CHAPTER 21

The Role of the Anterior Cingulate Cortex in Posttraumatic Stress and Panic Disorders

Lisa M. Shin, Paul J. Whalen,
Roger K. Pitman, and Scott L. Rauch

Chapter contents

Anxiety and fear are normal human emotional states that serve to alert an individual to potential threat in the environment. However, individuals with anxiety disorders persistently experience such emotional states in the absence of true danger, leading to significant distress and impairment (APA, 2000). Anxiety disorders are marked by episodes of fear or apprehension that may be either elicited by a specific stimulus or unprovoked. In posttraumatic stress disorder (PTSD), such episodes of intense fear may be triggered by recollections of a previous traumatic event and are typically accompanied by heightened physiologic arousal. In panic disorder (PD), periods of intense fear and physiologic arousal may be initially unprovoked and over time may tend to occur in specific settings from which escape would be difficult. Patients with PD often report fearing that they may have a heart attack or die or lose control, and they typically develop apprehension concerning further attacks.

With the advent of neuroimaging techniques, researchers have begun to investigate the brain systems mediating anxiety disorders and to formulate neurocircuitry models of them. Medial prefrontal cortical regions, including anterior cingulate cortex (ACC), have typically been included in such models of anxiety disorders. The ultimate goal of this type of research is to understand the neurobiological substrates of anxiety disorders in order to assist in diagnosis, improve treatment, and predict treatment response. We consider PTSD and PD together in this chapter because the two disorders have overlapping symptoms (fear and physiologic arousal in response to situations involving past or perceived threat of serious injury), often appear comorbidly, have similar proposed neurocircuitry, and currently similar treatments (e.g., serotonin reuptake inhibitors, cognitive behavioral therapy).

Goals of This Chapter

In this chapter, we focus on two anxiety disorders, PTSD and PD. For each disorder we will present the syndrome, discuss relevant neurocircuitry models, and review the literature suggesting a possible role of ACC in its pathogenesis and/or maintenance. This review will cover findings in the subgenual and pregenual parts of ACC.

1 Describe functional, structural, and neurochemistry findings in ACC in PTSD and PD.

2 Evaluate the relationship between ACC and amygdala function in PTSD.

3 Consider the effect of treatment on ACC function in PTSD.

4 Assess the relationship between ACC activation and symptom severity in PTSD and PD.

5 Evaluate the location of functional neuroimaging findings within the ACC.

6 Consider whether ACC pathology represents pathophysiology or vulnerability factors.

Symptoms and Neurocircuitry Model of Posttraumatic Stress Disorder

PTSD can occur in individuals who have experienced an event or events involving death or serious injury and reacted with fear, helplessness, or horror (APA, 2000). Such events include but are not limited to combat, sexual or physical abuse, assault, terrorist attacks, and natural disasters. Individuals with PTSD typically report experiencing intrusive recollections, nightmares, and distress and physiologic arousal in response to reminders of trauma. Given that the acquisition of PTSD resembles in some respects the process of fear conditioning, recent neurocircuitry models of PTSD have included brain structures and systems known to be involved in the process of fear conditioning and extinction (Bremner, 2002; Rauch *et al.* 1998). The three brain regions of primary interest in PTSD have been the amygdala, ACC, and hippocampus.

The amygdala is a medial temporal lobe structure that appears to be involved in the assessment of threat or potential threat (Davis & Whalen, 2001; Morris *et al.* 1998; Whalen *et al.*, 1998b) and plays a crucial role in Pavlovian fear conditioning (Davis & Whalen, 2001; LeDoux, 2000). Individuals with PTSD have shown heightened acquisition of conditioned fear in such fear conditioning paradigms (Orr *et al.*, 2000; Peri *et al.*, 2000), and functional neuroimaging studies have suggested that the amygdala is hyper-responsive in individuals with this disorder (Fredrikson & Furmark, 2003, Liberzon *et al.*, 1999; Pissiota *et al.*, 2002; Rauch *et al.*, 1996; 2000; Semple *et al.*, 2000; Shin *et al.*, 1997, 2005).

