INTRODUCTION

In attempting to construct a neuropsychology of anxiety, findings can be drawn from several related, yet often perceived as separate, domains of research, including cognitive science and neuroscience. The relatively new fields of cognitive neuroscience and affective neuroscience are concerned with very similar questions regarding brain–behaviour relationships as were fundamental to the older field of neuropsychology, and the neuroimaging tools central to those disciplines are no less pertinent to neuropsychology than are traditional neuropsychological test batteries or cognitive/behavioural paradigms. Thus, this review of the neuropsychological 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.

Although often overlooked by neuroscientists studying brain function in anxiety, 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 review, see McNally, 1998). 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 upon remission (for review, see McNally, 1998), 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, Heller and Miller, 2000; see also Compton et al., 2000, 2002).

In addition to these cognitive biases, cognitive deficits have been documented in anxiety disorders. One is a tendency to do poorly on tasks that require selective attention and concentration. This deficit has been suggested to reflect a general problem of preoccupation and distraction due to worry or rumination that interferes with other mental processes (for review, see Nitschke, Heller and Miller, 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 behavioural and electroencephalographic (EEG) findings (for review, see Nitschke, Heller and Miller, 2000) and an extensive literature in non-human animals examining fear and anxiety (for reviews, see LeDoux, 1996; Davis and Lee, 1998), haemodynamic neuroimaging research has implicated a number of the suggested regions.

Although emotional, cognitive, and neural commonalities are apparent, 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 neuropsychological literature on anxiety and its disorders is the lack of clarity and specificity about what anxiety is. Views of anxiety range from its usage in contemporary clinical research as a rubric term that encompasses fear, panic, worry, and all the anxiety disorders listed in the DSM-IV 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). Further, 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, Heller and Miller, 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 neuropsychology and neural circuitry of anxiety disorders by examining the relevant cognitive research. Structural and functional neuroimaging data will also be reviewed, including morphometric magnetic resonance imaging (MRI), functional MRI (fMRI), positron emission tomography (PET) using various radiotracers such as [18F]fluorodeoxyglucose (FDG) for glucose metabolism and [15O]labelled 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 neuroscience literatures reveals that the anxiety disorders engage brain regions involved in threat perception (e.g., right hemisphere...
regions; Compton et al., 2000, 2002; Nitschke, Heller and Miller, 2000), anxious arousal (right posterior regions; Nitschke, Heller and Miller, 2000), fear (e.g., amygdala; LeDoux, 1996), vigilance for motivationally salient events (e.g., amygdala; Whalen et al., 1998; Davis and Whalen, 2001), decoding of motivationally relevant emotional information such as the reward and punishment value of a stimulus [e.g., orbital frontal cortex (OFC); Rolls, 1999], worry (e.g., left-hemisphere regions; Nitschke, Heller and Miller, 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 Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) although consistent patterns have emerged in studies using nonclinical and brain-lesioned human populations (for review, see Nitschke, Heller and Miller, 2000).

**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 with the experienced anxiety and distress reported by individuals suffering from OCD is unique among the anxiety disorders and can be linked to a number of neuropsychological abnormalities.

**Cognitive Studies**

An extensive cognitive literature on OCD points most strongly to non-verbal memory and other visual–spatial deficits (e.g., Boone et al., 1991; Zielinski, Taylor and Juzwin, 1991; Christensen et al., 1992; Cohen et al., 1996; Purcell et al., 1998; Savage et al., 1996, 1999; see also McNally and Kohlbeck, 1993; Constans et al., 1995). No evidence of a verbal memory deficit has been found (Foa et al., 1997). There is also ample documentation of impaired executive functions (e.g., Head, Bolton and Hymas, 1989; Veale, Owen and Marks, 1996; Abbruzzese, Ferri and Scarone, 1997; Purcell et al., 1998), with trends reported by Cohen et al. (1996) for several neuropsychological tests. 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 non-verbal memory deficit for reproducing a figure among OCD patients. Morphometric data for OCD subjects by the same group suggests that larger right prefrontal volumes are associated with worse non-verbal memory using the same task (Grachev et al., 1998). Should this finding be replicated, one possible explanation is that the heightened threat perception and negative affect accompanying OCD occupy the resources in the right prefrontal cortex (PFC) that are normally dedicated to non-verbal memory and also lead to structural changes.

