XIX-8

The Neuropsychology of Anxiety Disorders: Affect, Cognition, and Neural Circuitry

Jack B. Nitschke and Wendy Heller

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 [^{18}F]fluorodeoxyglucose (FDG) for glucose metabolism and ^{15}O-labelled water for blood flow, single-photon emission computed tomography (SPECT) with ^{133}Xenon or ^{99m}Tc-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

Biological Psychiatry: Edited by H. D'haenen, J.A. den Boer and P. Willner. ISBN 0-471-49198-5

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, Aylward *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 Martis *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 (Breiter *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 in non-psychiatric volunteers (Rauch *et al.*, 1995b, 1997c). As noted by Martis *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 (Nordahl *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 obsessive–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 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 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, Dalgleish 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 implicate 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 those 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 for 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/periacquenductal 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 (Merckelbach *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), 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 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, Foa 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 (1997) reported that singing in front of observers activated a number of cortical and subcortical regions, including lateral PFC, anterior temporal, and posterior cingulate regions, with trends noted in the ACC, medial PFC, amygdala, and hippocampus. In another PET study, Tillfors *et al.* (2001) found that social phobics exhibited larger blood flow increases than non-psychiatric controls in the right amygdaloid complex (extending into the hippocampus) while speaking in front of an audience. On the other hand, controls had larger increases in right parietal, restrosplenial, and right secondary visual cortices than social phobics did.

An fMRI study found that social phobics showed greater amygdala activation bilaterally to neutral faces than did non-psychiatric 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 appears 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 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 continuous 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 (Buchsbaum *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 Martis *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 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 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. 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. 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.

ACKNOWLEDGEMENTS

We gratefully acknowledge the assistance of Kristen Mackiewicz with the preparation of this chapter.

REFERENCES

Abbruzzese, M., Ferri, S. and Scarone, S., 1997. The selective breakdown of frontal functions in patients with obsessive–compulsive disorder and in patients with schizophrenia: A double dissociation experimental finding. *Neuropsychologia*, **35**, 907–912.

Adler, C.M., McDonough-Ryan, P., Sax, K.W., Holland, S.K., Arndt, S. and Strakowski, S.M., 2000. fMRI of neuronal activation with symptom provocation in unmedicated patients with obsessive–compulsive disorder. *Journal of Psychiatric Research*, **34**, 317–324.

Alexander, G.E., Crutcher, M.D. and DeLong, M.R., 1991. Basal ganglia-thalamocortical circuits: Parallel substrates for motor, oculomotor, "prefrontal" and "limbic" functions. *Progress in Brain Research*, **85**, 119–146.

Amir, N., McNally, R.J., Riemann, B.C., Burns, J., Lorenz, M. and Mullen, J.T., 1996a. Suppression of the emotional Stroop effect by increased anxiety in patients with social phobia. *Behaviour Research & Therapy*, **34**, 945–948.

Amir, N., McNally, R.J., Riemann, B.C. and Clements, C., 1996b. Implicit memory bias for threat in panic disorder: Application of the 'white noise' paradigm. *Behaviour Research & Therapy*, **34**, 157–162.

Amir, N., McNally, R.J. and Wiegartz, P.S., 1996c. Implicit memory bias for threat in posttraumatic stress disorder. *Cognitive Therapy and Research*, **20**, 625–635.

Amir, N., Foa, E.B. and Coles, M.E., 2000. Implicit memory bias for threat-relevant information in individuals with generalized social phobia. *Journal of Abnormal Psychology*, **109**, 713–720.

Amir, N., Coles, M.E., Brigidi, B. and Foa, E.B., 2001. The effect of practice on recall of emotional information in individuals with generalized social phobia. *Journal of Abnormal Psychology*, **110**, 76–82.

Aylward, E.H., Harris, G.J., Hoehn-Saric, R., Barta, P.E., Machlin, S.R. and Pearlson, G.D., 1996. Normal caudate nucleus in obsessive–compulsive disorder assessed by quantitative neuroimaging. *Archives of General Psychiatry*, **53**, 577–584.

Baxter, L.R., Jr., Phelps, M.E., Mazziotta, J.C., Guze, B.H., Schwartz, J.M. and Selin, C.E., 1987. Local cerebral glucose metabolic rates in obsessive–compulsive disorder. A comparison with rates in unipolar depression and in normal controls. *Archives of General Psychiatry*, **44**, 211–218.

Baxter, L.R., Jr., Schwartz, J.M., Mazziotta, J.C., Phelps, M.E., Pahl, J.J., Guze, B.H. and Fairbanks, L., 1988. Cerebral glucose metabolic rates

in nondepressed patients with obsessive–compulsive disorder. *American Journal of Psychiatry*, **145**, 1560–1563.

Baxter, L.R., Jr., Schwartz, J.M., Bergman, K.S., Szuba, M.P., Guze, B.H., Mazziotta, J.C., Alazraki, A., Selin, C.E., Ferng, H.K. and Munford, P., 1992. Caudate glucose metabolic rate changes with both drug and behaviour therapy for obsessive–compulsive disorder. *Archives of General Psychiatry*, **49**, 681–689.

Becker, E., Rinck, M. and Margraf, J., 1994. Memory bias in panic disorder. *Journal of Abnormal Psychology*, **103**, 396–399.

Becker, E.S., Roth, W.T., Andrich, M. and Margraf, J., 1999. Explicit memory bias in anxiety disorders. *Journal of Abnormal Psychology*, **108**, 153–163.

Benkelfat, C., Nordahl, T.E., Semple, W.E., King, A.C., Murphy, D.L. and Cohen, R.M., 1990. Local cerebral glucose metabolic rates in obsessive–compulsive disorder. Patients treated with clomipramine. *Archives of General Psychiatry*, **47**, 840–848.

Benkelfat, C., Bradwejn, J., Meyer, E., Ellenbogen, M., Milot, S., Gjedde, A. and Evans, A., 1995. Functional neuroanatomy of CCK_4-induced anxiety in normal healthy volunteers. *American Journal of Psychiatry*, **152**, 1180–1184.

Birbaumer, N., Grodd, W., Diedrich, O., Klose, U., Erb, M., Lotze, M., Schneider, F., Weiss, U. and Flor, H., 1998. fMRI reveals amygdala activation to human faces in social phobics. *Neuroreport*, **9**, 1223–1226.

Bisaga, A., Katz, J.L., Antonini, A., Wright, C.E., Margouleff, C., Gorman, J.M. and Eidelberg, D., 1998. Cerebral glucose metabolism in women with panic disorder. *American Journal of Psychiatry*, **155**, 1178–1183.

Boone, K.B., Ananth, J., Philpott, L., Kaur, A. and Djenderedjian, A., 1991. Neuropsychological characteristics of nondepressed adults with obsessive–compulsive disorder. *Neuropsychiatry, Neuropsychology, and Behavioural Neurology*, **4**, 96–109.