The second region of interest is ACC. The ACC is located around the genu of the corpus callosum as discussed in Chapters 1 and 3 and it is connected to the amygdala in primates (Aggleton *et al.*, 1980; Chiba *et al.*, 2001; Ghashghaei & Barbas, 2002; Stefanacci & Amaral, 2002; Chapters 6 and 9). The ACC and other ventral medial prefrontal regions appear to be critically involved in the extinction of fear conditioning and the retention of extinction (Milad & Quirk, 2002; Morgan *et al.*, 1993; Quirk *et al.*, 2000; Phelps *et al.,* 2004) as also discussed in detail in Chapter 9. Functional neuroimaging research in humans has implicated ACC in processing of emotional stimuli (Bush *et al.*, 2000; Canli *et al.*, 2004; Whalen *et al.*, 1998a; Vogt *et al.*, 2003). Apical dendrites in ACC in rats have decreased length and branching following chronic behavioral stress (Radley *et al.*, 2004). Interestingly, patients with PTSD exhibit

abnormal extinction of conditioned fear responses (Orr *et al.*, 2000, Rothbaum *et al.*, 2001) and have decreased ACC volumes and neuronal integrity (De Bellis *et al.*, 2000; Rauch *et al.*, 2003). As will be reviewed this chapter, recent neuroimaging studies have reported reduced responsivity of ACC in this disorder (e.g., Bremner *et al.*, 1999a; Bremner *et al.*, 1999b; Semple *et al.*, 2000; Shin *et al.*, 2001, 2004).

Lastly, the hippocampus is a medial temporal lobe structure posterior to the amygdala and is involved in memory processes (Eichenbaum, 2000; Schacter, 1997). The hippocampus and amygdala likely interact in the formation of emotional memories (Dolcos *et al.*, 2004; McGaugh, 2004). In addition, severe stressors and high levels of stress-related hormones can be associated with memory impairment and hippocampal cell damage (Sapolsky *et al.*, 1990; Sapolsky, 2000, Uno *et al.*, 1989; Watanabe *et al.*, 1992, Woolley *et al.*, 1990). Further evidence for the involvement of the hippocampus and other brain regions in PTSD is reviewed elsewhere (Bremner, 2002; Elzinga & Bremner, 2002; Hull, 2002; Pitman *et al.*, 2001).

According to neurocircuitry models of PTSD, the amygdala is hyper-responsive to threat-related stimuli. Amygdala hyper-responsivity may account for symptoms of hyperarousal, and interactions between the amygdala and hippocampus may explain the persistence of traumatic memories. In addition, ACC and neighboring medial prefrontal cortical structures are hyporesponsive in PTSD, failing to inhibit the amygdala and possibly accounting for impaired extinction in this disorder. (See also models described by Layton & Krikorian, 2002; Elzinga & Bremner, 2002; Hamner *et al.*, 1999).

Functional Neuroimaging: Neutral State

Three neutral state studies have reported functional abnormalities in ACC or other medial prefrontal regions in PTSD. In a positron-emission tomography (PET) study of seven PTSD patients with histories of cocaine and alcohol abuse, compared with six healthy comparison subjects, Semple *et al.* (2000) found lower regional cerebral blood flow (rCBF) in ACC/medial frontal gyrus during both rest and an auditory continuous performance task. In contrast, Sachinvala *et al.* (2000) found greater perfusion in ACC in 17 patients with PTSD and eight healthy comparison subjects during single-photon emission computed tomography (SPECT) imaging at rest. Finally, Bonne *et al.* (2003) used SPECT to study resting cerebral perfusion in 11 patients with PTSD, 17 trauma-exposed controls, and 11 non-traumatized control subjects. Although medial prefrontal cortex perfusion was not significantly different in the PTSD versus control groups, it was correlated positively with cortisol levels in the PTSD group only. Thus, in the small neutral state literature, there is evidence for functional abnormalities in ACC and other medial prefrontal regions in PTSD, although the findings are mixed with regard to the direction of functional changes compared with control groups. Further clarification comes from symptom provocation and cognitive activation studies of PTSD.

Functional Neuroimaging: Symptom Provocation

The goal of symptom provocation studies is to determine the patterns of brain activation that mediate symptomatic states. In the study of PTSD, symptom provocation paradigms have involved the presentation of imagery scripts or trauma-related audiovisual stimuli.

Script-driven imagery

Several studies have used the script-driven imagery paradigm and PET to study brain responses during the recollection and imagery of traumatic and neutral events (Pitman *et al.*, 1987). Scripts are descriptions of personal events that are written in participants' own words, audio-taped, and played back during or just before scanning to prompt recollection and imagery of those events. Most of these studies have revealed diminished activation or deactivation of the ACC or other medial prefrontal cortical regions in the traumatic versus neutral comparison. Rauch *et al.* (1996) reported activation in the pregenual ACC in PTSD during traumatic imagery, although whether this activation was diminished or exaggerated cannot be determined due to lack of a comparison group. In contrast, Bremner *et al.* (1999a) found decreased rCBF in subgenual ACC and a failure to activate pregenual ACC during traumatic imagery in 10 abused women with PTSD and 12 abused women without PTSD. Shin *et al.* (1999) also studied women with childhood abuse histories (eight with PTSD and eight without PTSD) and found that the PTSD group failed to activate the pregenual ACC. In a study of combat veterans with and without PTSD, Shin *et al.* (2004) found decreased activation in medial frontal gyrus in the PTSD group (n=17), compared with the control group (n=19). Furthermore, symptom severity was inversely related to rCBF in medial frontal gyrus in the traumatic imagery condition in the PTSD group; that is, as symptom severity increased, rCBF in medial frontal gyrus decreased. In a unique design with two comparison groups, Britton *et al.* (2005) studied 16 combat veterans with PTSD, 15 combat veterans without PTSD, and 14 healthy non-combat control subjects. They found that the PTSD group exhibited less activation in pregenual ACC than both control groups.

