (63,72) or pleasant picture (92) comparison condition. In a separate study, Lane et al. reported that anterior paralimbic regions were activated when study subjects attended to the emotions evoked by the pictures rather than when subjects attended to physical attributes of the depicted scenes (70). Functional imaging studies have also demonstrated a correlation between amygdala activity during encoding of emotionally arousing pictures or film clips and subjects' subsequent memory of them (29,59).

Several functional imaging studies have shown greater amygdala responses to overtly presented fearful human facial expressions in comparison with neutral or happy faces (14, 86). Whalen et al. used fMRI and a technique called "backward masking" to study amygdala responses to emotional faces in the absence of explicit knowledge (142). Although subjects were unaware of seeing the "masked" emotional faces, a comparison of the masked fear and masked happy conditions yielded activation in the amygdala bilaterally.

Habituation

The term *habituation* refers to a decrement in responses over repeated presentations of a stimulus. Measures of habituation can be obtained peripherally (e.g., skin conductance) or more centrally (e.g., rCBF or fMRI BOLD signal). For example, declining fMRI BOLD signal within the amygdala has been observed in response to repeated presentations of fearful faces, regardless of whether subjects are aware the stimuli are present (14,142).

A few studies have directly examined the neural correlates of habituation. Fischer et al. used PET to study rCBF changes over repeated presentation of videotaped scenes in healthy women (45). In separate scanning conditions, subjects watched two repeated videotaped presentations of neutral park scenes and snakes. From the first to the second presentation of the videotapes, rCBF decreased in bilateral secondary visual cortex and right medial temporal cortex, including amygdala and hippocampus. In an fMRI study, Fischer et al. also found response decrements over repeated presentations of human face stimuli in amygdala and hippocampus, as well as thalamus, and prefrontal, inferior temporal, and posterior cingulate cortex (47). Similar results have also been reported by Wright et al. (146).

Conditioning and Extinction

Fear conditioning involves the presentation of a neutral stimulus (i.e., a conditioned stimulus [CS]), such as a tone, that is temporally paired with an aversive stimulus (i.e., the unconditioned stimulus [US]), such as a shock. After repeated presentations of the CS and US, the CS alone begins to elicit fear-related autonomic changes, such as skin conductance responses. Subsequently, over repeated presentations of the CS without the US, fear responses decline, and this process is referred to as *extinction.* Existing research suggests that the amygdala plays a critical role in fear conditioning (27,35,74,75,141), and the medial prefrontal cortex may play a critical role in the process of extinction (56,83, 84).

Fredrikson and Furmark and their colleagues used PET to study healthy subjects who viewed a videotape of snakes (CS) both before and after the video was paired with shock (US) (49,52). The findings revealed a significant correlation between rCBF changes in right amygdala and electrodermal activity changes. Hugdahl et al. used PET to compare patterns of blood flow before and after classic conditioning in healthy male study subjects, by employing a paradigm in which a tone (CS) was paired with brief shock (US) (62). Extinction was associated with widespread activations in right prefrontal, including orbitofrontal, cortex, as well as left occipital and superior frontal cortex.

In a different conditioning paradigm, Morris et al. showed study subjects pictures of faces that were previously paired with an aversive burst of white noise (CS+) and faces that were never paired with the noise (CS−) (85). A comparison of the CS+ versus CS− conditions yielded activation in right thalamus, orbitofrontal cortex, and superior frontal gyrus. There was a positive correlation between

activation in thalamus and in right amygdala, orbitofrontal cortex, and basal forebrain. Morris and colleagues subsequently used PET and backward masking techniques to study rCBF responses to conditioned face stimuli with and without awareness in healthy male subjects (87). When all CS+ conditions were compared with all CS− conditions, bilateral activation in amygdala was observed. Right amygdala activation was found in the condition in which subjects were aware; left amygdala activation was found in the condition in which subjects were unaware of the emotionally expressive face stimuli.