Bradley, B.P., Mogg, K., Millar, N. and White, J., 1995. Selective processing of negative information: Effects of clinical anxiety, concurrent depression, and awareness. *Journal of Abnormal Psychology*, **104**, 532–536.

Bradley, B.P., Mogg, K., White, J., Groom, C. and de Bono, J., 1999. Attentional bias for emotional faces in generalized anxiety disorder. *British Journal of Clinical Psychology*, **38**, 267–278.

Breiter, H.C., Rauch, S.L., Kwong, K.K., Baker, J.R., Weisskoff, R.M., Kennedy, D.N., Kendrick, A.D., Davis, T.L., Jiang, A., Cohen, M.S., Stern, C.E., Belliveau, J.W., Baer, L., O'Sullivan, R.L., Savage, C.R., Jenike, M.A. and Rosen, B.R., 1996. Functional magnetic resonance imaging of symptom provocation in obsessive–compulsive disorder. *Archives of General Psychiatry*, **53**, 595–606.

Bremner, J.D., Randall, P., Scott, T.M., Bronen, R.A., Seibyl, J.P., Southwick, S.M., Delaney, R.C., McCarthy, G., Charney, D.S. and Innis, R.B., 1995a. MRI-based measurement of hippocampal volume in patients with combat-related posttraumatic stress disorder. *American Journal of Psychiatry*, **152**, 973–981.

Bremner, J.D., Randall, P., Scott, T.M., Capelli, S., Delaney, R., McCarthy, G. and Charney, D.S., 1995b. Deficits in short-term memory in adult survivors of childhood abuse. *Psychiatry Research*, **59**, 97–107.

Bremner, J.D., Randall, P., Vermetten, E., Staib, L., Bronen, R.A., Mazure, C., Capelli, S., McCarthy, G., Innis, R.B. and Charney, D.S., 1997. Magnetic resonance imaging-based measurement of hippocampal volume in posttraumatic stress disorder related to childhood physical and sexual abuse — a preliminary report. *Biological Psychiatry*, **41**, 23–32.

Bremner, J.D., Scott, T.M., Delaney, R.C., Southwick, S.M., Mason, J.W., Johnson, D.R., Innis, R.B., McCarthy, G. and Charney, D.S., 1993. Deficits in short-term memory in posttraumatic stress disorder. *American Journal of Psychiatry*, **150**, 1015–1019.

Bremner, J.D., Narayan, M., Staib, L.H., Southwick, S.M., McGlashan, T. and Charney, D.S., 1999a. Neural correlates of memories of childhood sexual abuse in women with and without posttraumatic stress disorder. *American Journal of Psychiatry*, **156**, 1787–1795.

Bremner, J.D., Staib, L.H., Kaloupek, D., Southwick, S.M., Soufer, R. and Charney, D.S., 1999b. Neural correlates of exposure to traumatic pictures and sound in Vietnam combat veterans with and without posttraumatic stress disorder: A positron emission tomography study. *Biological Psychiatry*, **45**, 806–816.

Brody, A.L., Saxena, S., Schwartz, J.M., Stoessel, P.W., Maidment, K., Phelps, M.E. and Baxter, L.R., Jr., 1998. FDG-PET predictors of response to behavioural therapy and pharmacotherapy in obsessive–compulsive disorder. *Psychiatry Research: Neuroimaging*, **84**, 1–6.

Bryant, R.A. and Harvey, A.G., 1995. Processing threatening information in posttraumatic stress disorder. *Journal of Abnormal Psychology*, **104**, 537–541.

Buchsbaum, M.S., Hazlett, E., Sicotte, N., Stein, M., Wu, J. and Zetin, M., 1985. Topographic EEG changes with benzodiazepine administration in generalized anxiety disorder. *Biological Psychiatry*, **20**, 832–842.

Buchsbaum, M.S., Wu, J., Haier, R., Hazlett, E., Ball, R., Katz, M., Sokoloski, K., Lagunas-Solar, M. and Langer, D., 1987. Positron emission tomography assessment of effects of benzodiazepines on regional glucose metabolic rate in patients with anxiety disorder. *Life Sciences*, **40**, 2393–2440.

Busatto, G.F., Buchpiguel, C.A., Zamignani, D.R., Garrido, G.E., Glabus, M.F., Rosario-Campos, M.C., Castro, C.C., Maia, A., Rocha, E.T., McGuire, P.K. and Miguel, E.C., 2001. Regional cerebral blood flow abnormalities in early-onset obsessive–compulsive disorder: An exploratory SPECT study. *Journal of the American Academy of Child & Adolescent Psychiatry*, **40**, 347–354.

Carter, C.S., Botvinick, M.M. and Cohen, J.D., 1999. The contribution of the anterior cingulate cortex to executive processes in cognition. *Reviews in the Neurosciences*, **10**, 49–57.

Carter, C.S., Macdonald, A.M., Botvinick, M., Ross, L.L., Stenger, V.A., Noll, D. and Cohen, J.D., 2000. Parsing executive processes: Strategic vs. evaluative functions of the anterior cingulate cortex. *Proceedings of the National Academy of Sciences*, **97**, 1994–1998.

Charney, D.S., Grillon, C.C.G. and Bremner, J.D., 1998. The neurobiological basis of anxiety and fear: Circuits, mechanisms, and neurochemical interactions (Part 1). *Neuroscientist*, **4**, 35–44.

Christensen, K.J., Kim, S.W., Dysken, M.W. and Hoover, K.M., 1992. Neuropsychological performance in obsessive–compulsive disorder. *Biological Psychiatry*, **31**, 4–18.

Cloitre, M. and Liebowitz, M.R., 1991. Memory bias in panic disorder: An investigation of the cognitive avoidance hypothesis. *Cognitive Therapy and Research*, **15**, 371–386.

Cloitre, M., Shear, M.K., Cancienne, J. and Zeitlin, S.B., 1994. Implicit and explicit memory for catastrophic associations to bodily sensation words in panic disorder. *Cognitive Therapy and Research*, **18**, 225–240.

Cohen, L.J., Hollander, E., DeCaria, C.M., Stein, D.J., Simeon, D., Liebowitz, M.R. and Aronowitz, B.R., 1996. Specificity of neuropsychological impairment in obsessive–compulsive disorder: A comparison with social phobic and normal control subjects. *Journal of Neuropsychiatry & Clinical Neurosciences*, **8**, 82–85.

Compton, R.J., Heller, W., Banich, M.T., Palmieri, P.A. and Miller, G.A., 2000. Responding to threat: Effects of hemispheric asymmetry and interhemispheric division of input. *Neuropsychology*, **14**, 254–264.

