DISTINGUISHING NEURAL SUBSTRATES OF HETEROGENEITY AMONG ANXIETY DISORDERS

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The cognitive and brain correlates of anxiety disorders are active areas of investigation that contribute importantly to the accruing knowledge base on pathological processes associated with anxiety. This chapter reviews cognitive and neuroimaging findings for each of six anxiety disorders: obsessive-compulsive disorder, posttraumatic stress disorder, panic disorder, specific phobia, social phobia, and generalized anxiety disorder. Cognitive biases toward threat are common to all six disorders and may correspond to hyperactivation of right hemisphere regions dedicated to threat. Brain structures subserving anxiety pathology include orbital frontal, prefrontal, anterior cingulate, and right parietal

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cortices, as well as the amygdala, hippocampus, and caudate. Neuropsychological data from extant research on cognitive, affective, and brain processes indicate that anxiety is not a homogenous entity and that attempts to map its neural circuitry must consider symptom variability and comorbidity with other types of psychopathology.

Numerous areas of research and an expansive corpus of literature contribute to current neuroscientific understanding of anxiety pathology. Basic neuroscience work explaining some of the key brain mechanisms and circuitry of fear and anxiety in nonhuman animals has served as a critical foundation for research on humans with anxiety disorders (e.g., Davis, 1999; Davis and Lee, 1998; Gray and McNaughton, 2000; LeDoux, 1996). Research with people who have brain damage has provided further links between anxiety and the brain (Nitschke *et al.*, 2000). The relatively new fields of cognitive neuroscience and affective neuroscience are concerned with very similar questions regarding brain–behavior relationships as were fundamental to the older field of neuropsychology. The neuroimaging tools central to those disciplines are important supplements to the traditional neuropsychological test batteries and cognitive/behavioral paradigms. Thus, this review of the neuroscience findings in anxiety disorders covers a wide array of methods that together inform knowledge of the brain mechanisms involved in the circuitry governing pathological forms of anxiety.

Cognitive science is another relevant domain of research that is often overlooked in discussions about brain substrates in anxiety (Nitschke and Heller, 2002; Nitschke *et al.*, 2000). Cognitive research over the past two decades has contributed substantially to knowledge about brain function in anxiety. A large body of work demonstrates that anxiety disorders are characterized by cognitive biases, indicating a heightened response to the possibility of threat (for reviews, see Heinrichs and Hofmann, 2001; McNally, 1998; Nitschke and Heller, 2002; Nitschke *et al.*, 2000). Attentional biases have been elicited very reliably across a variety of paradigms in which potentially threatening information is associated with greater attentional capture in individuals with anxiety disorders than in controls. The interference of this attentional capture with other cognitive processing serves as the operationalization of this bias in research studies. Furthermore, attentional biases have been found to disappear on remission (for reviews, see McNally, 1998; Nitschke and Heller, 2002), suggesting that such biases are state-dependent. Cognitive biases have also been observed in the form of interpretation and memory biases. Across a number of different paradigms involving ambiguous stimuli that can be interpreted as threatening or neutral, anxious people choose the threatening meaning. Accruing evidence suggests that anxiety disorders are also accompanied by enhanced memory for negative or threatening information under certain conditions. These cognitive data suggest dysfunctional

activation of a right hemisphere system involved in threat perception (for review, see Nitschke *et al.*, 2000; see also Compton et al., 2000, 2003).

In addition to these cognitive biases, cognitive deficits have been documented in anxiety disorders. One is a tendency to do more poorly on tasks that require selective attention and concentration. This deficit has been suggested to reflect a general problem of preoccupation and distraction because of worry or rumination that interferes with other mental processes (for review, see Nitschke *et al.*, 2000). Compromised visual–spatial functioning has also been reported. In addition, individuals with posttraumatic stress disorder often exhibit deficits in explicit memory. Taken together, these cognitive deficits suggest aberrant frontal, anterior cingulate, right parietal, and hippocampal functioning. Building on this cognitive research, as well as on behavioral and electroencephalographic (EEG) findings (for review, see Nitschke *et al.*, 2000) and an extensive literature in nonhuman animals examining fear and anxiety (for reviews, see LeDoux, 1996; Davis and Lee, 1998), hemodynamic neuroimaging research has implicated a number of the suggested regions (for reviews, see Martis *et al.*, 2002; Nitschke and Heller, 2002; Nitschke *et al.*, 2000).

Despite substantial evidence for abnormalities in cognitive processing and brain activation and for consistency across emotional, cognitive, and neural domains, the diversity of findings also warrants the importance of respecting unique patterns and heterogeneity both among and within the various anxiety disorders. An observation that has become increasingly salient in the burgeoning neurobiological literature on anxiety and its disorders is the lack of clarity and specificity about what anxiety is. Views of anxiety range from its use in contemporary clinical research as a rubric term that encompasses fear, panic, worry, and all the anxiety disorders listed in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV; APA, 1994) to its very specific operationalization referring to context conditioning and long-term sensitization (e.g., Davis and Lee, 1998) to a more generic personality dimension closely linked to neuroticism (e.g., Gray, 1982; Gray and McNaughton, 2000). Furthermore, the heterogeneity within each of the different anxiety disorders has become increasingly apparent and represents a major problem for investigators attempting to uncover the neurobiological correlates of individual anxiety disorders. Inconsistencies across studies may be explained by the fact that anxiety is not a unitary phenomenon and that different types and symptoms of anxiety are associated with particular cognitive patterns (Heller and Nitschke, 1998; Nitschke *et al.*, 2000). An important mission of neuroscience research in this area is to help unravel the inchoate notions of anxiety that currently exist. Thus, although it is important to look for generalizations regarding the neural mechanisms of anxiety, it is also necessary to consider the possibility of heterogeneity by being as specific as possible regarding the disorder or type of anxiety under investigation.

The aim of this chapter is to assess what is known about the neural circuitry of anxiety disorders by examining the relevant cognitive research and structural and functional neuroimaging data, including morphometric magnetic resonance imaging (MRI), functional MRI (fMRI), and positron emission tomography (PET), using various radiotracers such as [18F]fluorodeoxyglucose (FDG) for glucose metabolism and 15O-labeled water for blood flow, single-photon emission computed tomography (SPECT) with 133Xenon or 99mTc-HMPAO, and scalp-recorded EEG. This review of the cognitive and human neuroimaging literatures reveals that the anxiety disorders engage brain regions involved in threat perception (e.g., right prefrontal cortex [PFC], parietal, and temporal regions; Compton *et al.*, 2000, 2003; Davidson *et al.*, 2000; Nitschke and Heller, 2002; Nitschke *et al.*, 2000), anxious arousal (right parietal and temporal cortices; Nitschke *et al.*, 2000), fear (e.g., amygdala; LeDoux, 1996), vigilance for motivationally salient events (e.g., amygdala; Davis and Whalen, 2001; Whalen, 1998), decoding of motivationally relevant emotional information such as the reward and punishment value of a stimulus (e.g., orbital frontal cortex [OFC]; Rolls, 1999a,b), worry (e.g., left PFC, parietal, and temporal regions; Nitschke *et al.*, 2000), response conflict (e.g., anterior cingulate cortex [ACC]; Carter *et al.*, 1999, 2000; Davidson *et al.*, 2002), and memory (e.g., hippocampus; Squire, 1992). The aforementioned heterogeneity should also lead to some diverse findings for the different anxiety disorders. The focus here is on the anxiety disorders as defined by the DSM-IV, although consistent patterns have emerged in studies using nonclinical and brain-lesioned human populations (for review, see Nitschke *et al.*, 2000).

I. Obsessive-Compulsive Disorder

The most widely investigated anxiety disorder from a neuropsychological perspective has been obsessive-compulsive disorder (OCD). The emphasis on obsessions and compulsions in connection to the experienced anxiety and distress reported by individuals with OCD is unique among the anxiety disorders and can be linked to a number of neuropsychological abnormalities.

A. Cognitive Studies

An extensive cognitive literature on OCD points most strongly to nonverbal memory and other visual–spatial deficits (e.g., Boone *et al.*, 1991; Christensen *et al.*, 1992; Cohen *et al.*, 1996; Kim *et al.*, 2002; Kwon *et al.*, 2003; Purcell *et al.*, 1998; Savage *et al.*, 1996, 1999; Zielinski *et al.*, 1991; see also Constans *et al.*, 1995; McNally and Kohlbeck, 1993). No evidence of a verbal memory deficit has been

found (Foa *et al.*, 1997). Ample documentation of impaired executive functions including verbal fluency also exists (e.g., Abbruzzese *et al.*, 1997; Head *et al.*, 1989; Kim *et al.*, 2002; Kwon *et al.*, 2003; Moritz *et al.*, 2001; Purcell *et al.*, 1998; Veale *et al.*, 1996), with trends reported by Cohen *et al.* (1996) for several neuropsychological tests. Recent data suggest that these cognitive deficits are for the most part not due to medication (serotonin reuptake inhibitors, benzodiazepines), although there was some evidence for benzodiazepines affecting verbal fluency (Mataix-Cols *et al.*, 2002).