In a single-trial fMRI study, LaBar et al. examined amygdala activation during both acquisition and extinction in a mixed-gender cohort (69). In the acquisition condition, a colored shape (CS+) was paired with a shock (US), whereas a different colored shape (CS−) was never paired with shock. No shocks were delivered during the extinction condition. Comparing CS+ with CS− trials revealed activation in periamygdaloid cortex and amygdala during early acquisition and early extinction trials, respectively. Activation in both these regions declined over time. Büchel and colleagues also used a single-trial fMRI to study the neural correlates of fear conditioning in healthy subjects (26). Study subjects were scanned during an acquisition phase in which two neutral faces (CS+) were presented with a loud tone (US) and two other neutral faces were presented alone (CS−). To disambiguate the effects of the CS+ and US, the US was not presented on half of the CS+ trials (i.e., $CS+_{unpaired}$). The critical comparison, $CS+_{unpaired}$ versus CS−, revealed activation in anterior cingulate, bilateral insular, parietal, supplementary motor, and premotor cortex. A time by event type interaction revealed that fMRI signal in amygdala decreased over time in the $CS+_{unpaired}$ condition relative to the CS− condition. Similar results were reported by Büchel et al. in a trace conditioning study, in which a temporal gap occurs between the offset of the CS and onset of the US (28). These researchers also found conditioning-related hippocampal activation that declined over time.

Summary

Taken together, functional imaging studies in healthy human subjects extend findings from animal research. Normal anxiety and fear reactions are associated with increased activity in limbic and paralimbic regions, whereas other territories of heteromodal association cortex exhibit decreased activity. However, similar patterns of limbic and paralimbic activation may be observed in association with other emotional states, and hence this general profile should not be taken as specific to anxiety or fear. Exposures to unpleasant, arousing, or threat-related stimuli often produce detectable amygdala responses, which can be associated with enhanced memory. Additional paralimbic recruitment may be related to a person's attention to his or her emotional state. Habituation can be observed in widely distributed brain regions, including limbic, paralimbic, and sensory areas. Consistent with animal data, human imaging results point to a role for the amygdala in fear conditioning and for the frontal cortex in extinction. The accessory role of the hippocampus in these processes remains less well defined.

POSTTRAUMATIC STRESS DISORDER

Amygdalocentric Neurocircuitry Model

We previously presented a neurocircuitry model of PTSD that emphasizes the central role of the amygdala and its interactions with the hippocampus, medial prefrontal cortex, and other heteromodal cortical areas purported to mediate higher cognitive functions (103). Briefly, this model hypothesizes hyperresponsivity within the amygdala to threat-related stimuli, with inadequate top-down governance over the amygdala by medial prefrontal cortex, specifically, the affective division of anterior cingulate cortex (142), and the hippocampus. Amygdala hyperresponsivity mediates symptoms of hyperarousal and explains the indelible quality of the emotional memory for the traumatic event; inadequate influence by the anterior cingulate cortex underlies deficits of habituation, and decreased hippocampal function underlies deficits in identifying safe contexts, as well as accompanying explicit memory difficulties (21). Further, we propose that in threatening situations, patients with PTSD exhibit an exaggerated reallocation of resources to regions that mediate fight-or-flight responses and away from widespread heteromodal cortical areas, as a neural substrate for dissociation.

Structural Imaging Findings

mMRI studies have reported smaller hippocampal volumes in veterans with PTSD than in comparison subjects. Bremner and colleagues (21) found that right hippocampal volumes were 8% smaller in 26 veterans with PTSD than in 22 civilians without PTSD. In addition, the PTSD group exhibited poorer performance on a standard measure of verbal memory, and their percent retention scores on this test were directly correlated with right hippocampal volume (i.e., lower scores were associated with smaller right hippocampal volumes). Gurvits and colleagues (58) used mMRI to study seven Vietnam combat veterans with PTSD, seven Vietnam combat veterans without PTSD, and eight nonveterans without PTSD. These investigators found significantly smaller hippocampal volumes bilaterally for the PTSD group in comparison with both control groups. Across the 14 veterans, hippocampal volume was inversely correlated with extent of combat exposure and PTSD symptom severity.

Similar hippocampal volumetric differences also have been reported in mMRI studies of PTSD resulting from childhood abuse. Bremner and colleagues (22) found 12%

smaller left hippocampal volumes in 17 adult survivors of childhood abuse with PTSD than in 21 nonabused comparison subjects. Stein and colleagues (134) found 5% smaller left hippocampal volumes in 21 adult survivors of childhood sexual abuse (most of whom had PTSD) than in 21 nonabused comparison subjects. Furthermore, total hippocampal volume was smaller in abused subjects with high PTSD symptom severity than in those with low PTSD symptom severity. In contrast to these results, DeBellis et al. (36) failed to find decreased hippocampal volumes in 44 maltreated children and adolescents with PTSD, compared with 61 nonabused healthy subjects. However, the PTSD group had smaller intracranial and cerebral volumes than did the comparison group.