In addition, consistent with previous studies, they also reported an inverse correlation between dorsomedial prefrontal cortex activation and PTSD symptom severity scores.

The script-driven imagery paradigm has also been employed in the context of SPECT and functional magnetic resonance imaging (fMRI). Lindauer *et al.* (2004) used SPECT to study brain responses to traumatic and neutral imagery scripts in 11 police officers with PTSD and 15 police officers without PTSD. In the Traumatic versus Neutral comparison, the PTSD group had less activation in the ACC/medial frontal gyrus compared with the control group. Using fMRI, Lanius *et al.* (2001) studied nine patients with PTSD and nine trauma-exposed participants without PTSD. In the traumatic script-driven imagery versus implicit baseline contrast, the PTSD group showed less activation than the comparison group in pregenual ACC and medial frontal gyrus, among other regions. The findings of relatively smaller fMRI signal responses in ACC in PTSD were also observed in other negative emotional states (sadness and anxiety) in PTSD (Lanius *et al.*, 2003). Interestingly, PTSD patients who dissociated during script-driven imagery had greater activation than control participants in ACC and medial frontal gyrus (Lanius *et al.*, 2002), suggesting that re-experiencing and dissociation may be associated with opposite responses in medial prefrontal regions.

Combat audiovisual stimuli

In three studies, participants with combat-related PTSD were presented with visual and/or auditory stimuli related to combat in Vietnam during PET or SPECT scanning. In a PET study involving the presentation of combat sights and sounds, Bremner *et al.* (1999b) found that relative to combat veterans without PTSD (n=10), combat veterans with PTSD (n=10) exhibited rCBF decreases in subgenual ACC and a failure to activate pregenual ACC. In contrast, in a SPECT study involving the presentation of combat sounds versus white noise, Zubieta *et al.* (1999) found greater blood flow increases in medial prefrontal cortex in 12 PTSD patients compared with 12 healthy control participants. Using a similar design with SPECT, Liberzon *et al.* (1999) reported no group differences in ACC activation in PTSD.

In summary, most of the existing research suggests relatively diminished activation of ACC and/or neighboring medial prefrontal cortical regions during symptom provocation in PTSD (see also Fig. 21.1). In addition, two studies have reported an inverse correlation between PTSD symptom severity and medial prefrontal cortex responses. However, two SPECT studies with apparently adequate control groups did not provide evidence consistent with these findings (Liberzon *et al.*, 1999; Zubieta *et al.*, 1999). Possible reasons for these discrepant results include the different imaging technique used in these latter two studies and/or the dissociative state of the participants (Lanius *et al.*, 2002).