It is possible that problems in executive function could account for at least some of the visual–spatial deficits found. For example, Savage *et al.* (1999) found that poor organizational strategies for copying a figure mediated the nonverbal memory deficit for reproducing a figure among patients with OCD. In addition, that laboratory found worse nonverbal memory using the same task to be associated with larger right PFC volumes in patients with OCD (Grachev *et al.*, 1998). Should these findings be replicated, one possible explanation is that such morphometry differences may be a manifestation of heightened threat perception and negative affect occupying right PFC resources normally dedicated to nonverbal memory.

Two very recent studies (Cavedini *et al.*, 2002; Nielen *et al.*, 2002) examined decision-making function in patients with OCD using a standard gambling task found to be sensitive to PFC damage, especially ventromedial regions (Bechara *et al.*, 1994). Cavedini *et al.* (2002) reported poorer performance in patients with OCD, especially treatment nonresponders, than patients with panic disorder or nonpsychiatric controls. Using the identical task, Nielen *et al.* (2002) found a similar pattern with patients with severe OCD performing more disadvantageously than nonpsychiatric controls and patients with OCD scoring below the mean on measures of symptom severity (pairwise comparisons were not reported).

Of additional relevance to cognitive functioning in OCD, Foa *et al.* (1993) documented that the attentional bias toward threat-related material seen across all the anxiety disorders for the emotional Stroop paradigm also emerges in OCD. In this paradigm, subjects are asked to name the color of words varying in emotional content while ignoring their meanings. Foa *et al.* (1993) found that patients with OCD with washing rituals took longer to name the color for contamination words than for neutral words, suggesting that the threatening nature of the contamination words interfered with the task of naming the color. They also had longer response latencies to contamination words than did OCD nonwashers or nonpsychiatric controls. On the other hand, OCD nonwashers had longer latencies to negative than neutral words, whereas the opposite pattern was seen in controls. In similar studies in which the OCD-relevant words did not necessarily reflect the primary concerns of the patients with OCD, no interference effects were observed (Kampman *et al.*, 2002; McNally *et al.*, 1990). Another

possible explanation for these null findings is that emotional Stroop effect sizes are very small (Koven *et al.*, 2003). These and other inconsistencies in the literature on attention bias in anxiety disorders may, therefore, be due to a lack of power. These attentional findings implicate the involvement of right hemisphere regions important for threat perception (Compton *et al.*, 2000, 2003; Nitschke and Heller, 2002; Nitschke *et al.*, 2000).

With regard to memory biases, Foa *et al.* (1997) found no bias for contamination sentences for either explicit or implicit memory. However, they did replicate the finding that patients with OCD are less confident than nonpsychiatric controls about memory-related judgments (Constans *et al.*, 1995; McNally and Kohlbeck, 1993). Thus, the cognitive literature is fairly conclusive in demonstrating that the memory concerns frequently voiced by patients with OCD (e.g., "Did I lock the door?) are not the result of a memory deficit or a memory bias but rather a lack of confidence in their memory. This lack of confidence is likely to be related to the characteristic fear of forgetting some activity that has become a target for compulsive behavior, and thus is a reflection of the underlying anxiety in OCD. As such, the degree to which confidence is lacking might correlate with activity in neural structures associated with fear and other anxiety-related features.

B. Neuroimaging Studies

The most common finding to emerge in morphometric MRI studies to date is a reduction in caudate volume (Robinson *et al.*, 1995; Rosenberg *et al.*, 1997), with a trend also reported by Jenike *et al.* (1996). However, Aylward *et al.* (1996) found no caudate differences, and Scarone *et al.* (1992) reported an increase in right caudate volume. Similar inconsistencies for the caudate have emerged in functional imaging studies examining resting states using PET and SPECT to measure glucose metabolism and blood flow. Increases were reported in three samples (Baxter *et al.*, 1987, 1988; Rubin *et al.*, 1992), with Perani *et al.* (1995) reporting a trend in the same direction. However, Lucey *et al.* (1997a,b) found a reduction, and others observed no differences from nonpsychiatric controls (e.g., Swedo *et al.*, 1989). In contrast, symptom provocation paradigms using PET (McGuire *et al.*, 1994; Rauch *et al.*, 1994) and fMRI (Breiter *et al.*, 1996) have consistently shown caudate activation.

The corticostriatal model of OCD proposed by Rauch *et al.* (1998) posits that pathology within the caudate results in OFC and ACC hyperactivity by means of inefficient thalamic gating. An OFC–caudate loop may comprise much of the neural circuitry associated with the repetitive and perseverative nature of obsessions and compulsions (see also Alexander *et al.*, 1991). Further pursuing the evidence of caudate abnormalities, Rauch *et al.* used PET and fMRI while

patients with OCD performed an implicit learning task shown to be dependent on striatal function in nonpsychiatric volunteers (Rauch *et al.*, 1995b, 1997c). The striatum was not activated in subjects with OCD (Rauch *et al.*, 1997a), suggesting that OCD symptoms pertinent to perseveration occupy the resources normally allocated to implicit learning. The caudate activation observed in the symptom provocation studies suggests that inconsistencies in other reported findings may be due to heterogeneity in the degree of symptom severity among OCD patient samples. Taken together, these data suggest that augmented caudate activation is associated with the perseverative nature of obsessions and compulsions, which also may serve to enlarge that structure.

Hemodynamic studies of OCD have implicated a number of other regions, most consistently OFC and ventral ACC, areas of the brain involved in various affective and cognitive processes. PET and SPECT studies using protocols not involving a task have revealed that patients with OCD have more blood flow or glucose metabolism than nonpsychiatric controls in OFC (Baxter *et al.*, 1987, 1988; Kwon *et al.*, 2003; Rubin *et al.*, 1992; Swedo *et al.*, 1989; but see Machlin *et al.*, 1991; but see Busatto *et al.*, 2001) and regions of interest (ROIs) including the ventral ACC (Machlin *et al.*, 1991; Perani *et al.*, 1995; but see Busatto *et al.*, 2001). Similar findings for the OFC have been observed during an auditory continuous performance task using PET to measure glucose metabolism (Nordahl *et al.*, 1989). OFC and ventral ACC activations have also been reported in fMRI (Adler *et al.*, 2000; Breiter *et al.*, 1996) and PET (Rauch *et al.*, 1994) studies using symptom provocation paradigms with actual obsessional stimuli. In another study using symptom provocation by means of presentation of idiographically selected contaminants in patients with OCD, McGuire *et al.* (1994) found symptom intensity to be correlated with right inferior frontal/OFC but not ACC activation. Busatto *et al.* (2001) found that obsessive-compulsive symptoms correlated positively with left OFC blood flow. A less potent experimental elicitation of symptoms by means of auditory presentation of obsessional material did not induce blood flow changes in these areas using PET (Cottraux *et al.*, 1996). Further evidence of frontal and ACC dysfunction in OCD can be inferred from two EEG studies examining event-related potentials (ERPs) in a Go-NoGo task (Malloy *et al.*, 1989) and a selective attention task (Towey *et al.*, 1994).

With the amygdala often highlighted in models of the neural circuitry of fear, anxiety, and emotion (e.g., Charney *et al.*, 1998; LeDoux, 1996), it is worth noting that amygdala activation has not been routinely documented in human neuroimaging research on OCD. In fact, only Breiter *et al.* (1996) reported amygdala activation in subjects with OCD, who were exposed to stimuli highly relevant to their obsessions. One of the subjects studied by McGuire *et al.* (1994) also showed amygdala activation, as did two of the seven patients with OCD examined by Adler *et al.* (2000). Because the documented rapid habituation of the amygdala and the vulnerability of the amygdala to susceptibility artifact in fMRI research

may have precluded detection of amygdala activation in previous research, studies addressing these issues (e.g., analysis of early trials, event-related fMRI, attention to data acquisition parameters to maximize signal in the amygdala) are needed to further assess whether the amygdala plays a role in OCD.