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 colour of words varying in emotional content while ignoring their meanings. Foa et al. (1993) found that OCD patients with washing rituals took longer to name the colour for contamination words than for neutral words, suggesting that the threatening nature of the contamination words interfered with the task of naming the colour. They also had longer response latencies to contamination words than did OCD non-washers or non-psychiatric controls. On the other hand, OCD non-washers had longer latencies to negative than neutral words, whereas the opposite pattern was seen in controls. In a similar study in which the contamination words did not reflect the primary concerns of the OCD patients, no interference effects were observed (McNally et al., 1990). These attentional findings implicate the involvement of right hemisphere regions important for threat perception (Compton et al., 2000, 2002; Nitschke, Heller and Miller, 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 OCD patients are less confident than non-psychiatric controls about memory-related judgements (McNally and Kohlbeck, 1993; Constans et al., 1995). Thus, the cognitive literature is fairly conclusive in demonstrating that the memory concerns frequently voiced by OCD patients (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 behaviour, 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.

**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, Alyward et al. (1996) found no caudate differences, and Scarone et al. (1992) reported an increase in right caudate volume (see Table XIX-9.3A in Martin et al., Chapter XIX-9). 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, 1997b) found a reduction, and others observed no differences from non-psychiatric controls (e.g., Swedo et al., 1989). In contrast, symptom provocation paradigms employing PET (McGuire et al., 1994; Rauch, Jenike and Alpert, 1994) and fMRI (Breitier et al., 1996) have consistently shown caudate activation.

The cortico-striatal model of OCD proposed by Rauch et al. (1998) posits that pathology within the caudate results in OFC and ACC hyperactivity via 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, Crutcher and DeLong, 1991). Further pursuing the evidence of caudate abnormalities, Rauch and colleagues employed PET and fMRI while OCD patients performed an implicit learning task shown to be dependent on striatal function. Increases were reported in right caudate volume (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, 1997b) found a reduction, and others observed no differences from non-psychiatric controls (e.g., Swedo et al., 1989). In contrast, symptom provocation paradigms employing PET (McGuire et al., 1994; Rauch, Jenike and Alpert, 1994) and fMRI (Breitier et al., 1996) have consistently shown caudate activation.

As noted by Martin et al. (Chapter XIX-9), the striatum was not activated in OCD subjects (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.

Haemodynamic studies of OCD have implicated a number of other regions, most consistently OFC and ventral ACC, areas of the brain frequently found to be involved in aspects of emotion and
attention. PET and SPECT studies using protocols not involving a task have revealed that patients with OCD have more blood flow or glucose metabolism than non-psychiatric controls in OFC (Baxter et al., 1987, 1988; Swedo et al., 1989; Rubin et al., 1992; but see Machlin et al., 1991; Busatto et al., 2001) and ventral ACC (Machlin et al., 1991; Perani et al., 1995; but see Busatto et al., 2001; see Table XIX-9.3B in Martis et al., Chapter XIX-9). Similar findings for the OFC were also observed during an auditory continuous performance task in a PET study measuring glucose metabolism (Nordlähli et al., 1989). OFC and ventral ACC activations have also been reported in fMRI (Breiter et al., 1996; Adler et al., 2000) and PET (Rauch, Jenike and Alpert, 1994) studies employing symptom provocation paradigms with actual obsessional stimuli. In another study employing symptom provocation via presentation of individually specified contaminants in OCD patients, McGuire et al. (1994) found symptom intensity to be correlated with right inferior frontal/OFC but not ACC activation. Busatto et al. (2001) also found that obsessional-compulsive symptoms correlated positively with left OFC blood flow. A less potent experimental elicitation of symptoms via auditory presentation of obsessional material did not induce blood flow changes in these areas using PET (Cottraux et al., 1996).

With the amygdala often highlighted in models of the neural circuitry of fear, anxiety and emotion (e.g., LeDoux, 1996; Charney, Grillon and Bremner, 1998), it is worth noting that amygdala activation has been documented in only one study examining OCD, that conducted by Breiter et al. (1996), who exposed 10 OCD subjects 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 OCD patients examined by Adler et al. (2000). 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).