Taken together, the results of structural neuroimaging studies of adult samples suggest that PTSD is associated with reduced hippocampal volume, which, in turn, may be associated with cognitive deficits and PTSD symptom severity. Although the extent of traumatic exposure may be correlated with hippocampal volume, it appears that differences between PTSD and control groups cannot be explained by traumatic exposure alone (58). The results of DeBellis et al. (36) suggest that hippocampal volumetric differences between groups may not be evident in samples of children and adolescents or in samples of persons with relatively recent traumatic exposures.

Stress, Glucocorticoids, and the Hippocampus

In this review about neuroimaging of anxiety and stress disorders, it is worth elaborating on the potential relationship between stress and hippocampal findings in PTSD. Animal research has provided evidence that stress is associated with damage to the hippocampus (16). For example, sustained, fatal social stress in vervet monkeys was associated with degeneration of neurons in the CA3 region of the hippocampus (139); chronic restraint stress in rats was associated with atrophy of apical dendrites of hippocampal CA3 pyramidal neurons (140); and exposure to cold water immersion stress in rats was related to structural damage to hippocampus (CA3 and CA2 fields) and deceased local CBF in hippocampus (42).

The effect of stress on hippocampus appears to be mediated by glucocorticoid hormones. Exposure to glucocorticoids is associated with hippocampal damage in both rats and primates. For example, Sapolsky et al. reported that chronic exposure to corticosterone in rats led to a loss of neurons in the CA3 region of the hippocampus (115). Woolley and colleagues found that daily corticosterone injections decreased dendritic branching and length in the CA3 region of the rat hippocampus (145). In a study of primates, Sapolsky et al. reported that chronic exposure to cortisol (through steroid-secreting pellets stereotactically implanted in hippocampus) was related to neuronal shrinkage and dendritic atrophy in the CA3 region (117). Moreover, chronic stress during development is capable of inhibiting normal cellular proliferation within the hippocampus, a process mediated by glucocorticoids and glutamatergic transmission by an *N*-methyl-D-aspartate receptor–dependent excitatory pathway (57).

Clinical research has also revealed decreased hippocampal volumes in humans with elevated cortisol levels resulting from Cushing's syndrome (130); furthermore, in these patients, a treatment-related reduction of cortisol levels is associated with increased hippocampal volumes (131). High cortisol levels and decreased hippocampal volumes have also been found in patients with major depressive disorder (25). The hippocampus is also involved in the modulation of the hypothalamic-pituitary-adrenal (HPA) axis, and lesions to hippocampus appear to increase the release of glucocorticoids during stress (43,60); this, in turn, may further damage the hippocampus (116).

Although these findings may have great relevance to anxiety and stress disorders, the picture is complicated by the finding that cortisol levels are characteristically reduced, rather than elevated, in PTSD (147). One parsimonious theory suggests that patients with PTSD suffer hypersensitivity to glucocorticoids, resulting in both reduced levels of cortisol (because of accentuated feedback inhibition) and reduced hippocampal volume (147).

Functional Imaging Findings

Semple and colleagues used PET to study six patients with combat-related PTSD and comorbid substance abuse versus seven normal control subjects (125). rCBF was measured in three conditions: resting state, an auditory continuous performance task, and a word generation task. Compared with the control group, the PTSD group exhibited greater rCBF during both task conditions within orbitofrontal cortex.

Rauch and colleagues studied a mixed-gender cohort of eight subjects with PTSD, using PET and a script-driven imagery method for inducing symptoms (104). In the provoked versus control condition, patients exhibited increased rCBF within anterior cingulate cortex, right orbitofrontal, insular, anterior temporal and visual cortex, and right amygdala. rCBF decreases occurred within left inferior frontal (Broca's area) and left middle temporal cortex. Interpretations of this initial study, with regard to the pathophysiology of PTSD, were limited by the absence of a comparison group.