Treatment studies further inform the neural circuitry characterizing OCD. Both cognitive-behavioral and pharmacological therapies have been associated with normalized (i.e., decreased) glucose metabolism in the caudate nucleus (Baxter *et al.*, 1992; Benkelfat *et al.*, 1990; Saxena *et al.*, 1999, 2002; Schwartz *et al.*, 1996; but see Baxter *et al.*, 1987; Swedo *et al.*, 1992), and OFC (Benkelfat *et al.*, 1990; Saxena *et al.*, 1999, 2002; Swedo *et al.*, 1992; but see Baxter *et al.*, 1987, 1992; Schwartz *et al.*, 1996). Results for the ventral ACC are less certain, because relevant reports have either not examined that area or have not distinguished ventral and dorsal sectors. A recent report explicitly delineating a ventral ACC region found no treatment effect (Saxena *et al.*, 2002). Some studies examining ROIs including the ventral ACC have found reductions in glucose metabolism (Baxter *et al.*, 1992; Perani *et al.*, 1995), whereas others have not (Brody *et al.*, 1998; Saxena *et al.*, 1999; Swedo *et al.*, 1992). Similar findings have emerged for blood flow measured by SPECT in the OFC (Rubin *et al.*, 1995) and ACC (Hoehn-Saric *et al.*, 1991). Baxter *et al.* have reported that pretreatment correlations between caudate and orbital regions ranging from 0.44 to 0.74 decreased significantly after effective treatment (Baxter *et al.*, 1992; Schwartz *et al.*, 1996). In addition, lower pretreatment OFC glucose metabolism may be associated with better response to medications, whereas the converse may be true for psychotherapy (Brody *et al.*, 1998; Saxena *et al.*, 1999; Swedo *et al.*, 1989). Response to pharmacotherapy has also been predicted by glucose metabolic reductions in the ACC (Swedo *et al.*, 1989) and left caudate (Benkelfat *et al.*, 1990); however, Brody *et al.* (1998) did not replicate those findings (Saxena *et al.*, 1999 only reported conducting tests for the OFC). Overall, treatment studies further implicate the caudate, OFC, and ACC in OCD. They suggest that the hyperactivity of these structures in OCD is state-dependent and that pretreatment levels of activity may have prognostic value. The inconsistencies in findings remain to be addressed in further research.

The cognitive data implicating right hemisphere regions suggest the importance of threat perception and evaluation in OCD. The functional significance of the caudate, OFC, and ACC hyperactivity often reported before treatment are consistent with their roles in the perseverative nature of obsessions and compulsions, in decoding reward and punishment values of perceived and real events (c.f. Rolls, 1999; Rauch, 2003), and in response conflict about whether to perform some mental activity or compulsive behavior. These abnormalities may disrupt decision-making, consistent with recent work in that area (Cavedini *et al.*, 2002; Nielen *et al.*, 2002). As noted previously, the cognitive data imply the

involvement of right hemisphere regions involved in threat perception. The absence of more right-sided effects in the imaging data should be interpreted with caution, because it may be due to the difficulty of conducting adequate tests of asymmetry (Davidson and Irwin, 1999).

A final important consideration is the high level of comorbid depression in people with OCD. Visual–spatial (including nonverbal memory) and executive deficits in depression are well established and are congruent with the reduced activity in right parietal and bilateral frontal regions often reported for depression (Heller and Nitschke, 1997, 1998). The extent to which the nonverbal memory and executive deficits in OCD can be attributed to depression, anxiety, obsessions, or compulsions has not been determined, in part because the co-occurrence of these various symptoms makes disentangling their effects exceedingly difficult. Moritz *et al.* (2001) reported recent evidence for the importance of depression in their study of 36 patients with OCD using a median split according to Hamilton Rating Scale for Depression (HRSD) scores. Patients with OCD with high HRSD scores performed more poorly than nonpsychiatric controls on six measures of executive function and more poorly than those with low scores on four of those measures. Furthermore, the pronounced brain abnormalities accompanying depression (for reviews, see Davidson *et al.*, 2002; Mohanty and Heller, 2002) certainly have consequences for neuroimaging research on OCD. For example, Martinot *et al.* (1990) reported a bilateral diminution of PFC glucose metabolism in 16 patients with OCD compared with 8 nonpsychiatric controls and no effects for OFC; however, despite not meeting criteria for DSM-III, current major depressive episode, these patients likely were characterized by significantly higher levels of depression than the controls.

II. Posttraumatic Stress Disorder

The past decade has witnessed an explosion of research examining the neurobiological mechanisms and neuropsychological, behavioral, and cognitive concomitants of posttraumatic stress disorder (PTSD). The diagnostic requirement of exposure to a traumatic event makes this disorder an ideal candidate for testing etiological hypotheses based on the rich conditioning literature, including classical cue conditioning, operant conditioning, and context conditioning. However, the array of reexperiencing, avoidance, and arousal symptoms and the common comorbidity with depression (and substance abuse in war veterans) add layers of complexity that make unraveling the neural circuitry of PTSD seem an intractable enterprise. Moreover, classification of PTSD remains a highly controversial topic, not only with regard to prototypic symptoms and

subtyping but also with regard to whether it should be considered an anxiety disorder. Despite these obstacles, the emerging body of research is contributing to understanding this elusive condition.

A. Cognitive Studies

As with OCD, a commonly reported cognitive abnormality in PTSD is an attentional bias toward threat-related stimuli on tasks such as the emotional Stroop test. This effect has been reported for rape victims (e.g., Foa *et al.*, 1991), combat veterans (e.g., Kaspi *et al.*, 1995; McNally *et al.*, 1990, 1993, 1996; Vrana *et al.*, 1995), motor vehicle accident victims (Bryant and Harvey, 1995; Buckley *et al.*, 2002), crime victims (Paunovic *et al.*, 2002), and people involved in a ferry disaster (Thrasher *et al.*, 1994). Recovery from PTSD has been shown to eliminate the attentional bias (Foa *et al.*, 1991), whereas patients with PTSD who have not recovered continue to show the bias toward threat cues when retested (McNally *et al.*, 1993). A memory bias toward trauma-relevant material has also been found in patients with PTSD for explicit memory (Paunovic *et al.*, 2002; Vrana *et al.*, 1995; but see Bremner *et al.*, 2003) and conceptual implicit memory dependent on the meaning of the words used (Amir *et al.*, 1996c), suggesting a more pervasive proclivity toward threat-related material that is not confined to the frequently reported attentional effect. No bias was found on tasks of implicit memory depending on physical, perceptual features of the words rather than on their meaning (McNally and Amir, 1996; Paunovic *et al.*, 2002). Recent evidence suggests that individuals with PTSD also show an interpretation bias for threat meanings of homographs (Amir *et al.*, 2002). Consistent with these cognitive data, a recent ERP study using threat words as the low-probability stimulus type in an oddball paradigm reported that patients with PTSD had larger P3 amplitudes than nonpsychiatric controls for trauma-relevant but not trauma-irrelevant threat words (Stanford *et al.*, 2001). The oddball paradigm is composed of frequent presentations of one stimulus type and infrequent presentations of a second stimulus type, which typically elicits an enlarged ERP component known as P3 or P300. Taken together, these data are suggestive of right hemisphere abnormalities pertinent to threat perception.

The other salient cognitive finding in PTSD is an explicit memory deficit. Compromised memory performance has been observed in combat veterans (e.g., Bremner *et al.*, 1993; McNally *et al.*, 1994, 1995; Uddo *et al.*, 1993; Yehuda *et al.*, 1995), rape victims (Jenkins *et al.*, 1998), and adult survivors of childhood abuse (e.g., Bremner *et al.*, 1995b; but see Stein *et al.*, 1997). A recent study evaluating the relationship between PTSD symptoms and cognitive functioning within 10 days of traumatic events (primarily motor vehicle accidents and terror attacks) found converging evidence for an association with nonverbal but not verbal

memory (Brandes *et al.*, 2002). These data corroborate the reports of reduced hippocampal volume in PTSD to be reviewed next.

B. Neuroimaging Studies

Most studies examining structural abnormalities in PTSD have implicated the hippocampi, with reduced volume ranging from 8–30% (Bremner *et al.*, 1995a, 1997; Gilbertson *et al.*, 2002; Gurvits *et al.*, 1996; Villarreal *et al.*, 2002; but see Fennema-Notestine *et al.*, 2002). Similarly, Schuff *et al.* (1997) reported a trend for a 6% right hippocampal reduction in combat veterans, and Stein *et al.* (1997) observed a 5% reduction on the left in adult survivors of childhood abuse, most of whom met DSM-IV criteria for PTSD.

