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The Neurocircuitry of Fear, Stress, and Anxiety Disorders

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Anxiety disorders are a significant problem in the community, and recent neuroimaging research has focused on determining the brain circuits that underlie them. Research on the neurocircuitry of anxiety disorders has its roots in the study of fear circuits in animal models and the study of brain responses to emotional stimuli in healthy humans. We review this research, as well as neuroimaging studies of anxiety disorders. In general, these studies have reported relatively heightened amygdala activation in response to disorder-relevant stimuli in post-traumatic stress disorder, social phobia, and specific phobia. Activation in the insular cortex appears to be heightened in many of the anxiety disorders. Unlike other anxiety disorders, post-traumatic stress disorder is associated with diminished responsivity in the rostral anterior cingulate cortex and adjacent ventral medial prefrontal cortex. Additional research will be needed to (1) clarify the exact role of each component of the fear circuitry in the anxiety disorders, (2) determine whether functional abnormalities identified in the anxiety disorders represent acquired signs of the disorders or vulnerability factors that increase the risk of developing them, (3) link the findings of functional neuroimaging studies with those of neurochemistry studies, and (4) use functional neuroimaging to predict treatment response and assess treatment-related changes in brain function.

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INTRODUCTION

Anxiety disorders are marked by excessive fear (and avoidance), often in response to specific objects or situations and in the absence of true danger, and they are extremely common in the general population. According to a recent epidemiological study, the lifetime prevalence of any anxiety disorder is 28.8% (Kessler *et al*, 2005). Anxiety disorders are associated with impaired workplace performance and hefty economic costs (Greenberg *et al*, 1999), as well as an increased risk of cardiovascular morbidity and mortality (Albert *et al*, 2005; Kawachi *et al*, 1994; Smoller *et al*, 2007). Given that anxiety disorders are a significant problem in the community, recent neuroimaging research has focused on determining the brain circuits that underlie them to inform the use of existing treatments and guide the possible development of new treatments. In the future, neuroimaging studies of anxiety disorders may also prove to be clinically helpful in the prediction of treatment response.

Given that excessive fear is a key component of anxiety disorders, it is not surprising that the search for the neurocircuitry of anxiety disorders has its roots in and has been closely intertwined with studies of fear circuits in animal models. A large volume of experimental work has examined the neurocircuitry associated with fear responses, mainly in rodents, using primarily fear conditioning, inhibitory avoidance, and fear-potentiated startle models. Key components of fear circuitry including the amygdala (and its subnuclei), nucleus accumbens (including bed nucleus of stria terminalis BNST), hippocampus, ventromedial hypothalamus, periaqueductal gray, a number of brain stem nuclei, thalamic nuclei, insular cortex, and some prefrontal regions (mainly infralimbic cortex) have been identified in these studies (for recent reviews see Davis, 2006; Maren, 2008; Quirk and Mueller, 2008). These regions have their respective roles in the various components of fear processing such as the perception of threat or of unconditioned stimuli, the pairing of an unconditioned stimulus and conditioned response (learning/conditioning), the execution of efferent components of fear response, and

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the modulation of fear responses through potentiation, contextual modulation, or extinction. Some key findings from animal literature, such as the central role of amygdaloid nuclei in the acquisition of fear conditioning and expression of fear responses, the involvement of the hippocampus in contextual processing, and the importance of the infralimbic cortex in extinction recall, have been replicated across different studies and laboratories. These basic components of fear circuitry are well preserved across species and likely support similar functions in humans. Animal work using *in vivo* electrophysiological recording, tracing and lesions/reversible inactivation techniques was indispensable in acquiring this knowledge. Some recent work had even suggested that there might be separate fear and anxiety systems orchestrated through the central nucleus of the amygdala and the BNST, respectively (Davis, 2006). These types of findings are particularly exciting as they might allow for a better focus on the neurocircuits involved in pathological anxiety.