Using a similar paradigm and a comparison group, Shin and colleagues studied eight women with childhood sexual abuse–related PTSD and eight matched trauma-exposed control subjects without PTSD (129). In the traumatic versus neutral comparison, both groups exhibited anterior paralimbic activation. However, a group-by-condition interaction revealed that the control group manifested a

significantly greater rCBF increase within anterior cingulate cortex than did the PTSD group, whereas the PTSD group showed significantly greater rCBF increases within anterior temporal and orbitofrontal cortex. Bremner and colleagues (20) also used script-driven imagery and PET to study rCBF in ten female survivors of childhood sexual abuse with PTSD and 12 without PTSD. Consistent with the findings of Shin et al. (129), Bremner and colleagues (20) reported relatively attenuated recruitment of anterior cingulate cortex in the PTSD group.

Bremner and colleagues (23) studied rCBF responses to trauma-related pictures and sounds in ten Vietnam veterans with PTSD and in ten veterans without PTSD. In the combat versus neutral comparison, the PTSD group exhibited rCBF decreases in medial prefrontal cortex (subcallosal gyrus) and anterior cingulate cortex. Liberzon and colleagues (76) used SPECT to study rCBF in 14 Vietnam veterans with PTSD, 11 veteran control subjects, and 14 healthy nonveterans. In separate scanning sessions, subjects listened to combat sounds and white noise. In the combat sounds versus white noise comparison, all three groups showed activation in anterior cingulate/medial prefrontal cortex, but only the PTSD group exhibited activation in the left amygdaloid region.

Bremner et al. (17) used PET to examine the effect of yohimbine challenge on glucose metabolic rates in ten combat veterans with PTSD and in ten nonveteran subjects without PTSD. Yohimbine administration was associated with increased anxiety and panic symptoms , as well as widespread decreases in cerebral glucose metabolism in the PTSD group.

Shin and colleagues studied seven patients with combat-related PTSD and seven matched trauma-exposed control subjects without PTSD in the context of a PET cognitive activation paradigm (128). Subjects were required to make judgments about pictures from three categories: neutral, general negative, and combat-related. Subjects performed two types of tasks: one involved responding while actually seeing the pictures (perception), and another involved responding while recalling the pictures (imagery). In the combat imagery versus control conditions, the PTSD group exhibited rCBF increases in right amygdala and ventral anterior cingulate gyrus and rCBF decreases in left inferior frontal gyrus (Broca's area).

Using another cognitive activation paradigm, Rauch et al. studied the functional integrity of the amygdala in eight combat veterans with PTSD and eight healthy combat veterans (108). During fMRI, subjects viewed fearful and happy faces temporally masked by neutral faces. Healthy persons are typically aware of seeing only the neutral faces, although they show amygdala activation to the masked fearful faces (142). Rauch and colleagues found greater amygdala activation to masked fearful faces in persons with PTSD than in control subjects (108). Furthermore, the magnitude of amygdala activation was correlated with PTSD severity. These results suggest that PTSD may be characterized by amygdala hyperresponsivity to general threat-related stimuli, consistent with our neurocircuitry model of PTSD.

Imaging Studies of Neurochemistry

Schuff and colleagues used mMRI and MRS to study seven veterans with PTSD and seven nonveteran control subjects (123). Although these investigators found a nonsignificantly smaller (6%) right hippocampus in the PTSD group by mMRI, they found an 18% reduction in right hippocampal NAA by MRS, a finding suggestive of reduced density or viability of neurons in this region.

DeBellis and colleagues used MRS to study NAA/creatine ratios in 11 maltreated children and adolescents with PTSD and 11 healthy comparison subjects without histories of maltreatment (37). The PTSD group had lower NAA/creatine ratios in pregenual anterior cingulate gyrus. This result is consistent with those of symptom provocation PET studies (20,23,129), which have reported failure to activate anterior cingulate in PTSD.

Bremner et al. (18) used SPECT and [^{123}I]iomazenil to study benzodiazepine-receptor binding in 13 veterans with PTSD and 13 nonveterans without PTSD. These investigators found decreased benzodiazepine-receptor binding in prefrontal cortex in the PTSD group, relative to the control group.

Summary

Taken together, data from neuroimaging studies are consistent with the current neurocircuitry model of PTSD that emphasizes the functional relationship among the amygdala, hippocampus, and medial prefrontal cortex. Hippocampal volumes and NAA levels appear to be decreased in persons with PTSD. These findings dovetail with animal research that points to a relationship among stress, HPA axis function, and cell viability within the hippocampus. Functionally, in comparison with control subjects, patients with PTSD exhibit the following: (a) greater activation within orbitofrontal cortex, anterior temporal poles, and the amygdala; (b) diminished activation in anterior cingulate and medial prefrontal cortex, as well as reduced NAA/creatine ratios in pregenual anterior cingulate; and (c) decreased activation within widespread areas that are associated with higher cognitive functions, such as Broca's area and dorsolateral prefrontal cortex.