It is not known whether smaller hippocampal size is due to cell loss, cell atrophy, or to some other cause (Rajkowska, 2000; Sapolsky, 2000; Sheline, 2000). Controversy persists with regard to the role of cortisol as a causative factor in the hippocampal reductions observed in PTSD (Yehuda, 1997). A recent study with monozygotic twins discordant for combat exposure suggests that smaller hippocampi may be a predisposing factor for PTSD (Gilbertson *et al.*, 2002), although data on pediatric PTSD are not in line with this. In two independent samples, De Bellis *et al.* (1999, 2002a) observed no hippocampal volumetric differences in children and adolescents with PTSD (ages 4–17), a finding replicated in another pediatric sample composed of individuals either meeting criteria for PTSD or with subthreshold PTSD symptoms (Carrion *et al.*, 2001). Regardless, hippocampal abnormalities are likely critical for the aforementioned explicit memory deficit in PTSD. Indeed, Bremner *et al.* (1995a) reported a strong correlation ($r = 0.64$) between explicit verbal memory and right hippocampal volume in combat veterans with PTSD. On the other hand, Stein *et al.* (1997) found no relationship between hippocampal volume and explicit verbal memory in women with a history of childhood sexual abuse, although there was an association ($r = -0.73$) between the left hippocampus and dissociative symptom severity. Further research is needed on factors (e.g., chronicity of PTSD) contributing to relations among PTSD symptoms, hippocampal volume, and memory.

In contrast to the preceding morphometric data, functional neuroimaging studies examining PTSD have implicated a host of structures. Two recent symptom provocation studies used script-driven imagery in conjunction with PET in adult female victims of childhood sexual abuse with and without PTSD (Bremner *et al.*, 1999a; Shin *et al.*, 1999). Bremner *et al.* found that personalized traumatic scripts were associated with less blood flow in the right hippocampus and more blood flow in ventral ACC, PFC, insula, posterior cingulate, and motor cortex for women with PTSD than those without. Shin *et al.* reported more blood

flow in the ventral ACC, OFC, and insula for childhood abuse victims with than those without PTSD. Two more recent studies using script-driven imagery with fMRI are characterized by substantial methodological differences in the samples and paradigm used from the preceding PET studies that may explain the absence of activation in the regions observed by Bremner *et al.* and Shin *et al.* (Lanius *et al.*, 2001, 2002). In other relevant research, combat-related pictures and sounds activated the ventral ACC in combat veterans with PTSD and combat controls without PTSD (Bremner *et al.*, 1999b; Liberzon *et al.*, 1999). Using SPECT, Liberzon *et al.* observed activation of the ventral ACC/medial PFC in nonpsychiatric controls as well. Another report from this group indicated that only subjects with PTSD showed more blood flow in the medial PFC, whereas both subjects with PTSD and nonpsychiatric controls showed a trend for increased blood flow in the ventral ACC (Zubieta *et al.*, 1999). Using PET, Bremner *et al.* (1999b) also found PTSD to be associated with increased blood flow in parietal, posterior cingulate, and motor areas. In a more recent study of women with PTSD related to severe childhood sexual abuse (rape before the age of 13), Bremner *et al.* (2003) found more activation in those same three brain areas along with less activation of a large anterior area spanning the OFC, ACC, and medial PFC during retrieval of trauma-related than neutral word-pairs. It remains to be seen whether activation in some of these regions (e.g., ventral ACC) is specific to PTSD or has more to do with task demands or other phenomena (e.g., mood, comorbid depression, the presence of other types of anxiety).

Several symptom provocation studies of PTSD have reported amygdala activation (Liberzon *et al.*, 1999; Rauch *et al.*, 1996; Shin *et al.*, 1997). Other areas implicated by Rauch *et al.* in a PET study using script-driven imagery were the ventral ACC and right OFC, insula, and temporal cortex. In an independent sample, they found increased ventral ACC blood flow in combat veterans with PTSD when generating a mental image of a previously studied combat picture (Shin *et al.*, 1997). Both those studies also reported a blood flow decrease in Broca's area in response to trauma-related stimuli (see also Fischer *et al.*, 1996), perhaps indicative of downregulation of this verbal generation region in the service of more effective recruitment of phylogenetically older structures more appropriate for the extreme fear and horrific traumas experienced by people who go on to develop PTSD.

The importance of the amygdala and OFC for the circuitry implicated in PTSD is further underscored by research not targeting symptom-related stimuli. Using fMRI and a backward masking paradigm previously shown to activate the amygdala in nonpsychiatric volunteers (Whalen *et al.*, 1998), Rauch *et al.* (2000) found that combat veterans with PTSD had larger right amygdala responses to fearful faces masked by neutral faces than did combat controls without PTSD. These responses to fear expressions are consistent with cognitive biases toward

threat discussed earlier for patients with PTSD. An older study conducted by Semple *et al.* (1993) reported more OFC blood flow as measured by PET during an auditory CPT and a word-generation task in combat veterans with PTSD and substance abuse than nonpsychiatric controls. Less parietal blood flow during the continuous performance task was also observed (Semple *et al.*, 1996). A newer study from that group found that a similar sample of patients with PTSD had more right amygdalar and left parahippocampal blood flow during the same continuous performance task than nonpsychiatric controls (Semple *et al.*, 2000), adding further support to the symptom provocation findings in the preceding.

In sum, both cognitive and neuroimaging findings suggest the engagement of several right hemisphere regions, consistent with evidence that these areas are differentially involved in responding to threat. In addition, the neuroimaging data highlight a distributed array of structures not clearly lateralized, including the OFC, ACC, amygdala, and hippocampus, regions associated with decoding motivationally salient material, response conflict, fear, vigilance for motivationally salient events, and memory. As with OCD, the OFC and ventral ACC seem to be involved in the brain circuitry associated with the pathogenesis and expression of PTSD. Important points of divergence between the two disorders emerge in the subcortex, with the caudate specific to OCD and the amygdala and hippocampus implicated in numerous studies examining PTSD. It is unclear whether the decrease in Broca's area is unique to PTSD, in part because deactivations often are not reported. As with OCD, the rate of depressive disorders in PTSD populations is extremely high, which again warrants attention to the known cognitive and neurobiological correlates of depression in any discussion of the brain circuitry central to PTSD.

III. Panic Disorder

Characterized by recurrent unexpected panic attacks that share many features with basic fear responses, panic disorder has been viewed as the preeminent candidate condition for postulating dysfunction of the fear circuitry identified in research with nonhuman animals. However, the literature has shown this to be a disappointing enterprise, and the neural machinery affected in panic disorder remains largely a mystery. It is important to note that even in most individuals experiencing frequent panic attacks (once or more per day), more time is spent worrying about having future attacks or about the implications of those attacks than having actual attacks. Addressing this issue, we have previously described the importance of anxious apprehension and anxious arousal as distinct dimensions of anxiety that are manifest to varying degrees at different times both within and across individuals with panic disorder, as well as other anxiety disorders

(Nitschke *et al.*, 2000). Central to worry, anxious apprehension is characterized by a concern for the future and verbal rumination about negative expectations and fears, whereas anxious arousal is defined by panic symptoms and an immediate fear response. For obvious reasons, animal models are not particularly conducive to tracking the circuitry associated with worry, although research on context conditioning, long-term sensitization, and anticipatory anxiety is certainly relevant (e.g., Davis and Lee, 1998; Nitschke *et al.*, 2001). In addition to the need for careful dissection of the affective processes involved, the various neuroscience research tools now available with humans hold considerable promise for identifying the neural correlates of panic disorder.

A. Cognitive Studies

Cognitive reports in the literature on panic disorder have been sparser than for OCD or for PTSD. The most common finding is a bias for panic-relevant words on implicit and explicit memory tasks (e.g., Amir *et al.*, 1996b; Becker *et al.*, 1994, 1999; Cloitre and Liebowitz, 1991; Cloitre *et al.*, 1994; McNally *et al.*, 1989), although negative findings have been reported (Otto *et al.*, 1994; Rapee, 1994). Perceptual asymmetry on a dichotic listening task suggestive of more left than right hemisphere activity was associated with better memory for threat words in patients with panic disorder but not in nonpsychiatric controls (Otto *et al.*, 1994). These results suggest a pattern akin to the increased left hemisphere activity characterizing generalized anxiety disorder (see later), anxious apprehension, and worry (for review, see Nitschke *et al.*, 2000). There is also evidence of a bias toward threatening words in a priming task involving lexical and nonlexical word pairs, one presented above the other (McNally *et al.*, 1997). Patients with panic showed faster reaction times in naming the threat targets after the threat prime but only when the target was in the bottom position.