Treatment studies further inform the neural circuitry characterizing OCD (see also Martis et al., Chapter XIX-9). Both cognitive-behavioural and pharmacological therapies have been associated with normalized (i.e., decreased) glucose metabolism in the caudate nucleus (Benkelfat et al., 1990; Baxter et al., 1992; Schwartz et al., 1996; Saxena et al., 1999; but see Baxter et al., 1987; Swedo et al., 1992), OFC (Benkelfat et al., 1990; Swedo et al., 1992; Saxena et al., 1999; but see Baxter et al., 1987, 1992; Schwartz et al., 1996), and ventral ACC (Perani et al., 1995; marginally significant in Baxter et al., 1992, and Swedo et al., 1992). Similar findings have emerged for blood flow measured by SPECT in the OFC (Rubin et al., 1995) and ventral ACC (Hoehn-Saric et al., 1991). Baxter and colleagues have reported that pre-treatment 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 pre-treatment OFC glucose metabolism may be associated with better response to medications, whereas the converse may be true for psychotherapy (Swedo et al., 1989; Brody et al., 1998; Saxena et al., 1999). Response to psychotherapy 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 pre-treatment 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 prior to 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. Rauch, in press), and in response conflict about whether to perform some mental activity or compulsive behaviour. As noted above, the cognitive data suggest the engagement of right hemisphere regions involved in threat perception. The absence of more right-sided effects in the imaging data should be interpreted with caution, as 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 non-verbal 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 non-verbal 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. Furthermore, the pronounced brain abnormalities accompanying depression (for reviews, see Davidson et al., 2002; Mohanty and Heller, 2002, Chapter XVIII-7) certainly have consequences for the neuropsychology of OCD. For example, Martinot et al. (1990) reported a bilateral diminution of PFC glucose metabolism in 16 OCD patients as compared to eight non-psychiatric controls and no effects for OFC; however, despite not meeting criteria for DSM-III current major depressive episode, these patients were characterized by significantly higher levels of depression than the controls.

POSTTRAUMATIC STRESS DISORDER

The past decade has witnessed an explosion of research examining the neurobiological mechanisms and neuropsychological, behavioural, 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 aetiological hypotheses based on the rich conditioning literature, including classical cue conditioning, operant conditioning, and context conditioning. However, the array of re-experiencing, 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 at all. Despite these obstacles, the emerging body of research is contributing to understanding this elusive condition.

Cognitive Studies

As with OCD, a commonly reported cognitive abnormality in PTSD is an attentional bias towards 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., McNally et al., 1990, 1993, 1996; Kips et al., 1995; Vrana, Roodman and Beckham, 1995), motor vehicle accident victims (Bryant and Harvey, 1995), and people involved in a ferry disaster (Thrasher, Dagleish and Yule, 1994). Recovery from PTSD has been shown to eliminate the attentional bias (Foa et al., 1991), whereas PTSD patients who have not recovered continue to show the bias toward threat cues when retested (McNally and Kohlbeck, 1993). A memory bias toward trauma-relevant material has also been found in PTSD patients for explicit memory (Vrana, Roodman and Beckham, 1995) and conceptual implicit memory (Amir, McNally and Wiegartz, 1996c), suggesting a more pervasive proclivity towards
threat-related material that is not confined to the frequently reported attentional effect. No bias was found on an implicit-memory task that depended more on physical, perceptual features of the words than on their meaning (McNally and Amir, 1996). Consistent with these cognitive data, a recent ERP study using threat words as the low-probability stimulus type in an oddball paradigm reported that PTSD patients had larger P3 amplitudes than non-psychiatric controls for trauma-relevant but not trauma-irrelevant threat words (Stanford et al., 2001). The oddball paradigm is comprised 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; Uddo et al., 1993; McNally et al., 1994, 1995; 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). These data corroborate the reports of reduced hippocampal volume in PTSD to be reviewed next.

**Neuroimaging Studies**

As covered by Martis et al. (Chapter XIX-9), the handful of studies examining structural abnormalities in PTSD consistently implicates the hippocampi, with reduced volume ranging from 8% to 30% (Bremner et al., 1995a, 1997; Gurvits et al., 1996). A 5% reduction in the left hippocampus was observed by Stein et al. (1997) in 21 adult survivors of childhood abuse, 15 of whom met DSM-IV criteria for PTSD. Schuff et al. (1997) also reported a trend for a 6% right hippocampal reduction in combat veterans. It is not known whether this 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). Regardless of this, these hippocampal data are clearly linked to the aforementioned explicit memory deficit in PTSD. Indeed, Bremner et al. (1995a) reported a strong correlation \( r = 0.64 \) between verbal memory and right hippocampal volume in combat veterans with PTSD.