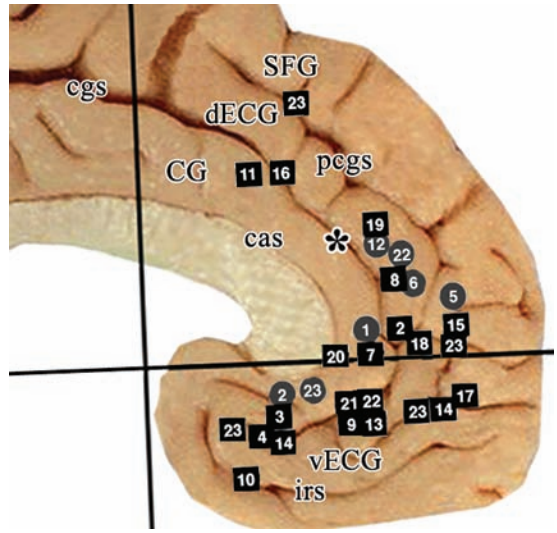

Fig. 21.1 Distribution of emotion responses and differences between control groups and PTSD. Squares represent studies showing relatively less activation in the PTSD versus Control group. Circles represent studies showing greater or equal activation in the PTSD versus Control group (except for study 1 with no controls). Studies in which anatomic location of findings was not specified were not included. 1. Rauch *et al.* (1996); 2. Shin *et al.* (1997); 3. Bremner *et al.* (1999a); 4. Bremner *et al.* (1999b); 5. Zubieta *et al.* (1999); 6. Liberzon *et al.* (1999); 7. Shin *et al.* (1999); 8. Semple *et al.* (2000); 9. Lanius *et al.* (2001); 10. Fernandez *et al.* (2001); 11. Shin *et al.* (2001); 12. Lanius *et al.* (2002); 13. Lanius *et al.* (2003); 14. Bremner *et al.* (2003); 15. Shin *et al.* (2004); 16. Lindauer *et al.* (2004); 17. Seedat *et al.* (2004); 18. Yang *et al.* (2004); 19. Bremner *et al.* (2004); 20. Britton *et al.* (2005); 21. Shin *et al.* (2005); 22. Bryant *et al.* (2005); 23. Bremner *et al.* (2005). The asterisk marks the border between ACC and the caudal midcingulate cortex. Sulci; callosal (cas), cingulate (cgs), inferior rostral (irs), paracingulate (pcgs). Gyri; cingulate (CG), dorsal external cingulate (dECG), superior frontal (SFG), ventral external cingulate (vECG).

Functional Neuroimaging: Cognitive Activation

Eight cognitive activation studies in the literature have provided information regarding the functional integrity of ACC in PTSD. Using PET, Shin *et al.* (1997) studied visual perception and visual mental imagery in seven combat veterans with PTSD and seven combat veterans without PTSD. In the perception conditions, participants viewed and evaluated previously seen pictures; in the imagery conditions, participants imagined and evaluated previously seen pictures. Within the perception and imagery conditions, participants saw neutral, negative, and combat-related pictures. Findings in the

ACC in PTSD were mixed, with evidence of both increased rCBF in subgenual ACC (during the combat imagery versus neutral imagery condition) and decreased rCBF in pregenual ACC (during the combat perception versus neutral perception condition). Of note, this early study lacked direct statistical comparisons between groups. Using the same paradigm in fMRI, Yang *et al.* (2004) studied visual perception and imagery in 11 adolescent earthquake survivors: five with PTSD and six without PTSD. While viewing earthquake versus neutral scenes, the control subjects without PTSD activated pregenual ACC and the PTSD group did not.

Later fMRI and PET research implemented variants of the Stroop task specifically to investigate the functional integrity of ACC in PTSD. Shin *et al.* (2001) administered the emotional counting Stroop task (Whalen *et al.*, 1998a) during fMRI to 16 combat veterans: eight with PTSD and eight without PTSD. In this task, participants viewed words of different valence (neutral, generally negative, and trauma-related) on a computer screen, counted the number of words presented at each trial, and then pressed the corresponding response button. The fMRI signal in the trauma-word condition was then compared with signal in the generally negative condition. In contrast to the control group, the PTSD group failed to activate a dorsal portion of pregenual ACC. Bremner *et al.* (2004) utilized PET and two different versions of the Stroop task to study ACC function in 12 women with childhood sexual abuse histories and PTSD and nine women with abuse but without PTSD. In all conditions, the task was to name the color of words presented. In the neutral baseline condition, colored Xs were presented. In the classic color Stroop interference condition, the color of the ink conflicted with the meaning of the color word presented (e.g., the word 'red' printed in green ink). In the emotional Stroop condition, rape-related words were shown in colored ink. In the classic color Stroop versus neutral comparison, both the PTSD and control groups activated pregenual ACC. In the emotional Stroop versus neutral condition, the control group activated pregenual ACC to a greater extent than the PTSD group.

Other cognitive activation studies have revealed decreased activation in ACC in PTSD. Using PET, Bremner *et al.* (2003) studied the retrieval of negatively valenced versus neutral word pairs in 10 abused women with PTSD and 11 healthy comparison subjects. During the retrieval of deeply encoded negative words versus deeply encoded neutral words, the PTSD group showed greater rCBF decreases in subgenual and pregenual ACC/medial frontal gyrus relative to the comparison group. In an fMRI study, Shin *et al.* (2005) presented fearful and happy facial expressions to 13 individuals with PTSD and 13 trauma-exposed individuals without PTSD. Relative to the control group, in the Fearful versus Happy comparison, the PTSD group showed decreased activation in pregenual ACC, as well as dorsal and ventral medial frontal gyrus. Furthermore, symptom severity was negatively correlated with fMRI responses in the pregenual ACC. Bremner *et al.* (2005) used PET to study rCBF during fear acquisition and extinction in eight women with childhood abuse-related PTSD and 11 non-abused women without PTSD. In the fear acquisition condition, exposure to a blue square was followed by a shock to the forearm. In the extinction condition, the blue square was presented without shock. Relative to a control condition during which shocks were unpaired with the blue square, the active fear acquisition condition was associated with greater left amygdala activation and less ACC activation in the PTSD than the control group. Relative to an extinction control condition, the extinction condition was associated with decreased activation in ACC in the PTSD group compared with the control group.