With regard to other forms of cognitive bias, emotional Stroop interference has been observed in patients with panic disorder (Buckley *et al.*, 2002; Ehlers *et al.*, 1988; McNally *et al.*, 1990, 1994; but see Kampman *et al.*, 2002). Interpretation bias in the form of a bias toward catastrophic interpretation of panic-relevant stimuli in ambiguous scenarios was first documented in individuals with agoraphobia (McNally and Foa, 1987) and subsequently in panic disorder (Clark *et al.*, 1997; Harvey *et al.*, 1993). A recent study found such a bias for ambiguous scenarios in children of individuals with panic disorder after viewing a video clip of a woman with panic disorder describing a severe panic attack, suggesting that the increase in panic interpretations for these children may serve as a vulnerability factor for the development of panic disorder (Schneider *et al.*, 2002). These memory, attentional, and interpretation biases again point to the involvement of right hemisphere systems that mediate anxious arousal in response to threat,

with dichotic listening data suggesting left hemisphere engagement, perhaps reflecting anxious apprehension.

B. Neuroimaging Studies

The one known quantitative morphometric study found that patients with panic disorder had smaller temporal lobes than nonpsychiatric controls but no hippocampal differences (Vythilingam *et al.*, 2000). Evidence for temporal lobe aberrations has also been documented by use of qualitative grading methods (Fontaine *et al.*, 1990). Eleven patients exhibited abnormal signal activity in the temporal lobes, which was most prominent at the interface of the right medial temporal lobe and parahippocampal cortex.

Consistent with these data, hemodynamic imaging studies have repeatedly implicated abnormalities in hippocampal and parahippocampal regions. The first report was a PET study finding more right than left parahippocampal blood flow in patients with panic disorder who responded to lactate infusion (Reiman *et al.*, 1984). This finding held for the full sample, with right-sided parahippocampal asymmetries also observed for blood volume and oxygen metabolism (Reiman *et al.*, 1986). Differential hippocampal asymmetries in the same direction were found for glucose metabolism in patients with panic disorder while engaged in an auditory continuous performance task (Nordahl *et al.*, 1990, 1998).

Other investigators have reported different hippocampal and parahippocampal effects. Bisaga *et al.* (1998) found that patients with panic disorder exhibited more glucose metabolism in the left hippocampus and parahippocampal area than nonpsychiatric controls. Those patients also exhibited less glucose metabolism in right inferior parietal and right superior temporal regions, which could be due to comorbid depression (Heller and Nitschke, 1998). Patients with panic disorder showed more left hippocampal blood flow measured by PET than nonpsychiatric controls in anticipation of a pentagastrin challenge and subsequently when its effects had subsided (Boshuisen *et al.*, 2002). In a SPECT study, De Cristofaro *et al.* (1993) found no differences in hippocampal asymmetry, but rather patients showed bilateral decreases. In light of hippocampal involvement in explicit memory, these findings suggest that the hippocampi and surrounding parahippocampal areas may play a role in the explicit memory bias toward threat emerging in the cognitive literature.

The PFC has also figured importantly in the neuroimaging data published to date. In addition to the hippocampal asymmetries noted previously, Nordahl *et al.* (1990, 1998) observed an inferior frontal asymmetry with more right than left metabolism in both patient samples with panic disorder. In the 1990 study, patients also exhibited more right frontal and occipital metabolism and less left parietal metabolism than nonpsychiatric controls. Similar group differences

in inferior PFC asymmetry (right > left), right frontal (marginally significant), and occipital cortex were reported by De Cristofaro *et al.* (1993). Anticipation of and rest after pentagastrin challenge were both accompanied by less left inferior frontal activation in patients with panic disorder than controls; asymmetry was not formally tested (Boshuisen *et al.*, 2002). Consistent with findings for OCD and PTSD reviewed previously, patients in that study also showed more ventral ACC and bilateral OFC activation than controls; however, bilateral insula activation showed the converse pattern. The first quantitative EEG study on panic disorder documented abnormal patterns of asymmetry in both frontal and parietal regions, with patients exhibiting relatively more right-sided activity than nonpsychiatric controls (Wiedemann *et al.*, 1999). More right than left frontal activity was documented for the patients but not the controls, whereas the patients did not exhibit the parietal left > right asymmetry observed in controls. Furthermore, the same frontal asymmetry was also present while the patients viewed a spider, an erotic, and an emergency picture, but not a mushroom.

Symptom provocation studies of panic disorder using hemodynamic methods have assumed the form of pharmacological challenges. Using SPECT during sodium lactate infusion that induced global blood flow increases, Stewart *et al.* (1988) found that patients who panicked after infusion exhibited larger occipital increases, especially on the right, than nonpanicking subjects, whereas the nonpanicking subjects showed larger global increases, especially over the left hemisphere. In a PET study, Reiman *et al.* (1989) found no blood flow increases after sodium lactate infusion among nonpanicking subjects, whereas the patients with panic disorder who had panic attacks exhibited increased blood flow in anterior temporal, insula/claustrum/putamen, superior colliculus/periaqueductal gray, and cerebellar vermis regions. Of note, the anterior temporal findings may be an artifact of muscular contraction of the jaw (Benkelfat *et al.*, 1995; Drevets *et al.*, 1992), such that more recent imaging studies on anxiety often use teeth-clenching control conditions (e.g., Javanmard *et al.*, 1999; Rauch *et al.*, 1996; Reiman, 1997).

The parallel between the most frequently observed cognitive and neuroimaging findings is noteworthy. As the only anxiety disorder with a memory bias toward threat just as reliable as an attentional bias, if not more so, panic disorder also is unique with regard to frequently reported hippocampal findings in functional imaging studies. With the hippocampus known to be the critical structure for explicit memory function, these findings suggest that the commitment of certain right hemisphere regions to threat may extend to the hippocampus. Consistent with the argument forwarded for OCD and PTSD, the involvement of broader right hemisphere systems encompassing various territories governing threat perception corresponds to findings of memory and attentional biases. The PFC asymmetry observed in four studies using different

technologies is in concordance with that position. The issue of comorbidity with depression again deserves mention, because the explicit memory bias and the PFC asymmetry are commonly seen in depression. The OFC, ACC, and caudate regions highlighted in the preceding sections for OCD and PTSD have not emerged with any consistency in research on patients with panic disorder, notwithstanding the recent OFC and ACC findings reported by Boshuisen *et al.* (2002).

IV. Specific Phobia (Simple Phobia)

Characterized by a persistent, excessive, and unreasonable fear of a specific object or situation, this disorder is very amenable to research investigation both with regard to experimental designs (e.g., presenting subjects with phobic stimuli) and subject sampling because of the prevalence of specific phobias and the relatively low rates of comorbidity with other mental disorders. However, studies with phobics are few, perhaps because of minimal public health interest in specific phobias, because they generally do not compromise the occupational or social functioning of affected individuals to the same extent as do other anxiety disorders. The preponderance of physiological research to date has focused on peripheral psychophysiological measures such as skin conductance, cardiovascular, and neuroendocrine activity (for review, see Fyer, 1998). No structural imaging data are available for specific phobias, and other neuropsychological research has been quite limited.

A. Cognitive Studies

The handful of studies investigating cognitive function in phobic individuals has documented the presence of an attentional bias but no memory bias. In women with spider phobia, Van Den Hout *et al.* (1997) documented interference for both masked and unmasked words associated with spiders on a modified Stroop task similar to those used in the OCD, PTSD, and panic disorder studies previously. Using Stroop tests involving spider, general negative, and neutral words, Watts *et al.* (1986) and Lavy *et al.* (1993) found larger interference for the spider words in spider phobics than matched nonanxious controls. No Stroop interference effects were observed in driving phobics for motor vehicle accident words; however, the words did not reflect their primary concerns but rather were designed for accident victims who had PTSD (Bryant and Harvey, 1995). Other cognitive findings for specific phobia include the absence of memory (Watts and Coyle, 1993) and interpretation (Schneider *et al.*, 2002) biases.

B. Neuroimaging Studies

Functional neuroimaging data have been inconclusive as to the brain circuitry of specific phobias. When small animal phobics were exposed to containers housing the feared animal, Rauch *et al.* (1995a) found blood flow increases using PET in a number of regions implicated in the preceding studies for OCD and PTSD (see Rauch *et al.*, 1997b), including the left OFC, right ACC, and left insula. Conversely, two earlier PET studies by Fredrikson *et al.* using film clips of the feared stimuli with snake and spider phobics did not find blood flow increases in any region except the secondary visual cortex (Fredrikson *et al.*, 1993, 1995; Wik *et al.*, 1993). The only other PET study conducted with specific phobics found that confronting animal phobics with their feared animal did not elicit blood flow changes in any region of the brain, although significant cardiovascular and self-reported anxiety changes were observed (Mountz *et al.*, 1989). They also reported no resting baseline differences between the phobics and nonpsychiatric controls. In a SPECT study of women with spider phobia, those reporting panic while watching a video of spiders exhibited less frontal blood flow, especially on the right side, than during a neutral film (Johanson *et al.*, 1998). The remaining phobic women who reported anxiety but did not panic showed more right frontal blood flow to the spider film (although significance level was not reported). The sole published EEG study of specific phobia found more right than left parietal activity to be associated with higher pretreatment spider phobia scores, whereas frontal activity was not related to pretreatment or posttreatment clinical measures (Merckelbach *et al.*, 1998).