Compton, R.J., Banich, M.T., Mohanty, A., Milham, M.P., Miller, G.A., Scalf, P.E. and Heller, W., 2002. Paying attention to emotion: An fMRI investigation of cognitive and emotional Stroop tasks. Submitted for publication.

Constans, J.I., Foa, E.B., Franklin, M.E. and Mathews, A., 1995. Memory for actual and imagined events in OC checkers. *Behaviour Research & Therapy*, **33**, 665–671.

Cottraux, J., Gerard, D., Cinotti, L., Froment, J.C., Deiber, M.P., Le Bars, D., Galy, G., Millet, P., Labbe, C., Lavenne, F., Bouvard, M. and Mauguiere, F., 1996. A controlled positron emission tomography study of obsessive and neutral auditory stimulation in obsessive–compulsive disorder with checking rituals. *Psychiatry Research*, **60**, 101–112.

Davidson, R.J. and Irwin, W., 1999. The functional neuroanatomy of emotion and affective style. *Trends in Cognitive Sciences*, **3**, 11–21.

Davidson, R.J., Marshall, J.R., Tomarken, A.J. and Henriques, J.B., 2000. While a phobic waits: Regional brain electrical and autonomic activity in social phobics during anticipation of public speaking. *Biological Psychiatry*, **47**, 85–95.

Davidson, R.J., Pizzagalli, D., Nitschke, J.B. and Putnam, K., 2002. Depression: Perspectives from affective neuroscience. *Annual Review of Psychology*, **53**, 545–574.

Davis, M. and Lee, Y., 1998. Fear and anxiety: Possible roles of the amygdala and bed nucleus of the stria terminalis. *Cognition and Emotion*, **12**, 277–305.

Davis, M. and Whalen, P.J., 2001. The amygdala: Vigilance and emotion. *Molecular Psychiatry*, **6**, 13–34.

De Bellis, M.D., Casey, B.J., Dahl, R.E., Birmaher, B., Williamson, D.E., Thomas, K.M., Axelson, D.A., Frustaci, K., Boring, A.M., Hall, J. and Ryan, N.D., 2000. A pilot study of amygdala volumes in pediatric generalized anxiety disorder. *Biological Psychiatry*, **48**, 51–57.

De Cristofaro, M.T., Sessarego, A., Pupi, A., Biondi, F. and Faravelli, C., 1993. Brain perfusion abnormalities in drug-naive, lactate-sensitive panic patients: A SPECT study. *Biological Psychiatry*, **33**, 505–512.

Drevets, W.C., Videen, T.O. and MacLeod, A.K., 1992. PET images of blood flow changes during anxiety: A correction. *Science*, **256**, 1696.

Ehlers, A., Margraf, J., Davies, S. and Roth, W.T., 1988. Selective processing of threat cues in subjects with panic attacks. *Cognition and Emotion*, **2**, 201–219.

Eysenck, M.W., 1992. *Anxiety: The Cognitive Perspective*. Lawrence Erlbaum Associates Ltd., Hove, UK.

Eysenck, M.W., Mogg, K., May, J., Richards, A. and Mathews, A., 1991. Bias in interpretation of ambiguous sentences related to threat in anxiety. *Journal of Abnormal Psychology*, **100**, 144–150.

Fischer, H., Wik, G. and Fredrikson, M., 1996. Functional neuroanatomy of robbery re-experience: Affective memories studied with PET. *Neuroreport*, **7**, 2081–2086.

Foa, E.B., Feske, U., Murdock, T.B., Kozak, M.J. and McCarthy, P.R., 1991. Processing of threat-related information in rape victims. *Journal of Abnormal Psychology*, **100**, 156–162.

Foa, E.B., Ilai, D., McCarthy, P.R., Shoyer, B. and Murdock, T.B., 1993. Information processing in obsessive–compulsive disorder. *Cognitive Therapy and Research*, **17**, 173–189.

Foa, E.B., Franklin, M.E., Perry, K.J. and Herbert, J.D., 1996. Cognitive biases in generalized social phobia. *Journal of Abnormal Psychology*, **105**, 433–439.

Foa, E.B., Amir, N., Gershuny, B., Molnar, C. and Kozak, M.J., 1997. Implicit and explicit memory in obsessive–compulsive disorder. *Journal of Anxiety Disorders*, **11**, 119–129.

Foa, E.B., Gilboa-Schechtman, E., Amir, N. and Freshman, M., 2000. Memory bias in generalized social phobia: Remembering negative emotional expressions. *Journal of Anxiety Disorders*, **14**, 501–519.

Fontaine, R., Breton, G., Dery, R., Fontaine, S. and Elie, R., 1990. Temporal lobe abnormalities in panic disorder: An MRI study. *Biological Psychiatry*, **27**, 304–310.

Fredrikson, M., Wik, G., Greitz, T., Eriksson, L., Stone-Elander, S., Ericson, K. and Sedvall, G., 1993. Regional cerebral blood flow during experimental phobic fear. *Psychophysiology*, **30**, 126–130.

Fredrikson, M., Wik, G., Annas, P., Ericson, K. and Stone-Elander, S., 1995. Functional neuroanatomy of visually elicited simple phobic fear: Additional data and theoretical analysis. *Psychophysiology*, **32**, 43–48.

Friedman, B.H., Thayer, J.F. and Borkovec, T.D., 2000. Explicit memory bias for threat words in generalized anxiety disorder. *Behaviour Therapy*, **31**, 745–756.

Fyer, A.J., 1998. Current approaches to etiology and pathophysiology of specific phobia. *Biological Psychiatry*, **44**, 1295–1304.

Gilboa-Schechtman, E., Foa, E.B. and Amir, N., 1999. Attentional bias for facial expressions in social phobia: The face-in-the-crowd paradigm. *Cognition and Emotion*, **13**, 305–318.

Grachev, I.D., Breiter, H.C., Rauch, S.L., Savage, C.R., Baer, L., Shera, D.M., Kennedy, D.N., Makris, N., Caviness, V.S. and Jenike, M.A., 1998. Structural abnormalities of frontal neocortex in obsessive–compulsive disorder. *Archives of General Psychiatry*, **55**, 181–182.

Gray, J.A., 1982. *The Neuropsychology of Anxiety: An Enquiry into the Functions of the Septo-Hippocampal System*. Oxford University Press, Oxford, UK.

Grillon, C. and Buchsbaum, M.S., 1987. EEG topography of response to visual stimuli in generalized anxiety disorder. *Electroencephalography and Clinical Neurophysiology*, **66**, 337–348.

Gurvits, T.V., Shenton, M.E., Hokama, H., Ohta, H., Lasko, N.B., Gilbertson, M.W., Orr, S.P., Kikinis, R., Jolesz, F.A., McCarley, R.W. and Pitman, R.K., 1996. Magnetic resonance imaging study of hippocampal volume in chronic, combat-related posttraumatic stress disorder. *Biological Psychiatry*, **40**, 1091–1099.