In contrast, one recent fMRI study utilizing a trauma-unrelated auditory oddball paradigm reported mixed findings in the ACC. Bryant *et al.* (2005) examined brain activity in 14 individuals with PTSD and 14 trauma-unexposed control subjects. In the target tone versus non-target tone contrast, the PTSD group had greater activation in the amygdala and in dorsal portions of ACC compared with control subjects. However, the PTSD group had less activation than controls in a more ventral region of ACC. The authors speculated that ACC responses in PTSD might not be uniformly attenuated in response to affectively neutral and trauma-unrelated stimuli.

In summary, the majority of cognitive activation studies of PTSD have reported a failure to activate or deactivation in the ACC. Furthermore, one of these studies reported an inverse correlation between PTSD symptom severity and ACC responses, and this leads to important new views of the mechanisms whereby cingulate functions are impaired in this syndrome.

Anterior Cingulate Cortex/Amygdala Correlations in PTSD

Current functional neurocircuitry models of PTSD make predictions about relationships between brain regions or systems of interest in this disorder, and researchers have just begun to apply statistical techniques to permit the examination of such relationships (e.g., Lanius *et al.*, 2004, 2005; Shaw *et al.*, 2002). Relevant to the current chapter is the relationship between medial prefrontal structures and the amygdala. Three recent studies have provided data relevant to this topic.

In a script-driven imagery PET study, Shin *et al.* (2004) found that in the PTSD group, rCBF changes in medial

frontal gyrus (just anterior to pregenual ACC) were significantly inversely related to rCBF changes in bilateral amygdala, that is, as rCBF changes in medial frontal gyrus decreased, rCBF changes in amygdala increased. In an fMRI study involving the passive viewing of fearful versus happy facial expressions in an independent sample, Shin *et al.* (2005) reported an inverse correlation between amygdala responses and dorsal medial frontal gyrus responses in PTSD. In both studies, the inverse correlation remained even when participants with comorbid depression were removed from the analyses. Taken together, these two findings suggest a reciprocal relationship between medial prefrontal and amygdala function in PTSD, although the direction of causality remains undetermined.

In contrast, Gilboa *et al.* (2004) provided evidence for a positive relationship between the amygdala and ACC in PTSD. Using PET and script-driven imagery, Gilboa *et al.* (2004) studied 10 patients with PTSD and 10 trauma-exposed individuals who never had PTSD. PET data were analyzed with partial least squares, which identifies groups of brain regions that covary with a particular region-of-interest, and structural equation modeling, which is used to test models regarding the direction of influence between regions. Unlike the control group, the PTSD group exhibited a positive relationship between the amygdala, pregenual ACC, and subgenual ACC, among other regions.

In summary, there is preliminary evidence for a functional relationship between ACC/medial frontal gyrus and the amygdala in PTSD. Although two out of three studies suggest an inverse relationship between these regions, additional research will be required to confirm the direction of this relationship and to identify other important relationships among brain systems in this disorder.

PTSD Treatment Studies

Two recent studies have examined brain function in PTSD before and after treatment with serotonergic reuptake inhibitors. In an early case report using PET, Fernandez *et al.* (2001) found that successful treatment of war/torture-related PTSD with fluoxetine was associated with increased activation in ventral prefrontal cortex. Using SPECT and technetium-99m hexamethylpropylene amine oxime (Tc^{99m} HMPAO), Seedat *et al.* (2004) examined brain activation in 11 individuals with PTSD both before and after 8 weeks of treatment with citalopram. Perfusion increases in the external cingulate gyrus in response to treatment were correlated with symptomatic improvement. Pre-treatment perfusion in ACC did not differ between those who did and did not respond to treatment. Thus, symptomatic improvement following treatment with serotonin reuptake inhibitors appears to be associated with increased activation in the external cingulate gyrus and ventral medial prefrontal cortex. Future research should evaluate whether response to cognitive-behavioral therapy is similarly related to medial prefrontal cortex function.