There are exciting new data in the first two fMRI studies—both event-related—of specific phobia. Larson *et al.* (2002) collected data using five slices centered on the amygdala to examine the time course of amygdala activation in spider phobia because of its clear relevance for the fear response evoked by confronting phobic stimuli. With time points every 300 ms, they found that phobics displayed faster bilateral amygdalae responses to spider pictures than did nonpsychiatric controls. The amygdala activation was also more rapid to spider pictures than to nonphobogenic negative and neutral slides. No differences in the magnitude of activation were observed, whereas a subsequent study found that 1-s video clips of striking snakes elicited more amygdala activation than crawling snakes, which in turn elicited more than swimming fish in questionnaire-defined snake phobics but not in nonphobic controls (Schaefer *et al.*, 2002). A number of other regions differentiated the phobic and nonphobic subjects when both sets of snake stimuli were compared with fish stimuli. Phobics had more activation than controls to the snakes in the insula, precentral gyrus, thalamus, and right hippocampus (image distortion compromised the reliability of images from PFC, OFC, and ventral ACC). These data suggest that video clips presenting movement may be more potent elicitors of amygdala response than

still photographs and that the finer temporal resolution provided by fMRI than PET assists in explaining brain responses that are short-lived.

Because of the dearth of cognitive and neuroimaging research investigating specific phobias, little is known about the neurobiology accompanying such intense, long-standing fear of an object that is often harmless. The findings of an attentional bias toward threat suggest the involvement of right hemisphere regions oriented toward threat; however, the neuroimaging studies are too few and equivocal to provide a consistent picture of the critical brain regions. The recent event-related fMRI studies of specific phobia point to the importance of the amygdala and suggest that chronometry is an often overlooked but key factor to consider in neuroimaging research. Data from the laboratories of Rauch and Davidson suggest further commonality with brain areas implicated in other anxiety disorders, including the OFC, ACC, and insula. It may be that the circuitry implicated is much less pronounced than seems to be the case for the other anxiety disorders, just as the impact on everyday functioning is on average far less than for the others.

V. Social Phobia (Social Anxiety Disorder)

Now often referred to as social anxiety disorder, social phobia can be viewed as a variant of specific phobia that pertains to social or performance situations. Individuals with social phobia fear that they will act in a humiliating or embarrassing way when in the presence of other people. Recent epidemiological studies have identified it as the third most prevalent psychological disorder in the United States, after depression and alcoholism. Accordingly, the past 5 years have witnessed an explosion of research interest in the disorder, with efforts to identify the affected neural circuitry very much in their infancy.

A. Cognitive Studies

Cognitive research has implicated a number of abnormalities in social phobia, most of which are consistent with the information-processing biases described in other anxiety disorders. The numerous studies examining attention, interpretation, and memory biases in social phobia have recently been reviewed (Heinrichs and Hofmann, 2001). This literature abounds in evidence of attention and interpretation biases toward social threat across multiple different paradigms. Moreover, successful treatment has resulted in the diminution of attention (e.g., Mattia *et al.*, 1993) and interpretation (e.g., Foa *et al.*, 1996) biases toward threat.

One relevant study not reviewed by Heinrichs and Hofmann (2001) examined attention bias for facial expressions in generalized social phobia (Gilboa-Schechtman *et al.*, 1999). Consistent with the dot probe and Stroop studies reviewed, phobic subjects showed an attentional bias toward angry faces as measured by several metrics using the face-in-the-crowd paradigm, whereas nonanxious controls did not. Convergent evidence was reported for social anxiety in a nonclinical sample using a modified version of the dot probe task pairing masked threat and neutral faces and using letters instead of dots (Mogg and Bradley, 2002). For a dot probe paradigm pairing unmasked faces and household objects, social phobics directed their attention away from faces regardless of facial expression (neutral, happy, or negative—the negative pictures contained equal numbers of anger, sadness, fear, and disgust), whereas nonpsychiatric controls did not exhibit an attentional preference (Chen *et al.*, 2002). These data suggest that competing stimuli may serve to distract social phobics and attenuate the attentional capture by threatening cues.

A similar distraction process may be at work in explaining the findings of Stroop interference suppression to social-threat words in social phobics but not nonpsychiatric controls before giving a speech (see Mathews and Sebastian, 1993, for comparable findings in snake-fearful subjects when in the presence of a snake they are told they will have to approach on completion of the Stroop task). In this case, the right hemisphere resources devoted to threat might all be allocated to the situation surrounding the impending social performance, such that the threat words no longer are perceived as threatening (relative to the impending speech) to the same degree as they are under nonanxious experimental conditions. The authors offered a different interpretation, suggesting that subjects use strategic processes to inhibit the competing meaning of the words when anxious. They found results for social phobia consistent with this line of reasoning in their subsequent study using a Stroop task that used different ratios of words to nonwords in an attempt to experimentally manipulate the degree to which such strategic processes are used (Amir *et al.*, 2002). Research eliciting anticipatory anxiety in interpretation/judgment bias paradigms is needed to determine whether these findings for attentional bias extend to other domains of information processing.

Until very recently, it was widely accepted that social phobia was not accompanied by a memory bias (e.g., Rapee *et al.*, 1994). However, recent evidence suggests otherwise (Amir *et al.*, 2000, 2001; but see Wenzel and Holt, 2002). Two reports using face stimuli provide further evidence for an explicit memory bias in social phobia. Lündh and Öst (1996) first documented the effect in a paradigm in which social phobics and nonpsychiatric controls were asked to judge faces as either critical or accepting. Unlike the controls, the phobics showed a memory bias for faces they had previously judged as critical. In two elegant experiments following up the seminal report by Lündh and Öst (1996), Foa *et al.* (2000) found

that social phobics recognized more angry and disgust faces than happy or neutral ones, whereas no differences were observed for nonanxious controls. The same pattern was seen for reaction time data, with social phobics showing longer latencies in making a decision about the negative than the nonnegative facial expressions. Furthermore, phobic subjects had longer latencies for angry than disgust faces, whereas controls did not. Similar specificity was observed in the attentional face-in-the-crowd paradigm using faces mentioned earlier, with social phobics detecting anger faces faster than disgust ones, whereas controls showed no difference (Gilboa-Schechtman *et al.*, 1999). Taken together, data from these face paradigms suggest a general negativity bias (e.g., all negative emotion expressions) that is amplified by faces connoting threat (e.g., anger expressions), again consistent with the engagement of right hemisphere regions implicated in threat perception.

Consistent with cognitive findings for OCD, visual–spatial impairment including nonverbal memory deficits has been documented in social phobia (Cohen *et al.*, 1996; Hollander *et al.*, 1996) as has executive dysfunction (Cohen *et al.*, 1996). Along with other findings of left-sided neurological soft signs (Hollander *et al.*, 1996), these visual–spatial deficits are consistent with right hemisphere dysfunction in social phobia. Possibly, these deficits are produced by the augmented engagement of the right hemisphere in threat perception, as indicated by the reviewed literature on cognitive bias, with a consequent lack of resources for other processes lateralized to the right hemisphere such as visual–spatial functions.