Head, D., Bolton, D. and Hymas, N., 1989. Deficit in cognitive shifting ability in patients with obsessive–compulsive disorder. *Biological Psychiatry*, **25**, 929–937.

Heinrichs, N. and Hofmann, S.G., 2001. Information processing in social phobia: A critical review. *Clinical Psychology Review*, **21**, 751–770.

Heller, W., 1990. The neuropsychology of emotion: Developmental patterns and implications for psychopathology. In: Stein, N., Leventhal, B.L. and Trabasso, T. (eds), pp. 167–211. *Psychological and Biological Approaches*. Lawrence Erlbaum, Hillsdale, NJ.

Heller, W. and Nitschke, J.B., 1997. Regional brain activity in emotion: A framework for understanding cognition in depression. *Cognition and Emotion*, **11**, 637–661.

Heller, W. and Nitschke, J.B., 1998. The puzzle of regional brain activity in depression and anxiety: The importance of subtypes and comorbidity. *Cognition and Emotion*, **12**, 421–447.

Hoehn-Saric, R., Pearlson, G.D., Harris, G.J., Machlin, S.R. and Camargo, E.E., 1991. Effects of fluoxetine on regional cerebral blood flow in obsessive–compulsive patients. *American Journal of Psychiatry*, **148**, 1243–1245.

Hollander, E., Weiller, F., Cohen, L.J., Kwon, J.H., DeCaria, C.M., Liebowitz, M.R. and Stein, D.J., 1996. Neurological soft signs in social phobia. *Neuropsychiatry, Neuropsychology, and Behavioural Neurology*, **9**, 182–185.

Javanmard, M., Shlik, J., Kennedy, S.H., Vaccarino, F.J., Houle, S. and Bradwejn, J., 1999. Neuroanatomic correlates of CCK-4-induced panic attacks in healthy humans: A comparison of two time points. *Biological Psychiatry*, **45**, 872–882.

Jenike, M.A., Breiter, H.C., Baer, L., Kennedy, D.N., Savage, C.R., Olivares, M.J., O'Sullivan, R.L., Shera, D.M., Rauch, S.L., Keuthen, N., Rosen, B.R., Caviness, V.S. and Filipek, P.A., 1996. Cerebral structural abnormalities in obsessive–compulsive disorder: A quantitative morphometric magnetic resonance imaging study. *Archives of General Psychiatry*, **53**, 625–632.

Jenkins, M.A., Langlais, P.J., Delis, D. and Cohen, R., 1998. Learning and memory in rape victims with posttraumatic stress disorder. *American Journal of Psychiatry*, **155**, 278–279.

Johanson, A.M., Smith, G., Risberg, J., Silfverskiöld, P. and Tucker, D., 1992. Left orbital frontal activation in pathological anxiety. *Anxiety, Stress, and Coping*, **5**, 313–328.

Johanson, A., Gustafson, L., Passant, U., Risberg, J., Smith, G., Warkentin, S. and Tucker, D., 1998. Brain function in spider phobia. *Psychiatry Research: Neuroimaging*, **84**, 101–111.

Kaspi, S.P., McNally, R.J. and Amir, N., 1995. Cognitive processing of emotional information in posttraumatic stress disorder. *Cognitive Therapy and Research*, **19**, 433–444.

Lavy, E., van den Hout, M. and Arntz, A., 1993. Attentional bias and spider phobia: Conceptual and clinical issues. *Behaviour Research & Therapy*, **31**, 17–24.

LeDoux, J.E., 1996. *The Emotional Brain*. Simon and Schuster, New York.

Lepola, U., Nousiainen, U., Puranen, M., Riekkinen, P. and Rimon, R., 1990. EEG and CT findings in patients with panic disorder. *Biological Psychiatry*, **28**, 721–727.

Liberzon, I., Taylor, S.F., Amdur, R., Jung, T.D., Chamberlain, K.R., Minoshima, S., Koeppe, R.A. and Fig, L.M., 1999. Brain activation in PTSD in response to trauma-related stimuli. *Biological Psychiatry*, **45**, 817–826.

Lucey, J.V., Costa, D.C., Adshead, G., Deahl, M., Busatto, G., Gacinovic, S., Travis, M., Pilowsky, L., Ell, P.J., Marks, I.M. and Kerwin, R.W., 1997a. Brain blood flow in anxiety disorders, OCD, panic disorder with agoraphobia, and post-traumatic stress disorder on 99m TcHMPAO single photon emission tomography (SPET). *British Journal of Psychiatry*, **171**, 346–350.

Lucey, J.V., Costa, D.C., Busatto, G., Pilowsky, L.S., Marks, I.M., Ell, P.J. and Kerwin, R.W., 1997b. Caudate regional cerebral blood flow in obsessive–compulsive disorder, panic disorder and healthy controls on single photon emission computerised tomography. *Psychiatry Research: Neuroimaging*, **74**, 25–33.

Lündh, L.G. and Öst, L.G., 1996. Recognition bias for critical faces in social phobics. *Behaviour Research & Therapy*, **34**, 787–794.

Machlin, S.R., Harris, G.J., Pearlson, G.D., Hoehn-Saric, R., Jeffery, P. and Camargo, E.E., 1991. Elevated medial-frontal cerebral blood flow in obsessive–compulsive patients: A SPECT study. *American Journal of Psychiatry*, **148**, 1240–1242.

MacLeod, C., 1990. Mood disorders and cognition. In: Eysenck, M.W. (ed.), pp. 9–56. *Cognitive Psychology: An International Review*. Wiley, Chichester, UK.

MacLeod, C. and Hagan, R., 1992. Individual differences in the selective processing of threatening information, and emotional responses to a stressful life event. *Behaviour Research & Therapy*, **30**, 151–161.

MacLeod, C. and McLaughlin, K., 1995. Implicit and explicit memory bias in anxiety: A conceptual replication. *Behaviour Research & Therapy*, **33**, 1–14.

MacLeod, C. and Rutherford, E.M., 1992. Anxiety and the selective processing of emotional information: Mediating roles of awareness, trait and state variables, and personal relevance of stimulus material. *Behaviour Research & Therapy*, **30**, 479–491.

MacLeod, C., Mathews, A. and Tata, P., 1986. Attentional bias in emotional disorders. *Journal of Abnormal Psychology*, **95**, 15–20.

Malloy, P., Rasmussen, S., Braden, W. and Haier, R.J., 1989. Topographic evoked potential mapping in obsessive–compulsive disorder: Evidence of frontal lobe dysfunction. *Psychiatry Research*, **28**, 63–71.

Martin, M., Williams, R. and Clark, D.M., 1991. Does anxiety lead to selective processing of threat-related information? *Behaviour Research & Therapy*, **29**, 147–160.