OBSESSIVE-COMPULSIVE DISORDER

Corticostriatal Model

One current neuroanatomic model of OCD focuses on corticostriatothalamocortical circuitry (98,106). According to

this model, the primary disorder lies within the striatum (specifically, the caudate nucleus). This leads to inefficient gating at the level of the thalamus, which results in hyperactivity within orbitofrontal cortex (corresponding to the intrusive thoughts) and hyperactivity within anterior cingulate cortex (corresponding to anxiety, in a nonspecific manner). Compulsions are conceptualized as repetitive behaviors that are performed to recruit the inefficient striatum ultimately to achieve thalamic gating and hence to neutralize the unwanted thoughts and anxiety.

Structural Imaging Findings

The results of several mMRI investigations of OCD have suggested volumetric abnormalities involving the caudate nucleus, although the nature of the observed abnormalities has been somewhat inconsistent. Scarone et al. (119) studied a mixed-gender cohort of 20 patients with OCD versus 16 matched controls and found increased right caudate volume in the OCD group. Robinson et al. (111) studied a mixed-gender cohort of 26 patients with OCD versus 26 matched controls and found bilaterally decreased caudate volumes in the OCD group. Jenike et al. (64) studied an all-female cohort of ten patients with OCD versus matched controls and found trends toward a rightward shift in caudate volume ($p = .06$) as well as overall reduced caudate volume ($p = .10$) in the OCD group. Aylward et al. (3) studied a mixed-gender cohort of 24 patients with OCD versus 21 matched controls and found no significant differences in striatal volumes. Rosenberg et al. (112) studied 19 treatment-naive pediatric subjects with OCD and 19 case-matched psychiatrically healthy comparison subjects. These investigators found reduced striatal volumes in the OCD group and an inverse correlation between striatal volume and OCD symptom severity.

Functional Imaging Findings

Neutral state paradigms employing PET and SPECT have most consistently indicated that patients with OCD exhibit increased regional brain activity within orbitofrontal and anterior cingulate cortex, in comparison with neurologically normal control subjects (6,7,78,89,113,136). Observed differences in regional activity within the caudate nucleus have been less consistent (6,113).

Pre/posttreatment studies have reported treatment-related attenuation of abnormal regional brain activity within orbitofrontal cortex, anterior cingulate cortex, and caudate nucleus (8,9,61,95,124,137). In addition, both pharmacologic and behavioral therapies appear to be associated with similar brain activity changes (8,124). Some treatment studies have also reported that lower pretreatment glucose metabolic rates in orbitofrontal cortex predict a better response to serotonergic reuptake inhibitors (24,118,136).

Symptom provocation studies employing PET (80,99) as well as functional MRI (15) have also most consistently shown increased brain activity within anterior-lateral orbitofrontal cortex, anterior cingulate cortex, and caudate nucleus during the OCD symptomatic state.

Cognitive activation studies using PET and fMRI have probed the functional integrity of the striatum in OCD (102,105). In these studies, patients with OCD perform an implicit (i.e., nonconscious) learning paradigm shown reliably to recruit striatum in healthy individuals (101,107). In both studies, patients with OCD failed to recruit striatum normally and instead activated medial temporal regions typically associated with conscious information processing.

Imaging Studies of Neurochemistry

Several MRS studies have been performed to measure NAA concentrations in patients with OCD versus healthy comparison subjects. Ebert and colleagues (41) found reduced relative NAA levels in right striatum and anterior cingulate cortex in 12 patients with OCD in comparison with six healthy control subjects. Bartha and colleagues (5) found lower left striatal NAA concentrations in 13 patients with OCD than in 13 matched control subjects.

MRS has also been used to demonstrate elevated glutamatergic concentrations within the striatum of a child with OCD (82). Glutamate is the principal transmitter mediating frontostriatal communication. Interestingly, elevated striatal glutamate levels were attenuated toward normal after successful pharmacotherapy. These findings suggest that orbitofrontal hyperactivity in OCD may be mirrored by elevated glutamate at the site of orbitofrontal ramifications in striatum, and treatment-related attenuation of orbitofrontal activity may be accompanied by decreased glutamate concentration within the striatum.