In contrast to the above morphometric data, functional neuroimaging studies examining PTSD have implicated a host of structures (see Table XIX-9.1B in Martis et al., Chapter XIX-9). 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. (1999a) 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. (1999) reported more blood flow in the ventral ACC, OFC, and insula for childhood abuse victims with PTSD than those without. Two studies reported activation of the ventral ACC in combat veterans with PTSD as well as in combat controls without PTSD (Bremner et al., 1999b; Liberzon et al., 1999). Using SPECT, Liberzon and coworkers observed activation of the ventral ACC/medial PFC in non-psychiatric controls as well. Another report from this group indicated that only PTSD subjects showed more blood flow in the medial PFC, whereas both PTSD subjects and non-psychiatric 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. 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 found amygdala activation (Rauch et al., 1996; Shin et al., 1997; Liberzon et al., 1999). Other areas implicated by Rauch et al. (1996) in a PET study using script-driven imagery were the ventral ACC and right OFC, insula, and temporal cortex. The same group also found increased blood flow in the ventral ACC in another sample of combat veterans for a paradigm involving combat, negative, and neutral pictures (Shin et al., 1997a, 1997b). Both these studies also reported a blood flow decrease in Broca’s area (see also Fischer, Wik and Fredrikson, 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 non-psychiatric 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 above for PTSD patients. An older study conducted by Semple et al. (1993) reported more OFC blood flow as measured by PET during an auditory continuous performance task and a word generation task in combat veterans with PTSD and substance abuse than non-psychiatric 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 PTSD patients had more right amygdalar and left parahippocampal blood flow during the same continuous performance task than non-psychiatric controls (Semple et al., 2000), adding further support to the symptom provocation findings above.

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 and vigilance for motivationally salient events, and memory. As with OCD, the OFC and ventral ACC appear 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 rates 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.

**Panic Disorder**

Characterized by recurrent unexpected panic attacks that share many features with basic fear responses, panic disorder has been viewed as the pre-eminent candidate condition for postulating dysfunction of the fear circuitry identified in research with non-human animals. However, the literature has shown this to be
a disappointing enterprise, and the neural machinery involved remains largely a mystery. It is important to note that even in the majority of 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. 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). The various neuropsychological research tools now available with humans may hold the most promise for identifying the circuitry affected in panic disorder.

**Cognitive Studies**

Cognitive reports in the literature on panic disorder have been more sparse than for OCD or PTSD. The most common finding is a bias for panic-relevant words on implicit and explicit memory tasks (e.g., McNally, Foa and Donnell, 1989; Cloitre and Liebowitz, 1991; Cloitre et al., 1994; Amir et al., 1996b; Becker et al., 1994, 1999), although negative findings have been reported (Otto et al., 1994; Rapee, et al., 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 panic disorder patients but not in non-psychiatric controls (Otto et al., 1994). These results suggest a pattern of brain activity akin to that found for generalized anxiety disorder (see below), anxious apprehension, and worry (for review, see Nitschke, Heller and Miller, 2000). There is also evidence of a bias towards threatening words in a priming task involving lexical and non-lexical word pairs, one presented above the other (McNally et al., 1997). Panic patients showed faster reaction times in naming the threat targets following the threat prime but only when the target was in the bottom position. Emotional Stroop interference has also been observed in panic disorder patients (Ehlers et al., 1988; McNally et al., 1990, 1994). These cognitive biases again point to the involvement of right hemisphere systems corresponding to threat, with dichotic listening data suggesting left-hemisphere engagement, perhaps reflecting anxious apprehension.