Structure and Neurochemistry

Although several morphometric MRI studies reported decreased volumes of frontal cortex in PTSD (Carrion *et al.*, 2001; De Bellis *et al.*, 2002; Fennema-Notestine *et al.*, 2002), only a few studies have examined the structural aspects of medial prefrontal cortex specifically. Using MRI and cortical parcellation techniques, Rauch *et al.* (2003) measured volumes of medial prefrontal cortical territories in nine women with PTSD and nine trauma-exposed women without PTSD. Volumes of pregenual and subgenual ACC were smaller in the PTSD group relative to the control group. In a study using MRI and voxel-based morphometry, Yamasue *et al.* (2003) found that nine individuals with PTSD had significantly smaller gray matter volumes in a dorsal part of ACC, compared with 16 trauma-exposed control participants without PTSD. In the PTSD group, severity of PTSD was inversely correlated with gray-matter volumes in the ACC. In the same sample, Araki *et al.* (2005) found a trend for a positive correlation between ACC gray-matter volumes and P300 responses in an auditory oddball task. Corbo *et al.* (2005) also used voxel-based morphometry to study 14 individuals with acute PTSD and 14 healthy control subjects. The acute PTSD group exhibited lower gray-matter density in pregenual ACC, although volumetric analyses of the ACC revealed no group differences. The authors speculated that shape differences in the ACC in PTSD might have driven their voxel-based morphometric findings.

Relatively few studies of neurochemistry exist in the PTSD neuroimaging literature. DeBellis *et al.* (2000) used magnetic resonance spectroscopy (MRS) to examine N-acetylaspartate (NAA)/creatine ratios in pregenual ACC in 11 maltreated children and adolescents with PTSD and 11 matched healthy control participants. The PTSD group had lower NAA/creatine ratios in pregenual ACC than the control group, consistent with decreased neuronal integrity in that region in PTSD. In a case report, NAA/creatine ratios in ACC in a maltreated boy with PTSD increased following successful treatment with clonidine (De Bellis *et al.* 2001). In a SPECT study, Bremner *et al.* (2000a) used [^{123}I]iomazenil to investigate benzodiazepine receptor binding in 13 combat veterans with PTSD and 13 healthy comparison participants. Compared with the control group, the PTSD group had lower binding in anterior medial prefrontal cortex. However, a subsequent attempt has failed to replicate this finding (Fujita *et al.*, 2004). In an initial

study, serotonin 1A receptor binding appears to be normal in PTSD (Bonne *et al.*, 2005), in contrast to findings in PD (Neumeister *et al.*, 2004).

Localization of Functional Changes in ACC

Evidence for diminished function of ACC in PTSD is relatively strong. As shown in Figure 21.1, most of the foci of diminished function fall within ACC on the external cingulate gyrus and subgenual ACC. In healthy individuals, ACC is activated during the processing of emotional information, such as in emotional Stroop tasks or the recollection of emotional events (Bush *et al.*, 2000; Canli *et al.*, 2004; George *et al.*, 1995, 1996; Vogt *et al.*, 2003; Whalen *et al.*, 1998a). The ACC activation may reflect a regulatory response allowing healthy individuals to process emotional information and efficiently complete the task at hand (Mayberg, 1997; Shin *et al.*, 2001; Whalen *et al.*, 1998a). In contrast, patients with PTSD show diminished activation in ACC, and an inverse relationship between symptom severity and ACC activation.

Figure 21.1 also shows that some foci of diminished function occurred in more dorsal cingulate cortex in the midcingulate region. Some variability across studies with regard to the location of foci of activation (or deactivation) is to be expected given the imperfect spatial resolution of functional neuroimaging scanners (especially PET and SPECT) and given the spatial smoothing techniques used to intentionally 'blur' the functional data to permit intersubject averaging. Although most studies of extinction and extinction retention have been conducted on rodents (Milad & Quirk, 2002; Quirk *et al.*, 2000), new data are emerging in humans to suggest that subgenual ACC (Phelps *et al.*, 2004) and medial orbitofrontal cortex (Milad *et al.* in press) may play a role in extinction. Additional research will be needed to determine whether diminished subgenual ACC function in PTSD is associated with impaired extinction in this disorder (see Bremner *et al.*, 2005).

Panic Disorder: Symptoms and Neurocircuitry Model

A panic attack is a period of intense fear and sympathetic nervous system arousal that occurs in the absence of true danger. An individual with PD experiences recurrent, unexpected panic attacks along with persistent concern about possible implications or consequences of the attacks (APA, 2000). As with PTSD, prevailing neurocircuitry models of PD involve brain systems implicated in fear conditioning (Coplan & Lydiard, 1998; Gorman *et al.*, 2000). According to these models of panic, the 'fear network' including amygdala, hippocampus, thalamus, and brainstem structures is hypersensitive. Furthermore, frontal, cingulate, and somatosensory cortices fail to provide top-down inhibitory input to the amygdala, leading to exaggerated amygdala activation and unnecessary activation of the entire 'fear network,' resulting in a panic attack (Gorman *et al.*, 2000).

The number of neuroimaging studies of PD is small and the literature is dominated by neutral state and pharmacologic challenge studies. However, there is some support for amygdala activation during panic attacks and for abnormal activation of ACC in PD.