Summary

Taken together, these neuroimaging findings are consistent with disorders in corticostriatothalamocortical circuitry. Consistent with the hypothesis of a primary abnormality in the striatum, MRI and MRS studies of OCD have shown reduced striatal volumes and reduced striatal NAA, respectively. PET studies have revealed hyperactivity within orbitofrontal cortex, and the magnitude of this hyperactivity predicts response to treatment. In addition, in neurologically normal persons, the performance of repetitive motor routines does facilitate striatal recruitment in the service of thalamic gating, whereas this pattern is not readily demonstrated in patients with OCD. These imaging data further support the working model of striatal pathology and striatothalamic inefficiency, together with orbitofrontal hyperactivity.

SOCIAL AND SPECIFIC PHOBIAS

Neuroanatomic Models

Currently, there are no cohesive neuroanatomically based models for the phobias (53,132). One possibility is that phobias are learned and hence reflect another example of fear conditioning to specific stimuli or situations. Alternatively, phobias may represent the product of dysregulated systems for detecting potentially threatening stimuli or situations. For instance, if humans have evolved a neural network specifically designed to assess social cues for threatening content, and another to assess threat from small animals, these may represent the neural substrates for the pathophysiology underlying phobias.

Structural Imaging Findings

Given the high prevalence of phobias and the relative ease with which medication-free phobic subjects without significant comorbidities can be recruited, it is striking how few imaging studies have been conducted in this arena. Potts et al. used mMRI to examine volumetric measures of total cerebrum, caudate, putamen, and thalamus in 22 patients with SoP and in 22 matched healthy control subjects (96). The groups did not significantly differ on any of these measures.

Functional Imaging Findings

Studies of SpP to date have principally employed PET symptom provocation paradigms and have reported somewhat inconsistent results. Mountz and colleagues found that persons with small-animal phobia exhibited increased heart rates, respiratory rates, and subjective reports of anxiety during exposure to phobic stimuli; however, no changes in rCBF measurements were observed (88).

Wik and colleagues studied six patients with snake phobias during exposure to videotapes of neutral, generally aversive, and snake-related scenes (143). During the phobic condition, they found significant rCBF increases in secondary visual cortex and rCBF decreases in prefrontal cortex, posterior cingulate cortex, anterior temporopolar cortex, and hippocampus. These findings were similar to those of two other studies of phobia from the same laboratory (50,51).

Using *in vivo* exposure and PET, Rauch and colleagues studied rCBF in seven persons with a variety of small animal phobias (100). In the provoked versus control condition, patients with phobias exhibited rCBF increases within multiple anterior paralimbic territories (i.e., right anterior cingulate, right anterior temporal pole, left posterior orbitofrontal cortex, and left insular cortex), left somatosensory cortex, and left thalamus.

Whereas one neutral-state SPECT study of patients with SoP and healthy control subjects found no significant between-group differences in rCBF (133), more recent cognitive activation studies performed in conjunction with fMRI have yielded more informative results. Birbaumer et al. (11) used fMRI to study seven patients with SoP and five healthy control subjects during exposure to slides of neutral human faces or aversive odors. In comparison with the control group, the SoP group exhibited hyperresponsivity within the amygdala that was specific to the human face stimuli. In a follow-up study, Schneider et al. used fMRI to study 12 patients with SoP and 12 healthy control subjects (122). The researchers used a classic conditioning paradigm in which neutral face stimuli were the conditioned stimuli and odors (negative odor and odorless air) served as the unconditioned stimuli. In response to conditioned stimuli associated with the negative odor, the SoP group displayed signal increases within amygdala and hippocampus, whereas healthy comparison subjects displayed signal decreases in these regions.

Imaging Studies of Neurochemistry

Davidson et al. (34) used MRS to study NAA in 20 patients with SoP and in 20 healthy control subjects. Relative to the control group, the SoP group exhibited decreased NAA in white matter and cortical and subcortical gray matter (e.g., caudate and thalamus).

Tiihonen et al. used SPECT and I-123–labeled β-CIT to measure the density of dopamine reuptake sites in 11 patients with SoP and in 28 healthy comparison subjects (138). They found significantly reduced striatal dopamine reuptake binding site density in the SoP versus control group.