Martinot, J.L., Allilaire, J.F., Mazoyer, B.M., Hantouche, E., Huret, J.D., Legaut-Demare, F., Deslauriers, A.G., Hardy, P., Pappata, S. and Baron, J.C., 1990. Obsessive–compulsive disorder: A clinical, neuropsychological and positron emission tomography study. *Acta Psychiatrica Scandinavica*, **82**, 233–242.

Martis, B., Malizia, A. and Rauch, S.L., 2002. Functional Neuroanatomy of Anxiety Disorders. In: D'Haenen, H., den Boer, J.A. and Wilner, P. (eds), *Textbook of Biological Psychiatry*. John Wiley & Sons, Chichester.

Mathews, A., 1984. Cognitive processes in generalised anxiety. Paper presented at the meeting of the European Association for Behaviour Therapy, Brussels.

Mathews, A. and MacLeod, C., 1985. Selective processing of threat cues in anxiety states. *Behaviour Research & Therapy*, **23**, 563–569.

Mathews, A. and MacLeod, C., 1986. Discrimination of threat cues without awareness in anxiety states. *Journal of Abnormal Psychology*, **95**, 131–138.

Mathews, A. and MacLeod, C., 1994. Cognitive approaches to emotion and emotional disorders. *Annual Review of Psychology*, **45**, 25–50.

Mathews, A. and Sebastian, S., 1993. Suppression of emotional Stroop effects by fear-arousal. *Cognition and Emotion*, **7**, 517–530.

Mathews, A., Mogg, K., May, J. and Eysenck, M., 1989a. Implicit and explicit memory bias in anxiety. *Journal of Abnormal Psychology*, **98**, 236–240.

Mathews, A., Richards, A. and Eysenck, M., 1989b. Interpretation of homophones related to threat in anxiety states. *Journal of Abnormal Psychology*, **98**, 31–34.

Mathews, A., May, J., Mogg, K. and Eysenck, M., 1990. Attentional bias in anxiety: Selective search or defective filtering? *Journal of Abnormal Psychology*, **99**, 166–173.

Mathews, A., Mogg, K., Kentish, J. and Eysenck, M., 1995. Effect of psychological treatment on cognitive bias in generalized anxiety disorder. *Behaviour Research & Therapy*, **33**, 293–303.

Mattia, J.I., Heimberg, R.G. and Hope, D.A., 1993. The revised Stroop color-naming task in social phobics. *Behaviour Research & Therapy*, **31**, 305–313.

McGuire, P.K., Bench, C.J., Frith, C.D., Marks, I.M., Frackowiak, R.S. and Dolan, R.J., 1994. Functional anatomy of obsessive–compulsive phenomena. *British Journal of Psychiatry*, **164**, 459–468.

McNally, R.J., 1998. Information-processing abnormalities in anxiety disorders: Implications for cognitive neuroscience. *Cognition and Emotion*, **12**, 479–495.

McNally, R.J. and Amir, N., 1996. Perceptual implicit memory for trauma-related information in post-traumatic stress disorder. *Cognition and Emotion*, **10**, 551–556.

McNally, R.J. and Kohlbeck, P.A., 1993. Reality monitoring in obsessive–compulsive disorder. *Behaviour Research & Therapy*, **31**, 249–253.

McNally, R.J., Foa, E.B. and Donnell, C.D., 1989. Memory bias for anxiety information in patients with panic disorder. *Cognition and Emotion*, **3**, 27–44.

McNally, R.J., Kaspi, S.P., Riemann, B.C. and Zeitlin, S.B., 1990. Selective processing of threat cues in posttraumatic stress disorder. *Journal of Abnormal Psychology*, **99**, 398–402.

McNally, R.J., Amir, N., Louro, C.E., Lukach, B.M., Riemann, B.C. and Calamari, J.E., 1994. Cognitive processing of idiographic emotional information in panic disorder. *Behaviour Research & Therapy*, **32**, 119–122.

McNally, R.J., Amir, N. and Lipke, H.J., 1996. Subliminal processing of threat cues in posttraumatic stress disorder? *Journal of Anxiety Disorders*, **10**, 115–128.

McNally, R.J., Hornig, C.D., Otto, M.W. and Pollack, M.H., 1997. Selective encoding of threat in panic disorder: Application of a dual priming paradigm. *Behaviour Research & Therapy*, **35**, 543–549.

Merckelbach, H., Muris, P., Pool, K. and de Jong, P.J., 1998. Resting EEG asymmetry and spider phobia. *Anxiety, Stress, and Coping*, **11**, 213–223.

Mogg, K., Mathews, A. and Weinman, J., 1987. Memory bias in clinical anxiety. *Journal of Abnormal Psychology*, **96**, 94–98.

Mogg, K., Mathews, A. and Eysenck, M., 1992. Attentional bias to threat in clinical anxiety states. *Cognition and Emotion*, **6**, 149–159.

Mogg, K., Bradley, B.P., Williams, R. and Mathews, A., 1993. Subliminal processing of emotional information in anxiety and depression. *Journal of Abnormal Psychology*, **102**, 304–311.

Mogg, K., Millar, N. and Bradley, B.P., 2000. Biases in eye movements to threatening facial expressions in generalized anxiety disorder and depressive disorder. *Journal of Abnormal Psychology*, **109**, 695–704.

Mohanty, A. and Heller, W., 2002. The neuropsychology of mood disorders. In: D'Haenen, H., den Boer, J.A. and Wilner, P. (eds), *Textbook of Biological Psychiatry*. John Wiley & Sons, Chichester.

Mountz, J.M., Modell, J.G., Wilson, M.W., Curtis, G.C., Lee, M.A., Schmaltz, S. and Kuhl, D.E., 1989. Positron emission tomographic evaluation of cerebral blood flow during state anxiety in simple phobia. *Archives of General Psychiatry*, **46**, 501–504.

Nitschke, J.B., Heller, W. and Miller, G.A., 2000. Anxiety, stress, and cortical brain function. In: Borod, J.C. (ed.), pp. 298–319. *The Neuropsychology of Emotion*. Oxford University Press, New York.

Nitschke, J.B., Schaefer, H.S., Mackiewicz, K.L., Skinner, B.T., Lee, H., Oakes, T.R., Anderle, M.J., Ihde-Scholl, T., Tartleton, L.C., Marler, C., Pederson, A.J.C., Ferber, K.L. and Davidson, R.J., 2001. Disentangling the anticipation of and response to aversive pictures: An event-related fMRI study. *Neuroscience Abstracts*, **27**, 840.

Nordahl, T.E., Benkelfat, C., Semple, W.E., Gross, M., King, A.C. and Cohen, R.M., 1989. Cerebral glucose metabolic rates in obsessive–compulsive disorder. *Neuropsychopharmacology*, **2**, 23–28.