**Neuroimaging Studies**

The one known quantitative morphometric study found that panic disorder patients had smaller temporal lobes than non-psychiatric controls but no hippocampal differences (Vythilingam et al., 2000). Evidence for temporal lobe aberrations has also been documented using 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 (see Table XIX-9.2A in Martis et al., Chapter XIX-9). Consistent with these data, haemodynamic 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 panic disorder patients 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 panic disorder patients while engaged in an auditory continuous performance task (Nordahl et al., 1990, 1998; see Table XIX-9.2B in Martis et al., Chapter XIX-9). In the first study, patients also exhibited more right frontal and occipital metabolism and less left parietal metabolism than non-psychiatric controls. An inferior frontal asymmetry with more right than left metabolism was observed in both patient samples. Similar group differences in inferior PFC asymmetry (right > left), right frontal (marginally significant), and occipital cortex were reported in a SPECT study conducted by De Cristofaro et al. (1993). There were no differences in hippocampal asymmetry, but rather patients showed bilateral decreases.

Consistent with the reports of hippocampal and parahippocampal asymmetries, Bisaga et al. (1998) found that panic disorder patients exhibited more glucose metabolism in the left hippocampus and parahippocampal area than non-psychiatric controls. Those patients also had less metabolism in right inferior parietal and right superior temporal regions, which could be due to comorbid depression (Heller and Nitschke, 1998). In light of hippocampal involvement in explicit memory, these findings suggest that hippocampal and parahippocampal asymmetries may play a role in the explicit memory bias toward threat emerging in the cognitive literature.

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 non-psychiatric 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 employing haemodynamic 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 following infusion exhibited larger occipital increases, especially on the right, than non-panicking subjects, whereas the non-panicking subjects showed larger global increases, especially over the left hemisphere. In a PET study, Reiman et al. (1989) found no blood flow increases following sodium lactate infusion among non-panicking subjects, whereas the panic disorder patients who had panic attacks exhibited increased blood flow in anterior temporal, insula/claustrum/putamen, superior colliculus/periaqueductal grey, and cerebellar vermis regions (see also Table XIX-9.2C in Martis et al., Chapter XIX-9). Of note, the anterior temporal findings may be an artifact of muscular contraction of the jaw (Drevets, Videen and MacLeod, 1992; Benkelfat et al., 1995), such that recent imaging studies on anxiety often employ teeth-clenching control conditions (e.g., Rauch et al., 1996; Reiman, 1997; Javanmard et al., 1999).

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 the consistent hippocampal findings across several 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 three studies using different technologies is in concordance with that position. The OFC, ACC, and caudate regions highlighted in the above sections for OCD and PTSD have not emerged with any consistency in research on patients with panic disorder.

Again, the issue of comorbidity with depression deserves mention, because the explicit memory bias and the PFC asymmetry are commonly seen in depression. However, evidence reviewed above suggests that increases in right PFC activity are driving this asymmetry in panic disorder, whereas the preponderance of literature on...
major depressive disorder indicates that decreased left PFC activity likely contributes to that asymmetry in depression.

**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 due to the prevalence of specific phobias and the relatively low rates of comorbidity with other mental disorders. However, studies with phobics are few, perhaps due to 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 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.

**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 employed in the OCD, PTSD, and panic disorder studies above. Using Stroop tests involving spider, general negative, and neutral words, Watts et al. (1986) and Lavy, Van den Hout and Arntz (1993) found larger interference for the spider words in spider phobics than matched non-anxious 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 developed PTSD (Bryant and Harvey, 1995). Evidence of a memory bias in spider phobia has not been reported (Watts and Coyle, 1993).

**Neuroimaging Studies**

Consistent with the conclusion drawn by Martis et al. (Chapter XIX-9), functional neuroimaging data have been inconsistent across studies. 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 above studies for OCD and PTSD (see Rauch et al., 1997b), including the right ACC, left insular cortex, and left OFC. Conversely, two earlier PET studies by Fredrikson and colleagues 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 non-psychiatric 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 pre-treatment spider phobia scores, whereas frontal activity was not related to pre-treatment or post-treatment clinical measures (Merkelbach et al., 1998). There have been no published findings of amygdala activation in specific phobia despite the clear relevance of that structure for the fear response evoked by confronting phobic stimuli.

Due to the dearth of cognitive and neuroimaging research investigating specific phobias, little is known about the neuropsychology accompanying such intense, long-standing fear of an object that is often harmless. The attentional bias suggests the involvement of right hemisphere regions oriented towards threat; however, the imaging data are inconsistent. Although the structures implicated in the study by Rauch et al. (1995a, 1997b) suggest some commonality with other anxiety disorders, those findings have not been supported by the other studies examining specific phobia. It may be that the circuitry implicated is much less pronounced or complex than appears 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.