Summary

Although relatively few neuroimaging studies of SpP have been conducted, findings from existing research suggest activation of anterior paralimbic regions and sensory cortex corresponding to stimulus inflow associated with a symptomatic state. Although such results are consistent with a hypersensitive system for assessment of or response to specific threat-related cues, they do not provide clear anatomic substrates for the pathophysiology of SpP. Cognitive activation neuroimaging studies of SoP reveal exaggerated responsivity of medial temporal lobe structures to human face stimuli; this hyperresponsivity may reflect a neural substrate for social anxiety in SoP.

PANIC DISORDER

Neuroanatomic Models

Neurobiological models of PD have emphasized a wide range of disparate elements (31). Satisfactory models of PD must account for spontaneous panic attacks, which are a

defining feature of PD. It is possible that spontaneous panic corresponds to a normal physiologic anxiety response that is mediated by intact fear-anxiety circuits but, owing to homeostatic deficits, occurs in inappropriate, threat-free situations. This is consistent with theories of hypersensitivity to carbon dioxide at the level of the brainstem (i.e., the suffocation false alarm model), as well as theories regarding fundamental monoaminergic dysregulation. Another possibility is that panic attacks emerge in the context of what should be minor anxiety episodes because of failures in the systems responsible for limiting such normal responses; hippocampal deficits may underlie such a failure to inhibit anxiety responses. Finally, panic episodes described as spontaneous (i.e., without identifiable precipitants) could reflect anxiety responses to stimuli that are not processed at the conscious (i.e., explicit) level, but instead, recruit anxiety circuitry without awareness (i.e., implicitly). There is strong evidence that the amygdala can be recruited into action in the absence of awareness that a threat-related stimulus has been presented (142). By this model, PD may be characterized by fundamental amygdala hyperresponsivity to subtle environmental cues, triggering full-scale threat-related responses in the absence of conscious awareness.

Structural Imaging Findings

Fontaine et al. (48) published a qualitative MRI study involving 31 patients with PD and 20 matched healthy control subjects. The frequency of gross structural abnormalities was higher in the PD group (40%) than in the control group (10%); the most striking focal findings in the PD group involved abnormal signal or asymmetric atrophy of the right temporal lobe.

Functional Imaging Findings

In an initial PET neutral-state study, Reiman and colleagues studied 16 patients with PD and 25 normal control subjects (109). In the subset of patients who were vulnerable to lactate-induced panic (n = 8), the investigators found abnormally low left/right ratios of parahippocampal blood flow. DeCristofaro et al. used SPECT to measure rCBF at rest in seven treatment-naive patients with PD and in five age-matched healthy control subjects (38). Relative to the control group, the PD group exhibited elevated rCBF in left occipital cortex and reduced rCBF in the hippocampal area bilaterally. Nordahl et al. used PET and FDG to measure regional cerebral metabolic rate glucose (rCMRglc) in 12 patients with PD and 30 normal control subjects during an auditory continuous performance task (90). The investigators found that the PD group exhibited a lower left/right hippocampal ratio. In a follow-up experiment (91), these investigators used PET-FDG methods to study imipramine-treated subjects with PD and found a rightward shift in symmetry of rCMRglc within hippocampus and posterior inferior frontal cortex. In comparison with the untreated group, the imipramine-treated group exhibited rCMRglc decreases in posterior orbital frontal cortex. Bisaga et al. (12) used PET and FDG to study a cohort of six women with PD and six matched control subjects. In contrast to previous studies, the PD subjects displayed elevated rCMRglc in the left hippocampus and parahippocampal area.

The literature contains three symptom provocation studies of PD, all of which have employed pharmacologic challenges. Stewart et al. used SPECT and the xenon inhalation method to measure CBF during lactate infusion in ten patients with PD and in five healthy control subjects (135). The patients with PD who experienced lactate-induced panic attacks (n = 6) displayed global cortical CBF decreases. Woods et al. used SPECT and yohimbine infusions to study six patients with PD and six normal control subjects (144). In the PD group, yohimbine administration increased anxiety and decreased rCBF in bilateral frontal cortex. In a PET study, Reiman et al. measured rCBF during lactate infusions in 17 patients with PD and in 15 normal control subjects (110). The eight patients who suffered lactate-induced panic episodes exhibited rCBF increases in bilateral temporopolar cortex and bilateral insular cortex/claustrum/putamen. Healthy control subjects and patients with PD who did not experience lactate-induced panic attacks did not exhibit such rCBF changes. Of note, the temporopolar findings were subsequently questioned as possibly reflecting extracranial artifacts from muscular contractions (40,10). In a symptom capture case report, Fischer and colleagues (44) found that a spontaneous panic attack was associated with rCBF decreases in right orbitofrontal, prelimbic (area 25), anterior cingulate, and anterior temporal cortex.