Nordahl, T.E., Semple, W.E., Gross, M., Mellman, T.A., Stein, M.B., Goyer, P., King, A.C., Uhde, T.W. and Cohen, R.M., 1990. Cerebral glucose metabolic differences in patients with panic disorder. *Neuropsychopharmacology*, **3**, 261–272.

Nordahl, T.E., Stein, M.B. and Benkelfat, C., 1998. Regional cerebral metabolic asymmetries replicated in an independent group of patients with panic disorders. *Biological Psychiatry*, **44**, 998–1006.

Nugent, K. and Mineka, S., 1994. The effect of high and low trait anxiety on implicit and explicit memory tasks. *Cognition and Emotion*, **8**, 147–163.

Otto, M.W., McNally, R.J., Pollack, M.H., Chen, E. and Rosenbaum, J.F., 1994. Hemispheric laterality and memory bias for threat in anxiety disorders. *Journal of Abnormal Psychology*, **103**, 828–831.

Perani, D., Colombo, C., Bressi, S., Bonfanti, A., Grassi, F., Scarone, S., Bellodi, L., Smeraldi, E. and Fazio, F., 1995. [^{18}F] FDG PET study in obsessive–compulsive disorder: A clinical/metabolic correlation study after treatment. *British Journal of Psychiatry*, **166**, 244–250.

Potts, N.L., Davidson, J.R., Krishnan, K.R. and Doraiswamy, P.M., 1994. Magnetic resonance imaging in social phobia. *Psychiatry Research*, **52**, 35–42.

Purcell, R., Maruff, P., Kyrios, M. and Pantelis, C., 1998. Neuropsychological deficits in obsessive–compulsive disorder: A comparison with unipolar depression, panic disorder, and normal controls. *Archives of General Psychiatry*, **55**, 415–423.

Rajkowska, G., 2000. Postmortem studies in mood disorders indicate altered numbers of neurons and glial cells. *Biological Psychiatry*, **48**, 766–777.

Rapee, R.M., McCallum, S.L., Melville, L.F., Ravenscroft, H. and Rodney, J.M., 1994. Memory bias in social phobia. *Behaviour Research & Therapy*, **32**, 89–99.

Rauch, S.L. (in press). Neuroimaging and the neurobiology of anxiety disorders. In: Davidson, R.J., Scherer, K. and Goldsmith, H.H. (eds), *Handbook of Affective Sciences*.

Rauch, S.L., Jenike, M.A. and Alpert, N.M., 1994. Regional cerebral blood flow measured during symptom provocation in obsessive–compulsive disorder using oxygen 15-labeled carbon dioxide and positron emission tomography. *Archives of General Psychiatry*, **51**, 62–70.

Rauch, S.L., Savage, C.R., Alpert, N.M., Miguel, E.C., Baer, L., Breiter, H.C., Fischman, A.J., Manzo, P.A., Moretti, C. and Jenike, M.A., 1995a. A positron emission tomographic study of simple phobic symptom provocation. *Archives of General Psychiatry*, **52**, 20–28.

Rauch, S.L., Savage, C.R. and Brown, H.D., 1995b. A PET investigation of implicit and explicit sequence learning. *Human Brain Mapping*, **3**, 271–286.

Rauch, S.L., van der Kolk, B.A., Fisler, R.E., Alpert, N.M., Orr, S.P., Savage, C.R., Fischman, A.J., Jenike, M.A. and Pitman, R.K., 1996. A symptom provocation study of posttraumatic stress disorder using positron emission tomography and script-driven imagery. *Archives of General Psychiatry*, **53**, 380–387.

Rauch, S.L., Savage, C.R., Alpert, N.M., Dougherty, D., Kendrick, A., Curran, T., Brown, H.D., Manzo, P., Fischman, A.J. and Jenike, M.A.,

1997a. Probing striatal function in obsessive–compulsive disorder: A PET study of implicit sequence learning. *Journal of Neuropsychiatry & Clinical Neurosciences*, **9**, 568–573.

Rauch, S.L., Savage, C.R., Alpert, N.M., Fischman, A.J. and Jenike, M.A., 1997b. The functional neuroanatomy of anxiety: A study of three disorders using positron emission tomography and symptom provocation. *Biological Psychiatry*, **42**, 446–452.

Rauch, S.L., Whalen, P.J., Savage, C.R., Curran, T., Kendrick, A., Brown, H.D., Bush, G., Breiter, H.C. and Rosen, B.R., 1997c. Striatal recruitment during an implicit sequence learning task as measured by functional magnetic resonance imaging. *Human Brain Mapping*, **5**, 124–132.

Rauch, S.L., Whalen, P.J., Dougherty, D.D. and Jenike, M.A., 1998. Neurobiological models of obsessive–compulsive disorders. In: Jenike, M.A., Baer, L. and Minichiello, W.E. (eds), pp. 222–253. *Obsessive–Compulsive Disorders: Practical Management*. Moby, Boston.

Rauch, S.L., Whalen, P.J., Shin, L.M., McInerney, S.C., Macklin, M.L., Lasko, N.B., Orr, S.P. and Pitman, R.K., 2000. Exaggerated amygdala response to masked facial stimuli in posttraumatic stress disorder: A functional MRI study. *Biological Psychiatry*, **47**, 769–776.

Reiman, E.M., 1997. The application of positron emission tomography to the study of normal and pathologic emotions. *Journal of Clinical Psychiatry*, **58**, S4–S12.

Reiman, E.M., Raichle, M.E., Butler, F.K., Herscovitch, P. and Robins, E., 1984. A focal brain abnormality in panic disorder, a severe form of anxiety. *Nature*, **310**, 683–685.

Reiman, E.M., Raichle, M.E., Robins, E., Butler, F.K., Herscovitch, P., Fox, P. and Perlmutter, J., 1986. The application of positron emission tomography to the study of panic disorder. *American Journal of Psychiatry*, **143**, 469–477.

Reiman, E.M., Raichle, M.E., Robins, E., Mintun, M.A., Fusselman, M.J., Fox, P.T., Price, J.L. and Hackman, K.A., 1989. Neuroanatomical correlates of a lactate-induced anxiety attack. *Archives of General Psychiatry*, **46**, 493–500.

Robinson, D., Wu, H., Munne, R.A., Ashtari, M., Alvir, J.M., Lerner, G., Koreen, A., Cole, K. and Bogerts, B., 1995. Reduced caudate nucleus volume in obsessive–compulsive disorder. *Archives of General Psychiatry*, **52**, 393–398.

Rolls, E.T., 1999. The functions of the orbitofrontal cortex. *Neurocase: Case Studies in Neuropsychology, Neuropsychiatry, and Behavioural Neurology*, **5**, 301–312.