**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 suffering from 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 largest psychological disorder in the United States, after depression and alcoholism. Accordingly, the past five years has witnessed an explosion of research interest in the disorder, with efforts to identify the affected neural circuitry very much in their infancy.

**Cognitive Studies**

Cognitive research has implicated a number of abnormalities in social phobia, the majority 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 towards social threat across multiple different paradigms.

One relevant study not reviewed by Heinrichs and Hofmann (2001) examined attention bias for facial expressions in generalized social phobia (Gilboa-Schechtman, Foa and Amir, 1999). Consistent with the dot probe and Stroop studies reviewed, phobic subjects showed an attentional bias toward angry faces as measured via several metrics using the face-in-the-crowd paradigm, whereas non-anxious controls did not. Moreover, successful treatment has resulted in the attenuation of attention (e.g., Mattia, Heimberg and Hope, 1993) and interpretation (e.g., Foa et al., 1996) biases.

In other findings, Amir et al. (1996a) found suppression of Stroop interference to social-threat words in social phobics but not non-psychiatric controls prior to 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 upon completion of the Stroop task). The authors suggested that subjects might increase their efforts when anxious, thereby compensating for the interference. Another possibility is that 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 non-anxious experimental conditions.
Research eliciting anticipatory anxiety in interpretation/judgement bias paradigms is needed to determine if this phenomenon extends 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). 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 where social phobics and non-psychiatric 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), Foia et al. (2000) found that social phobics recognized more angry and disgust faces than happy or neutral ones, whereas no differences were observed for non-anxious 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 non-negative facial expressions. Furthermore, phobic subjects had longer latencies for angry than disgust faces, whereas controls did not. Similar specificity was observed in the attentional paradigm employing faces mentioned above, with social phobics detecting anger faces faster than disgust ones, whereas controls showed no difference (Gilboa-Schechtman, Foia and Amir, 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 implying that the right hemisphere regions involved in threat perception should be involved.

Consistent with cognitive findings for OCD, visual–spatial impairment including non-verbal 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 with a consequent lack of resources for other processes lateralized to the right hemisphere such as visual–spatial functions.

**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 non-psychiatric controls. Using PET to measure blood flow in social phobics, Reiman et al. (1996) found that social phobics exhibiting more amygdalar and hippocampal activation than controls when neutral faces were paired with the aversive odors (see Table XIX-9.4A in Martis et al., Chapter XIX-9). Three additional neuroimaging reports presented pilot or preliminary data with mixed results for the structures implicated in the above studies on social phobia (Stein and Leslie, 1996; Van Ameringen et al., 1998; Van der Linden et al., 2000).

Overall, these cognitive and neuroimaging data point most strongly to the 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 involvement of the amygdala in fear and in vigilance for motivationally salient events is certainly applicable for the paradigms involving anticipatory anxiety and social performance.

**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 which 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.

**Cognitive Studies**

As with the other anxiety disorders covered above, GAD is characterized by an attentional bias towards threat in Stroop (Mathews and MacLeod, 1985; Mogg et al., 1987, 1993; Martin, Williams and Clark, 1991; Bradley et al., 1995; Mathews et al., 1995), dot probe (MacLeod, Mathews and Lata, 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 GAD patients had slower reaction times for threatening than neutral faces, compared to controls. Using a similar probe detection task, Mogg, Miller and Bradley (2000) measured eye movements and found that GAD subjects showed a bias toward threat faces for the two eye-movement metrics employed, 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 non-threat conditions. Despite earlier evidence to the contrary (Mathews et al., 1990), recovery from GAD does not appear to be accompanied by a residual attentional bias (Mathews et al., 1995; see also Mogg, Mathews...
and Eysenck, 1992), consistent with findings reviewed above for other anxiety disorders.

Findings of a memory bias in GAD have been mixed. A bias towards threat has generally not been observed for explicit memory tasks (Mogg, Mathews and Weinman, 1987; Mathews et al., 1989a; Otto et al., 1994; MacLeod and McLaughlin, 1995; Becker et al., 1999). However, Friedman, Thayer and Borkovec (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 above for panic disorder in a sample of GAD patients. 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 below.