Imaging Studies of Neurochemistry

Dager and colleagues used MRS to measure brain lactate levels during hyperventilation in seven treatment-responsive patients with PD and in seven healthy comparison subjects (32). The PD group showed a significantly greater rise in brain lactate in response to the same level of hyperventilation. Dager et al. also used MRS to measure brain lactate levels during lactate infusions in 15 patients with PD and in ten healthy comparison subjects (33). The PD group exhibited a significantly greater brain lactate level during lactate infusion, a finding consistent with the interpretation of reduced clearance, rather than higher production, of lactate in PD.

Three studies have used SPECT and [^{123}I]iomazenil to measure benzodiazepine-receptor binding in PD. Kuikka et al. (68) studied 17 subjects with PD and 17 matched healthy comparison subjects and found that the PD group exhibited a greater left/right ratio in benzodiazepine-receptor uptake that was most prominent in prefrontal cortex. Brandt et al. (13) studied 12 medication-naive patients with PD and nine

matched healthy control subjects and found that the PD group exhibited significantly elevated benzodiazepine-receptor binding within right supraorbital frontal cortex, as well as a trend toward elevated binding in the right temporal cortex. Bremner et al. (19) included 13 patients with PD and 16 healthy comparison subjects and found that the PD group showed decreased benzodiazepine-receptor binding in left hippocampus and precuneus.

Using PET and carbon-11–labeled flumazenil, Malizia et al. studied seven patients with PD and eight healthy comparison subjects (79). These investigators found that the PD group exhibited a global reduction in benzodiazepine binding that was most pronounced in right orbitofrontal and right insular cortex.

Summary

Resting state neuroimaging studies have suggested abnormal hippocampal activity in PD. Symptom provocation studies have revealed reduced activity in widespread cortical regions, including prefrontal cortex, during symptomatic states. MRS studies have reported greater brain lactate levels in response to hyperventilation and lactate infusions. Finally, receptor-binding studies of PD suggest widespread abnormalities in the GABAergic/benzodiazepine system. Consistent with prevailing neurobiological models of PD, it is possible that fundamental abnormalities in monoaminergic neurotransmitter systems, originating in the brainstem, underlie the abnormalities of metabolism, hemodynamics, and chemistry found in widespread territories of cortex. Further, regional abnormalities within the medial temporal lobes provide some support for theories regarding hippocampal or amygdala dysfunction in PD.

CONCLUSIONS AND FUTURE DIRECTIONS

Neuroimaging research is helping to advance neurobiological models of anxiety and stress disorders. At the current early stage of this scientific enterprise, there are hints of commonalities across anxiety disorders as well as leads regarding disorder-specific features. Beyond the need for a general expansion of the existing database, it will be critical to explore the specificity of initial findings by conducting studies with psychiatric comparison groups in addition to healthy control subjects. This is of particular relevance to the concept of stress disorders, in which common etiologic factors or vulnerability factors may have corresponding pathophysiologic profiles that are independent of our current diagnostic scheme. For instance, the relationship between early or chronic life stress and hippocampal structure and function may well span anxiety, mood, and even psychotic disorders. In this light, longitudinal and developmental studies may be of particular importance in elucidating the neural correlates and consequences of stress. Similarly, genetic studies in animals and humans will benefit from neuroimaging methods that can illuminate the bidirectional link from behavior to brain structure, function, and chemistry. For instance, research regarding the heritability of anxious temperament may be enhanced by using extended phenotypes of conditionability or distributed brain function within amygdala, hippocampus, and medial frontal cortex. In fact, the gamut of existing animal and human experimental paradigms with relevance to anxiety and stress disorders provides a promising context for advancing integrated models across scales and neuroscientific modes of inquiry. As such integrated models evolve, targets for new and improved neuropsychopharmacotherapies are destined to emerge. Indeed, neuroimaging is likely to play a role not only in conceptually motivating but also in discovering and testing such new therapies as part of the next generation of progress in this domain.

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