B. Neuroimaging Studies

Structural abnormalities of the brain have not been observed in social phobics (Potts *et al.*, 1994); however, a set of recent functional neuroimaging studies point to several critical regions. Surveying EEG at the scalp, Davidson *et al.* (2000) found that social phobics exhibited a larger anterior temporal right > left asymmetry (marginally significant for lateral frontal and parietal sites) during anticipation of making a public speech than nonpsychiatric controls. Using PET to measure blood flow in social phobics, Reiman (1997) reported that singing in front of observers activated a number cortical and subcortical regions, including lateral PFC, anterior temporal, and posterior cingulate regions, with trends noted in the ACC, medial PFC, amygdala, and hippocampus. Another PET study found that social phobics exhibited increased blood flow in the right dorsolateral PFC, left inferior temporal cortex, and left amygdaloid complex (extending into the hippocampus) during anticipation of a public speaking task (Tillfors *et al.*, 2002). Those subjects also exhibited larger blood flow increases than nonphobic controls in the right amygdaloid complex (again extending into the hippocampus) while speaking in front of an audience compared with speaking alone (Tillfors

et al., 2001). Increased blood flow in a number of regions including the OFC and insula were apparent for the controls but not the phobics. In that same sample of social phobics, patients treated with citalopram and those treated with cognitive-behavioral therapy showed a greater blood flow reduction during public speaking than wait-list controls in anterior and medial temporal cortex (including the amygdala and hippocampus), especially on the right (Furmark *et al.*, 2002). This same pattern was observed when comparing responders (four of six in each treatment group, one of six controls) to nonresponders. In addition, responders also showed larger blood flow decreases than nonresponders in the right dorsolateral PFC and in both ventral and dorsal ACC. Three additional neuroimaging reports presented pilot or preliminary SPECT and PET data with mixed results for the structures implicated in the preceding studies on social phobia (Stein and Leslie, 1996; Van Ameringen *et al.*, 1998; Van der Linden *et al.*, 2000). The emphasis on public speaking in this area of research has proven fruitful in highlighting the right PFC, ACC, and amygdala as important structures in the circuitry affected by social anxiety.

The first of several fMRI studies on social phobia to be published found that social phobics showed greater amygdala activation bilaterally to neutral faces than did nonpsychiatric controls despite no differences in subjective ratings of the faces, whereas both groups showed the expected activation of the amygdala to aversive odors (Birbaumer *et al.*, 1998). However, it seems that this effect for the amygdala did not maintain for the full sample (Schneider *et al.*, 1999), with social phobics only exhibiting greater amygdalar and hippocampal activation than controls when the neutral faces were paired with aversive odors. A subsequent study by the same group with a smaller sample (four social phobics, seven nonpsychiatric controls) did not replicate this effect in a similar conditioning paradigm using painful pressure as the unconditioned stimulus (Veit *et al.*, 2002). However, they did find right amygdala and bilateral OFC activation to the neutral faces before acquisition in the social phobics. In another fMRI study examining brain responses to human facial stimuli, individuals with social phobia showed greater left medial temporal cortex (including amygdala) activation than nonpsychiatric controls for angry and for contemptuous faces compared with happy faces (Stein *et al.*, 2002). No differences were observed for fearful or nonexpressive faces compared with happy faces. The fMRI research conducted to date provides further evidence of amygdala involvement in social phobia even in settings in which the threat of social evaluation is not as salient as in public speaking.

Overall, these cognitive and neuroimaging data point most strongly to right cortical regions and the amygdala, especially in paradigms involving methods that are ecologically relevant to social phobia such as face stimuli and social performance. The concordance of the cognitive findings with the right-sided

brain activation reported by Davidson *et al.* (2000) suggests that the circuitry of social phobia includes right hemisphere regions involved in threat perception. The recruitment of the amygdala in anticipation of and during public speaking and in response to human face stimuli with different facial expressions is consistent with amygdalar function in vigilance for motivationally salient events (Davis and Whalen, 2001).

VI. Generalized Anxiety Disorder

The salience of worry and verbal rumination in generalized anxiety disorder (GAD) suggests the involvement of left-hemisphere structures dedicated to language. In contrast to the other anxiety disorders that may involve varying degrees of worry about disorder-specific content, worry is the hallmark of GAD. Although worry about everyday problems is not pathological in itself, the person with GAD worries excessively, has difficulty controlling the worry, and experiences significant distress and impaired social and occupational functioning as a result. The exceedingly high rates of comorbidity with depression have made it very difficult to isolate brain abnormalities in GAD. Both cognitive and neuroimaging studies have, therefore, often been quite compromised in terms of diagnostic specificity.

A. Cognitive Studies

As with the other anxiety disorders covered previously, GAD is characterized by an attentional bias toward threat in Stroop (Bradley *et al.*, 1995; Martin *et al.*, 1991; Mathews and MacLeod, 1985; Mathews *et al.*, 1995; Mogg *et al.*, 1989, 1993), dot probe (MacLeod *et al.*, 1986), distractor (Mathews *et al.*, 1990, 1995), and dichotic listening (Mathews and MacLeod, 1986) paradigms. Consistent findings have emerged in two newer paradigms using emotional faces. Using a variant of the dot probe task, Bradley *et al.* (1999) reported that patients with GAD had slower reaction times for threatening than neutral faces compared with controls. Using a similar probe detection task, Mogg *et al.* (2000) measured eye movements and found that subjects with GAD showed a bias toward threat faces for the two eye-movement metrics used, but they did not replicate the reaction time differences documented by Bradley *et al.* (1999). Several of these studies reported the absence of an attentional bias in comparison groups with clinical depression (Mogg *et al.*, 1993, 2000) or with comorbid GAD and depression (Bradley *et al.*, 1995). Evidence for general rather than threat-specific distractibility

has also been found (Bradley *et al.*, 1999; see also Mathews *et al.*, 1990, 1995), although even these studies found results for threat conditions to be more robust than for nonthreat conditions. Despite earlier evidence to the contrary (Mathews *et al.*, 1990), recovery from GAD does not seem to be accompanied by a residual attentional bias (Mathews *et al.*, 1995; see also Mogg *et al.*, 1992), consistent with findings reviewed previously for other anxiety disorders.

Findings of a memory bias in GAD have been mixed. A bias toward threat has generally not been observed for explicit memory tasks (Becker *et al.*, 1999; MacLeod and McLaughlin, 1995; Mathews et al., 1989a; Mogg *et al.*, 1987; Otto *et al.*, 1994). However, Friedman *et al.* (2000) found an explicit memory bias in two separate GAD samples with extremely low rates of comorbid depression (although comorbidity with social phobia was 60%). Several important methodological differences from earlier studies (e.g., incidental learning task, no imagery instructions, longer stimulus exposure) suggest the presence of an explicit memory bias in GAD under conditions optimal for detecting memory biases in clinical anxiety (see Becker *et al.*, 1999). In addition, Otto *et al.* (1994) documented the same relationship between auditory perceptual asymmetry and memory bias toward threat discussed previously for panic disorder in a sample of patients with GAD. The inferred pattern of more left than right hemisphere activity was associated with better memory for threat words, consistent with left-sided neuroimaging findings for GAD reviewed in the following.

Implicit memory bias has emerged for GAD under some conditions (MacLeod and McLaughlin, 1995; Mathews *et al.*, 1989a) but not others (Mathews *et al.*, 1995), a discrepancy that cannot be explained by the type of implicit memory tested (see preceding discussion contrasting conceptual and perceptual implicit memory in PTSD). There is also evidence that patients with GAD have a bias to interpret ambiguous stimuli as threatening (Eysenck *et al.*, 1991; Mathews *et al.*, 1989b). Recovered patients do not show implicit memory or interpretive biases (Eysenck *et al.*, 1991; Mathews *et al.*, 1989b). Again, the cognitive bias literature suggests state-dependent recruitment of right hemisphere regions involved in threat perception, perhaps superimposed on the left-sided perceptual asymmetry and neuroimaging findings also observed in patients with GAD.

There is some indication of mild cognitive deficits in GAD that are consistent with the notion that worry occupies cognitive resources that otherwise might be deployed for various experimental tasks and everyday functions. Wolski and Maj (1998) documented performance deficits on a modified Sternberg memory task in a group of 87 patients with anxiety, 77 of whom had GAD. The general distractibility effects reviewed earlier (e.g., Bradley *et al.*, 1999) provide further support for this position. However, overall performance deficits are generally not seen on attention and memory tasks (e.g., Mathews *et al.*, 1990; Otto *et al.*, 1994).

B. Neuroimaging Studies

The sole morphometric MRI study on GAD was conducted with children and adolescents (De Bellis *et al.*, 2000, 2002b). Right amygdala and superior temporal gyrus volumes were larger in patients than in matched nonpsychiatric controls. No differences were found in the hippocampi, PFC, corpus callosum, thalamus, or basal ganglia or for total intracranial or total cerebral volumes.

In contrast to the other anxiety disorders covered here, functional neuroimaging studies are older, with almost no work published in the past decade. Wu *et al.* (1991) found that patients had less glucose metabolism in the basal ganglia (composed of caudate, putamen, and globus pallidus) and more in left inferior frontal, left inferior occipital, right posterior temporal, and right precentral regions than nonpsychiatric controls during a passive viewing task. The left inferior frontal finding and concomitant greater left than right frontal metabolism are in line with the hypothesis that language centers involved in worry (e.g., Broca's area) are activated. During a visual CPT using degraded stimuli performed only by the patients, basal ganglia and right parietal metabolism increased, whereas decreases were seen in right temporal and occipital lobes. Consistent with their earlier report (Buchsbaum *et al.*, 1987) claimed to be on the same GAD sample (the gender breakdown was slightly different), benzodiazepine therapy resulted in decreased occipital, basal ganglia, and limbic system (composed of the amygdala, hippocampus, and cingulate) metabolism. In a SPECT study, patients with GAD showed increased left orbital frontal blood flow when asked to freely associate about threatening pictures presented before blood flow measurement (Johanson *et al.*, 1992). The specificity of the effects to GAD in the latter two studies is not clear, because neither one included a control group.