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 above discussion contrasting conceptual and perceptual implicit-memory in PTSD). There is also evidence that GAD patients have a bias to interpret ambiguous stimuli as threatening (Mathews, Richards and Eysenck, 1989b; Eysenck et al., 1991). Recovered patients do not show implicit memory or interpretive biases (Mathews, Richards and Eysenck, 1989b; Eysenck et al., 1991). Again, the cognitive bias literature suggests state-dependent recruitment of right hemisphere regions involved in threat perception, perhaps superimposed upon the left-sided perceptual asymmetry and neuroimaging findings also observed in GAD patients.

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 anxiety patients, 77 of whom had GAD. The general distractibility effects reviewed above (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).

**Neuroimaging Studies**

The one published morphometric MRI study on GAD was conducted with children and adolescents (De Bellis et al., 2000). The right amygdala was larger in patients than in matched non-psychiatric controls. No differences were found in the temporal lobe, hippocampi, corpus callosum, 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 no work published in the past decade. Wu et al. (1991) found that patients had less glucose metabolism in the basal ganglia (comprised of caudate, putamen, and globus pallidus) and more in left inferior frontal, left inferior occipital, right posterior temporal, and right precentral regions than non-psychiatric 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 centres involved in worry (e.g., Broca’s area) are activated. During a visual consistent performance task 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 (Buchbaum et al., 1987), which they claimed was on the same GAD sample (the gender breakdown was slightly different), benzodiazepine therapy resulted in decreased occipital, basal ganglia, and limbic system (comprised of the amygdala, hippocampus, and cingulate) metabolism. In a SPECT study, GAD patients showed increased left orbital frontal blood flow when asked to freely associate about threatening pictures presented prior to RCBF 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.

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 GAD patients and non-psychiatric controls (Grillon and Buchsbaum, 1987). When presented with neutral lights in a basic orienting response paradigm, patients showed less alpha suppression (presumably reflecting decreased mental 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 non-psychiatric 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 left posterior temporal cortex. Drug effects were seen in different bands across several regions of the brain but were of limited utility in isolating patterns of brain activity critical for GAD because only four of the nine patients administered benzodiazepines showed clinical improvement as measured by the Hamilton Anxiety Scale (none of the 11 patients taking placebo improved). However, correlational analyses revealed that increased left frontal alpha decreased activity was associated with clinical improvement for patients in the drug group, consistent with above findings of left frontal involvement in GAD and worry.

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 following psychotherapy or pharmacotherapy showed dramatic clinical improvement, whereas the remaining two individuals continued to exhibit high levels of anxiety. Although these data are certainly preliminary, they again implicate the frontal cortex and suggest that worry interferes with the production of frontal midline theta.

The dearth of recent neuroimaging data for GAD—also noted by Martin et al. (Chapter XIX-9)—is striking when compared to the proliferation of such research conducted with the other five anxiety disorders covered in this review. The few studies conducted, along with the more extensive cognitive science literature examining GAD, point to several brain regions deserving further investigation. Based on 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.

**DISCUSSION**

Across the many cognitive and neuroimaging studies reviewed here, cognitive biases 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., judgement) 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 towards threat in anxiety disorder populations suggests the involvement of particular anterior and posterior right hemisphere regions (for reviews, see Compton et al., 2000, 2001; Nitschke, Heller and Miller, 2000). As described by Nitschke and coworkers (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 circuitry 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 involves left-hemisphere regions devoted to verbal processes needed for worry—may be a manifestation of the heightened reliance on this emotional 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 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. 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. OFC and ventral ACC activations have been reliably found only in OCD and PTSD. 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, neuropsychological data 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 proposed by Rauch et al. (1998) on OCD and another proposed by Charney, Grillon and Bremner (1998) concentrating primarily on PTSD. We have proposed a neuropsychological framework positing a distinction between two types of anxiety (e.g., Nitschke et al., 2000). 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 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 intra-individual differences across time. Although several models explain some of the variability in the neuropsychological findings, no current formulation can account for all the heterogeneity.

Attending to psychological and biological mechanisms should inform this heterogeneity that impedes attempts to unravel the neuropsychology and 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 (see Davidson et al., 2002). Basic research with humans and non-human 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 neuropsychological concomitants of anxiety that have been identified in the large corpus of cognitive and neuroimaging research examining anxiety disorders.

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