Rosenberg, D.R., Keshavan, M.S., O'Hearn, K.M., Dick, E.L., Bagwell, W.W., Seymour, A.B., Montrose, D.M., Pierri, J.N. and Birmaher, B., 1997. Frontostriatal measurement in treatment — naive children with obsessive–compulsive disorder. *Archives of General Psychiatry*, **54**, 824–830.

Rubin, R.T., Villanueva-Meyer, J., Ananth, J., Trajmar, P.G. and Mena, I., 1992. Regional xenon 133 cerebral blood flow and cerebral technetium 99m HMPAO uptake in unmedicated patients with obsessive–compulsive disorder and matched normal control subjects: Determination by high-resolution single-photon emission computed tomography. *Archives of General Psychiatry*, **49**, 695–702.

Rubin, R.T., Anath, J., Villanueva-Meyer, J., Trajmar, P.G. and Mena, I., 1995. Regional ^{133}xenon cerebral blood flow and cerebral ^{99m}Tc-HMPAO uptake in patients with obsessive–compulsive disorder before and during treatment. *Biological Psychiatry*, **38**, 429–437.

Sapolsky, R.M., 2000. Glucocorticoids and hippocampal atrophy in neuropsychiatric disorders. *Archives of General Psychiatry*, **57**, 925–935.

Savage, C.R., Keuthen, N.J. and Jenike, M.A., 1996. Recall and recognition memory in obsessive–compulsive disorder. *Journal of Neuropsychiatry & Clinical Neurosciences*, **8**, 99–103.

Savage, C.R., Baer, L., Keuthen, N.J., Brown, H.D., Rauch, S.L. and Jenike, M.A., 1999. Organizational strategies mediate nonverbal memory impairment in obsessive–compulsive disorder. *Biological Psychiatry*, **45**, 905–916.

Saxena, S., Brody, A.L., Maidment, K.M., Dunkin, J.J., Colgan, M., Alborzian, S., Phelps, M.E. and Baxter, L.R., Jr., 1999. Localized orbitofrontal and subcortical metabolic changes and predictors of response to paroxetine treatment in obsessive–compulsive disorder. *Neuropsychopharmacology*, **21**, 683–693.

Scarone, S., Colombo, C., Livian, S., Abbruzzese, M., Ronchi, P., Locatelli, M., Scotti, G. and Smeraldi, E., 1992. Increased right caudate nucleus size in obsessive–compulsive disorder: Detection with magnetic resonance imaging. *Psychiatry Research*, **45**, 115–121.

Schneider, F., Weiss, U., Kessler, C., Muller-Gartner, H.W., Posse, S., Salloum, J.B., Grodd, W., Himmelmann, F., Gaebel, W. and Birbaumer, N., 1999. Subcortical correlates of differential classical conditioning of aversive emotional reactions in social phobia. *Biological Psychiatry*, **45**, 863–871.

Schuff, N., Marmar, C.R., Weiss, D.S., Neylan, T.C., Schoenfold, F., Fein, G. and Weiner, M.W., 1997. Reduced hippocampal volume and N-acetyl aspartate in posttraumatic stress disorder. *Annals of the New York Academy of Sciences*, **821**, 516–520.

Schwartz, J.M., Stoessel, P.W., Baxter, L.R., Jr., Martin, K.M. and Phelps, M.E., 1996. Systematic changes in cerebral glucose metabolic rate after successful behaviour modification treatment of obsessive–compulsive disorder. *Archives of General Psychiatry*, **53**, 109–113.

Semple, W.E., Goyer, P., McCormick, R., Morris, E., Compton, B., Muswick, G., Nelson, D., Donovan, B., Leisure, G. and Berridge, M., 1993. Preliminary report: Brain blood flow using PET in patients with posttraumatic stress disorder and substance-abuse histories. *Biological Psychiatry*, **34**, 115–118.

Semple, W.E., Goyer, P.F., McCormick, R., Compton-Toth, B., Morris, E., Donovan, B., Muswick, G., Nelson, D., Garnett, M.L., Sharkoff, J., Leisure, G., Miraldi, F. and Schulz, S.C., 1996. Attention and regional cerebral blood flow in posttraumatic stress disorder patients with substance abuse histories. *Psychiatry Research: Neuroimaging*, **67**, 17–28.

Semple, W.E., Goyer, P.F., McCormick, R., Donovan, B., Muzic, R.F., Jr., Rugle, L., McCutcheon, K., Lewis, C., Liebling, D., Kowaliw, S., Vapenik, K., Semple, M.A., Flener, C.R. and Schulz, S.C., 2000. Higher brain blood flow at amygdala and lower frontal cortex blood flow in PTSD patients with comorbid cocaine and alcohol abuse compared with normals. *Psychiatry*, **63**, 65–74.

Sheline, Y.I., 2000. 3D MRI studies of neuroanatomic changes in unipolar major depression: The role of stress and medical comorbidity. *Biological Psychiatry*, **48**, 791–800.

Shin, L.M., Kosslyn, S.M., McNally, R.J., Alpert, N.M., Thompson, W.L., Rauch, S.L., Macklin, M.L. and Pitman, R.K., 1997a. Visual imagery and perception in posttraumatic stress disorder: A positron emission tomographic investigation. *Archives of General Psychiatry*, **54**, 233–241.

Shin, L.M., McNally, R.J., Kosslyn, S.M., Thompson, W.L., Rauch, S.L., Alpert, N.M., Metzger, L.J., Lasko, N.B., Orr, S.P. and Pitman, R.K., 1997b. A positron emission tomographic study of symptom provocation in PTSD. *Annals of the New York Academy of Sciences*, **821**, 1521–1523.

Shin, L.M., McNally, R.J., Kosslyn, S.M., Thompson, W.L., Rauch, S.L., Alpert, N.M., Metzger, R.L., Lasko, H.B., Orr, S.P. and Pitman, R.K., 1999. Regional cerebral blood flow during script-driven imagery in childhood sexual abuse-related PTSD: A PET investigation. *American Journal of Psychiatry*, **156**, 575–584.

Squire, L.R., 1992. Memory and the hippocampus: A synthesis from findings with rats, monkeys, and humans. *Psychological Review*, **99**, 195–231.

Stanford, M.S., Vasterling, J.J., Mathias, C.W., Constans, J.I. and Houston, R.J., 2001. Impact of threat relevance on P3 event-related potentials in combat-related post-traumatic stress disorder. *Psychiatry Research*, **102**, 125–137.

Stein, M.B. and Leslie, W.D., 1996. A brain single photon-emission computed tomography (SPECT) study of generalized social phobia. *Biological Psychiatry*, **39**, 825–828.

Stein, M.B. and Uhde, T.W., 1989. Infrequent occurrence of EEG abnormalities in panic disorder. *American Journal of Psychiatry*, **146**, 517–520.