Functional Neuroimaging: Neutral State

A few neutral state functional neuroimaging studies have been conducted to study PD, and most of these have reported abnormalities in hippocampal or parahippocampal blood flow and/or metabolic rates (Bisaga *et al.*, 1998; De Cristofaro *et al.*, 1993; Nordahl *et al.*, 1990; Nordahl *et al.*, 1998; Reiman *et al.*, 1986). To our knowledge, only one such study suggests possible abnormalities in ACC. Nordahl *et al.* (1990) measured cerebral glucose metabolic rates using PET in 12 patients with PD and 30 healthy control subjects during a tone discrimination task. Relative to normal control subjects, patients with PD had a trend for decreased glucose metabolic rates in the ACC and increased glucose metabolic rates in medial orbitofrontal cortex.

Functional Neuroimaging: Symptom Provocation

In contrast to the neutral state study suggesting decreased activity of the ACC in PD, symptom provocation studies have mainly revealed increased activation in ACC in PD during anxiety states. In an fMRI study, Bystritsky *et al.* (2001) studied six patients with PD and six healthy control participants during script-driven imagery of high anxiety versus neutral events. In the anxiety versus neutral contrast, the PD group exhibited greater activation than the control group in ACC and posterior cingulate cortex, as well as hippocampus, and inferior frontal cortex. Boshuisen *et al.* (2002) used PET to study rCBF in anticipation of a pentagastrin challenge in 17 PD patients and 21 healthy control participants. Relative to the control group, the PD group exhibited increased rCBF in the pregenual ACC during both rest and an anticipatory anxiety condition. In a very early SPECT study, Woods *et al.* (1988) examined the effects of yohimbine (versus saline placebo) on rCBF in six patients with PD and six healthy control participants. In the PD group, anxiety levels increased and

frontal blood flow decreased in the yohimbine versus placebo condition. However, whether these frontal rCBF decreases were medial or lateral or both are unclear.

Findings from neuroimaging studies of panic attacks in otherwise healthy individuals may also prove to be helpful in determining the mediating neuroanatomy of panic attacks in PD. With one exception, these studies generally have revealed increased activation of the ACC during panic compared with neutral states. Cholecystokinin tetrapeptide (CCK_4) has been used in two PET studies to evaluate the neural correlates of panic symptoms in healthy individuals. Benkelfat *et al.* (1995) found that CCK_4 administration was associated with increased blood flow in ACC, amygdala and other limbic regions in eight healthy individuals. Javanmard *et al.* (1999) found that in response to administration of CCK_4 versus placebo, 20 healthy individuals showed increased panic symptoms and decreased rCBF in medial frontal gyrus. In contrast, during an anticipatory anxiety condition during which participants expected to receive CCK_4 but instead received the placebo, subjects showed increased activation of ACC. In a similar pharmacologic challenge paradigm, Ketter *et al.* (1996) studied rCBF associated with procaine versus saline administration in 32 healthy individuals. In the procaine versus saline contrast, rCBF increases occurred in anterior limbic structures, including ACC, amygdala, insula, and orbitofrontal cortex. Similar results were reported by Servan-Schreiber *et al.* (1998) in a separate sample of 10 healthy volunteers. In contrast, in a PET case study of an unexpected panic attack in otherwise psychiatrically healthy woman, Fischer *et al.* (1998) found that panic was associated with decreased rCBF in ventromedial frontal cortex.

Functional Neuroimaging: Cognitive Activation

Though as yet unpublished, recently completed studies in our laboratory (Whalen, Pollack, Shin, Rauch *et al.*) have employed the cognitive activation approach in conjunction with fMRI to probe ACC and amygdala function in PD. Specifically, we applied the same masked faces (Whalen *et al.*, 1998a) and emotional counting Stroop (Whalen *et al.*, 1998b) paradigms that we previously used in studies of PTSD (Rauch *et al.*, 2000; Shin *et al.*, 2001). Interestingly, analyses of these data sets preliminarily yielded comparable findings in PD with those we reported in PTSD (Rauch *et al.*, 2000; Shin *et al.*, 2001); specifically, in comparison with control subjects, those with PD exhibited exaggerated amygdala responses to masked fearful versus masked happy faces, and attenuated ACC activation when counting panic-related versus control words. In addition, in the masked faces task, a measure of sensitivity to anxiety symptoms in PD patients was correlated positively with amygdala responses and negatively with pregenual ACC responses. Thus, preliminary findings in PD using cognitive activation and fMRI also indicate exaggerated responses in the amygdala to general threat-related stimuli, and attenuated responses in the ACC to disorder-specific threat-related cues.