Several recent fMRI studies have been undertaken to examine the neural substrates of affective processing in GAD. Thomas *et al.* (2001) reported that a pediatric sample predominantly composed of individuals with GAD showed a larger right amygdala response to fearful than neutral faces, a pattern not present for either comparison group (nonpsychiatric control children, girls with major depressive disorder). In another study using a similar face paradigm, adult patients with GAD exhibited more left amygdala activation to fearful than to neutral or happy expressions, whereas nonpsychiatric controls did not (Johnstone *et al.*, 2002). In that same sample using a paradigm that used warning cues that predict subsequent aversive or neutral pictures, Nitschke *et al.* (2002) found that patients with GAD showed more activation than controls in the left inferior PFC during anticipation of aversive pictures and in left OFC, bilateral PFC, and bilateral insula after those aversive pictures. As such, the recent fMRI work on GAD has reported findings for some of the same structures implicated in neuroimaging research on other anxiety disorders.

Involvement of different brain areas in GAD can also be gleaned from several EEG studies. EEG topography from 32 sites revealed no baseline differences between patients with GAD and nonpsychiatric controls (Grillon and Buchsbaum, 1987). When presented with neutral lights in a basic orienting response paradigm, those patients showed less alpha suppression (presumably reflecting decreased activity) than controls, especially over the occipital lobe, perhaps reflecting a diminution of attention to external stimulation because of competing processes devoted to worry. An earlier EEG study by the same group examined benzodiazepine treatment effects in patients with random assignment to placebo or drug group and in nonpsychiatric controls (Buchsbaum *et al.*, 1985). Using 16 midline and left-hemisphere sites, they found that patients had less delta and alpha (more activity) than controls, especially over the left posterior temporal cortex. Correlational analyses revealed that increased left frontal alpha (decreased activity) was associated with clinical improvement for patients in the drug group, consistent with left PFC findings in GAD and worry reviewed previously.

Of relevance to imaging research despite only recording from three midline electrodes, a recent treatment study of GAD explored frontal midline theta activity, which is thought to reflect reduction of anxiety during task performance (Suetsugi *et al.*, 2000). Criteria for frontal midline theta at the midfrontal site were not met for any of the 28 patients at the initial visit. The 26 patients for whom frontal midline theta appeared after psychotherapy or pharmacotherapy showed dramatic clinical improvement, whereas the remaining two individuals continued to exhibit high levels of anxiety. Although further research is needed to examine the reliability of these findings, one potentially noteworthy interpretation is that worry interferes with the production of frontal midline theta.

The dearth of recent neuroimaging data for GAD is striking compared with the proliferation of such research conducted with the other five anxiety disorders covered in this review. The recent fMRI work is consistent with neuroimaging work on those anxiety disorders documenting the hyperresponsivity of the amygdala to motivationally salient stimuli. The handful of other studies, along with the more extensive cognitive science literature examining GAD, point to several brain regions deserving further investigation. On the basis of the cognitive deficit and left-sided neuroimaging findings, the circuitry involved in worry and the structures overlapping with attention and working memory (e.g., PFC, parietal regions, particularly left hemisphere) are conspicuous candidates for uncovering brain aberrations in GAD. In addition, the right hemisphere territories implicated by the cognitive biases accompanying GAD are also likely constituents of the brain circuitry involved in the pathophysiology of GAD.

VII. Discussion

Across the many cognitive and neuroimaging studies reviewed here, cognitive bias toward threat is the one attribute common to all six anxiety disorders covered. Attentional biases have been observed in all disorders, whereas data for explicit and implicit memory biases have been mixed. Findings of a memory bias have been replicated most consistently for panic disorder, with substantial evidence also reported for PTSD, social phobia, and GAD. On the other hand, no studies have found a memory bias in OCD or specific phobia. Interpretation (i.e., judgment) biases have not been extensively examined among clinical populations, although there is ample evidence of such a bias in OCD, social phobia, and GAD. This orientation toward threat in anxiety disorder populations suggests the involvement of particular anterior and posterior right hemisphere regions (for reviews, see Compton *et al.*, 2000, 2003; Nitschke *et al.*, 2000; Nitschke and Heller, 2002). As described by Nitschke *et al.* (2000), these biases may be related to an emotion surveillance system of the right hemisphere designed to evaluate the presence of a threat in the external environment. This right hemisphere system may correspond to the cortical processes that McNally (1998) postulated to accompany a subcortical circuit involved in attentional biases toward threat. The hyperactivation of this right hemisphere system may interfere with visual spatial functions for which right posterior regions are specialized, as seen in OCD and social phobia. The right-sided increases in activation reported in many of the neuroimaging studies examining anxiety disorders—with the notable exception of GAD, which likely invokes left hemisphere regions devoted to verbal processes needed for worry—may be a manifestation of the heightened reliance on this emotion surveillance system governing threat perception and evaluation.

The anxiety disorders covered here are further characterized by a number of divergent neuropsychological patterns. In contrast to the morphometric and functional studies on OCD, the caudate nucleus is not implicated in any of the other anxiety disorders. PTSD is the only disorder to be accompanied by memory deficits and by reduced hippocampal volume. Findings of hippocampal asymmetries have been reported exclusively for panic disorder. Unlike the other disorders, the preponderance of imaging findings for GAD implicates left hemisphere regions. Amygdala activation has not been observed with any inconsistency, except in PTSD and social phobia, although amygdala involvement is likely underestimated because of the concerns about habituation and susceptibility artifact noted previously. OFC and ventral ACC activation has been reliably found only in OCD and PTSD. And, finally, visual spatial deficits have been observed for OCD and social phobia but not the others. This

summary of the findings points to the substantial heterogeneity among the anxiety disorders.

Although anxiety is often referred to as a homogenous construct, neuroscience findings for anxiety disorders clearly indicate the importance of noting distinctions and variable symptom expression both across and within diagnoses. Several useful neurobiological models have been proposed, including one for OCD (Rauch *et al.*, 1998) and another concentrating primarily on PTSD (Charney *et al.*, 1998). We have proposed a neuropsychological framework positing a distinction between two types of anxiety (e.g., Nitschke *et al.*, 2000). As noted previously, anxious apprehension is characterized primarily by worry and relies on left hemisphere processes, whereas anxious arousal is characterized by immediate fear and panic symptoms and is closely aligned with the emotion surveillance system of the right hemisphere. In general, GAD is characterized more strongly by anxious apprehension than are the other disorders, whereas panic disorder is likely accompanied by the highest levels of anxious arousal. However, it is important to note that these two forms of anxiety are not mutually exclusive and likely exist in all individuals with anxiety disorders to varying degrees. Pronounced individual differences within a disorder in the expression of both forms of anxiety are also likely, as are intraindividual differences across time. Although several models explain some of the variability in the cognitive and neuroimaging findings for anxiety disorders, no current formulation can account for all the heterogeneity.

Attending to psychological and biological mechanisms should inform this heterogeneity, which impedes attempts to unravel the neural circuitry of clinical anxiety. One means of accomplishing this is research with clinical populations that rigorously examines the brain correlates of specific anxiety symptoms, such as worry, contamination obsessions, and avoidance of feared objects or situations. Another approach is to appeal to knowledge about which brain regions govern specific functions relevant to anxiety pathology (c.f. Davidson *et al.*, 2002). Basic research with humans and nonhuman animals has uncovered some of the circuitry involved in those psychological phenomena central to anxiety disorders and showcased in this review (e.g., threat evaluation, fear, response conflict). This emphasis on mechanisms is also promising for research examining the interface with other neurobiological systems shown to be critical for the expression of fear and to manifest irregularities in anxiety disorders, such as cortisol, corticotropin-releasing factor (CRF), cholecystokinin (CCK), tachykinins, neuropeptide-Y, serotonin, norepinephrine, gamma-aminobutyric acid (GABA), and *N*-methyl-D-aspartate (NMDA). These are some of the areas that await synthesis with the neural correlates of anxiety that have been identified in the large corpus of cognitive and neuroimaging research examining anxiety disorders.

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