Stein, M.B., Koverola, C., Hanna, C., Torchia, M.G. and McClarty, B., 1997. Hippocampal volume in women victimized by childhood sexual abuse. *Psychological Medicine*, **27**, 951–959.

Stewart, R.S., Devous, M.D.S., Rush, A.J., Lane, L. and Bonte, F.J., 1988. Cerebral blood flow changes during sodium-lactate-induced panic attacks. *American Journal of Psychiatry*, **145**, 442–449.

Suetsugi, M., Mizuki, Y., Ushijima, I., Kobayashi, T., Tsuchiya, K., Aoki, T. and Watanabe, Y., 2000. Appearance of frontal midline theta activity in patients with generalized anxiety disorder. *Neuropsychobiology*, **41**, 108–112.

Swedo, S.E., Schapiro, M.B., Grady, C.L., Cheslow, D.L., Leonard, H.L., Kumar, A., Friedland, R., Rapoport, S.I. and Rapoport, J.L., 1989. Cerebral glucose metabolism in childhood-onset obsessive–compulsive disorder. *Archives of General Psychiatry*, **46**, 518–523.

Swedo, S.E., Pietrini, P., Leonard, H.L., Schapiro, M.B., Rettew, D.C., Goldberger, E.L., Rapoport, S.I., Rapoport, J.L. and Grady, C.L., 1992. Cerebral glucose metabolism in childhood-onset obsessive–compulsive

disorder: Revisualization during pharmacotherapy. *Archives of General Psychiatry*, **49**, 690–694.

Thrasher, S.M., Dalgleish, T. and Yule, W., 1994. Information processing in posttraumatic stress disorder. *Behaviour Research & Therapy*, **32**, 247–254.

Towey, J.P., Tenke, C.E., Bruder, G.E., Leite, P., Friedman, D., Liebowitz, M. and Hollander, E., 1994. Brain event-related potential correlates of over focused attention in obsessive–compulsive disorder. *Psychophysiology*, **31**, 535–543.

Trandel, D.V. and McNally, R.J., 1987. Perception of threat cues in post-traumatic stress disorder: Semantic processing without awareness? *Behaviour Research & Therapy*, **25**, 469–476.

Uddo, M., Vasterling, J.J., Brailey, K. and Sutker, P.B., 1993. Memory and attention in combat-related post-traumatic stress disorder (PTSD). *Journal of Psychopathology and Behavioural Assessment*, **15**, 43–51.

Van Ameringen, M., Mancini, C., Oakman, J.M., Kamath, M., Nahmias, C. and Szechtman, H., 1998. A pilot study of PET in social phobia. *Biological Psychiatry*, **43**, 31S.

Van den Hout, M., Tenney, N., Huygens, K. and de Jong, P., 1997. Preconscious processing bias in specific phobia. *Behaviour Research & Therapy*, **35**, 29–34.

Van der Linden, G., van Heerden, B., Warwick, J., Wessels, C., van Kradenburg, J., Zungu-Dirwayi, N. and Stein, D.J., 2000. Functional brain imaging and pharmacotherapy in social phobia: Single photon emission computed tomography before and after treatment with the selective serotonin reuptake inhibitor citalopram. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, **24**, 419–438.

Veale, D.M., Owen, A.M. and Marks, I.M., 1996. Specific cognitive deficits in tests sensitive to frontal lobe dysfunction in obsessive–compulsive disorder. *Psychological Medicine*, **26**, 1261–1269.

Vrana, S.R., Roodman, A. and Beckham, J.C., 1995. Selective processing of trauma-related words in posttraumatic stress disorder. *Journal of Anxiety Disorders*, **9**, 515–530.

Vythilingam, M., Anderson, E.R., Goddard, A., Woods, S.W., Staib, L.H., Charney, D.S. and Bremner, J.D., 2000. Temporal lobe volume in panic disorder — a quantitative magnetic resonance imaging study. *Psychiatry Research: Neuroimaging*, **99**, 75–82.

Watts, F.N., McKenna, F.P., Sharrock, R. and Trezise, L., 1986. Colour naming of phobia-related words. *British Journal of Psychology*, **77**, 97–108.

Watts, F.N. and Coyle, K., 1993. Phobics show poor recall of anxiety words. *British Journal of Psychology*, **66**, 373–382.

Whalen, P.J., Bush, G., McNally, R.J., Wilhelm, S., McInerney, S.C., Jenike, M.A. and Rauch, S.L., 1998. The emotional counting Stroop paradigm: A functional magnetic resonance imaging probe of the anterior cingulate affective division. *Biological Psychiatry*, **44**, 1219–1228.

Wiedemann, G., Pauli, P., Dengler, W., Lutzenberger, W., Birbaumer, N. and Buchkremer, G., 1999. Frontal brain asymmetry as a biological substrate of emotions in patients with panic disorders. *Archives of General Psychiatry*, **56**, 78–84.

Wik, G., Fredrikson, M., Ericson, K., Eriksson, L., Stone-Elander, S. and Greitz, T., 1993. A functional cerebral response to frightening visual stimulation. *Psychiatry Research*, **50**, 15–24.

Williams, J.M.G., Watts, F.N., MacLeod, C. and Mathews, A., 1988. *Cognitive Psychology and Emotional Disorders*. Wiley, Chichester, UK.

Wolski, P. and Maj, S., 1998. Performance of clinical anxiety group on Sternberg memory scanning task: Possible cognitive and affective effects of worry. *Polish Psychological Bulletin*, **29**, 47–56.

Wu, J.C., Buchsbaum, M.S., Hershey, T.G., Hazlett, E., Sicotte, N. and Johnson, J.C., 1991. PET in generalized anxiety disorder. *Biological Psychiatry*, **29**, 1181–1199.

Yehuda, R., Keefe, R.S., Harvey, P.D., Levengood, R.A., Gerber, D.K., Geni, J. and Siever, L.J., 1995. Learning and memory in combat veterans with posttraumatic stress disorder. *American Journal of Psychiatry*, **152**, 137–139.

Yehuda, R., 1997. Sensitization of the hypothalamic–pituitary–adrenal axis in posttraumatic stress disorder. *Annals of the New York Academy of Sciences*, **821**, 57–75.

Zielinski, C.M., Taylor, M.A. and Juzwin, K.R., 1991. Neuropsychological deficits in obsessive–compulsive disorder. *Neuropsychiatry, Neuropsychology, and Behavioural Neurology*, **4**, 110–126.

Zubieta, J.K., Chinitz, J.A., Lombardi, U., Fig, L.M., Cameron, O.G. and Liberzon, I., 1999. Medial frontal cortex involvement in PTSD symptoms: A SPECT study. *Journal of Psychiatric Research*, **33**, 259–264.