Structure and Neurochemistry

Although there is evidence for structural abnormalities in the temporal lobes in PD (Dantendorfer *et al.*, 1996; Fontaine *et al.*, 1990; Massana *et al.*, 2003; Vythilingam *et al.*, 2000), there is no support for structural abnormalities in ACC in this disorder. MRS studies have reported greater rises in brain lactate levels after hyperventilation in PD (Dager *et al.*, 1995, 1999), but those studies did not focus specifically on medial prefrontal cortex. One MRS study examined the metabolites creatine and phosphocreatine in PD and found lower concentrations in right medial temporal lobe, but not in medial prefrontal cortex (Massana *et al.*, 2002). Some studies of benzodiazepine receptor binding in PD have revealed abnormalities in lateral frontal cortex (Brandt *et al.*, 1998; Bremner *et al.*, 2000b; Kuikka *et al.*, 1995; Malizia *et al.*, 1998), but only two studies have found such abnormalities in medial prefrontal cortex. Using SPECT and [^{123}I]iomazenil to study 13 PD patients and 16 healthy individuals, Bremner *et al.* (2000b) found a negative correlation between panic attack symptom severity and benzodiazepine receptor binding in dorsal medial frontal gyrus. In a [^{11}C]PET study, Malizia *et al.* (1998) found decreased benzodiazepine binding in ACC and medial frontal cortex in seven patients with PD compared with eight healthy comparison participants. Finally, in a PET study of serotonin 1A receptor binding using ^{18}F-FCWAY, Neumeister *et al.* (2004) reported lower distribution volumes in the ACC, posterior cingulate cortex and raphe nuclei in 16 PD patients compared with 15 healthy individuals.

In summary, the results of neuroimaging studies suggest increased activation in the amygdala during anxiety in PD and during panic attacks in healthy individuals. Structural and functional abnormalities have also been reported in the hippocampus and parahippocampal gyrus in PD. However, evidence for abnormalities in ACC is mixed, with some studies finding increased activation and others finding decreased activation in PD and in healthy individuals during panic attacks. Initial fMRI cognitive activation studies have suggested increased activation of the amygdala and diminished activation of the ACC in PD, but these findings require replication in larger groups of participants. Lastly, benzodiazepine and serotonin 1A receptor

binding appears to be decreased in the ACC in PD. Additional research will be required to replicate and extend these findings, as well as to evaluate their diagnostic specificity.

Pathophysiology or Vulnerability?

Abnormalities in ACC in PTSD and PD could represent fundamental aspects of pathophysiology; alternatively, they may represent vulnerability factors that are present before the onset of the disorder. Twin, longitudinal, and genetics studies will be needed to determine which of these alternatives is more likely. For example, a recent twin study has reported decreased hippocampal volumes in both combat veterans with PTSD and in their trauma unexposed identical twins without PTSD, suggesting that reduced hippocampal volumes may be a vulnerability factor (Gilbertson *et al.*, 2002). Similar work is underway with regard to the ACC in PTSD (Kasai *et al.*, 2008). Another study has demonstrated amygdala hyper-responsivity in adults classified during childhood as having a behaviorally inhibited temperament, which is a risk factor for the development of anxiety disorders including PD (Schwartz *et al.*, 2003). Finally, other research has suggested that currently psychiatrically healthy carriers of the short allele of the serotonin transporter gene have exaggerated amygdala activation to affective stimuli (Hariri *et al.*, 2005), reduced gray matter volumes in the pregenual ACC and amygdala, as well as abnormal functional coupling of these regions (Pezawas *et al.*, 2005).

Summary of the Role of ACC in PTSD and PD

Evidence for diminished recruitment of ACC and neighboring medial prefrontal cortical regions in PTSD is relatively strong. In addition, three studies reported an inverse relationship between PTSD symptoms and responses in ACC or medial frontal gyrus. Furthermore, treatment response appears to be related to an increase in ACC and ventral medial prefrontal cortex activity. These findings, along with the reports of amygdala hyper-responsivity and an inverse relationship between amygdala and medial prefrontal cortex responses in PTSD, are consistent with current neurocircuitry models of this disorder. Future research using fear conditioning and extinction paradigms will help determine whether deficits in extinction are related to ACC function in PTSD. Additional research on brain correlates and predictors of treatment response ought to be helpful in further understanding the mediating neuroanatomy of this disorder.

Evidence for the role of ACC in PD is more limited and mixed, with some studies finding increased activation and some finding decreased activation in PD. However, some studies have reported decreased benzodiazepine and serotonin receptor binding in ACC and medial frontal gyrus in PD. In the future, treatment response studies and cognitive activation studies ought to provide further evidence for the role of ACC in this disorder.

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