On the other hand, other important issues, such as the exact neuroanatomical region that stores fear memory traces, or the exact role of a particular process (eg, the role of reconsolidation in fear memory, Nader and Hardt, 2009), or of a particular region (eg, the insular cortex) are intensely debated and actively studied. Nevertheless, the basic fear-related neurocircuitry identified in rodents is a useful place to start examining anxiety-related neurocircuitry in humans. It is important to note that the exact roles of many brain regions are yet to be firmly established and could differ across species. Even regions such as the amygdala, hippocampus, and nucleus accumbens might be involved in different, additional, or even unique tasks in humans (eg, the role of the hippocampus in explicit verbal memory in humans). Finally, there are major differences between human anxiety/anxiety disorders and fear conditioning models in animals. These differences include the frequent absence of clear unconditioned stimuli (US) in human anxiety disorders, and the central roles of avoidance and cognitive components (eg, anticipatory anxiety) in humans. These unique characteristics of anxiety disorders suggest potential involvement of other brain regions in addition to those identified in rodents, such as areas of prefrontal cortex that are more unique to humans. Thus, although animal studies are indispensable in understanding basic fear neurocircuitry, *in vivo* human studies are critical for understanding the neurocircuitry of anxiety disorders.

In this review, we will discuss three main topics: (1) fear neurocircuitry in healthy humans; (2) stress as a normal response to internal and external stimuli, and (3) anxiety disorders as defined in human psychopathology. The first of these topics will include a discussion of Pavlovian fear conditioning and extinction, pharmacologically induced fear and anxiety states, and the assessment of emotional stimuli in humans. In the third topic, we review the role of brain regions such as the amygdala, medial prefrontal cortex (including the rostral anterior cingulate cortex (rACC) and dorsal anterior cingulate cortex (dACC)), hippocampus, and insular cortex in anxiety disorders (Figure 1). Finally, we discuss some of the limitations of neuroimaging studies of anxiety disorders as well as the directions that we expect the field to take in the near future. (For an outline of this review see the Appendix.)

FEAR NEUROCIRCUITRY IN HUMANS

Pavlovian Fear Conditioning and Extinction

Fear conditioning. In its most basic form, Pavlovian fear conditioning involves repeatedly presenting a previously neutral conditioned stimulus (CS; eg, a tone) with an aversive unconditioned stimulus (US; eg, a shock). After repeated pairings, the CS alone comes to elicit a conditioned fear response (eg, increased freezing, fear-potentiated startle, or skin conductance responses). Pavlovian fear conditioning has been used as a testable and translational, though admittedly simplistic, model of the acquisition of fears that might be relevant to some anxiety disorders like phobias and possibly to some aspects of post-traumatic stress disorder (PTSD).

Studies of Pavlovian fear conditioning in non-humans have highlighted the importance of the amygdala in the acquisition of fear conditioning (LeDoux, 2000; LeDoux *et al*, 1990; Pare *et al*, 2004; Sananes and Davis, 1992). Similarly, functional neuroimaging studies in humans have reported amygdala activation during fear conditioning (Alvarez *et al*, 2008; Barrett and Armony, 2009; Buchel *et al*, 1998, 1999; Cheng *et al*, 2003, 2006; Gottfried and Dolan, 2004; Knight *et al*, 2004, 2005; LaBar *et al*, 1998; Milad *et al*, 2007b; Morris and Dolan, 2004; Pine *et al*, 2001; Tabbert *et al*, 2006), even when the CS is presented below perceptual thresholds (Critchley *et al*, 2002; Knight *et al*,

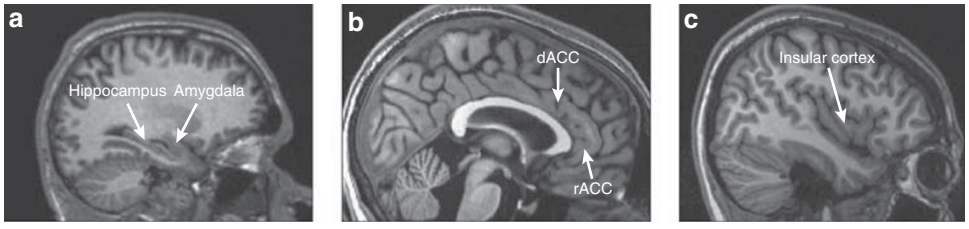

Figure 1. Magnetic resonance images (sagittal slices) showing the structures of interest in this review: (a) the hippocampus and the amygdala; (b) the dorsal anterior cingulate cortex (dACC) and the rostral anterior cingulate cortex (rACC); and (c) the insular cortex.

2009; Morris *et al*, 2001) and even when more complex USs are used (Doronbekov *et al*, 2005; Klucken *et al*, 2009). In addition, amygdala activity has been associated with skin conductance changes during fear conditioning (Cheng *et al*, 2006; Furmark *et al*, 1997; LaBar *et al*, 1998; Phelps *et al*, 2001). Interestingly, amygdala activation in humans also has been observed in response to cues following (1) verbal instructions that discriminate between cues that predict shock *vs* safety (even though no shock was actually administered) (Phelps *et al*, 2001), and (2) observational fear learning, whereby participants watch a video of another person experiencing a Pavlovian fear-conditioning paradigm (Olsson *et al*, 2007). What exactly amygdaloid activation represents in these latter paradigms is not entirely clear. It could suggest for example that: (1) higher order centers that decipher the anticipated predictive value of the cue, or that learn from observation using empathy, convey information to the amygdala, or (2) alternatively, that the human amygdala is less specific in its responses and is more sensitive to contextual modulation in the absence of a US. These interpretations could have potentially different implications for the understanding of the role of the amygdala in anxiety disorders.

Fear conditioning is also associated with increased activation in the dACC and rACC (Alvarez *et al*, 2008; Buchel *et al*, 1998, 1999; Dunsmoor *et al*, 2007; Klucken *et al*, 2009; LaBar *et al*, 1998; Marschner *et al*, 2008; Milad *et al*, 2007a, b; Morris and Dolan, 2004; Phelps *et al*, 2004). Activation in the dACC and rACC also occurs during observational fear learning (Olsson *et al*, 2007). In addition, dACC activation is positively correlated with differential skin conductance responses (Milad *et al*, 2007a). Fear conditioning studies (involving both specific CSs and contexts) also commonly report insular cortex activation (Alvarez *et al*, 2008; Buchel *et al*, 1999; Buchel *et al*, 1998; Critchley *et al*, 2002; Dunsmoor *et al*, 2007; Gottfried and Dolan, 2004; Klucken *et al*, 2009; Knight *et al*, 2009; Marschner *et al*, 2008; Morris and Dolan, 2004; Phelps *et al*, 2001, 2004) and hippocampal activation (Alvarez *et al*, 2008; Buchel *et al*, 1999; Knight *et al*, 2004, 2009; Lang *et al*, 2009; Marschner *et al*, 2008).

Extinction. Extinction learning occurs when a CS that previously predicted a US no longer does so, and over time, the conditioned response (eg, freezing or elevated skin conductance responses) decreases. Extinction learning or, more likely, the later recall of this learning involves the ventromedial prefrontal cortex (vmPFC) (Milad and Quirk, 2002; Morgan *et al*, 1993; Quirk *et al*, 2000, 2003, 2006) in rodents. Functional neuroimaging studies of healthy humans have reported vmPFC activation during extinction (Barrett and Armony, 2009; Gottfried and Dolan, 2004; Kalisch *et al*, 2006; Milad *et al*, 2007b) and the later recall of extinction (Milad *et al*, 2007b; Phelps *et al*, 2004). Skin conductance measures of extinction memory are positively correlated with vmPFC activation (Milad *et al*, 2007b; Phelps *et al*, 2004) and vmPFC cortical thickness (Milad *et al*, 2005). Activation of the amygdala and insular cortex also may occur during extinction learning or recall (Gottfried and Dolan, 2004; LaBar *et al*, 1998; Milad *et al*, 2007b; Phelps *et al*, 2004), and greater amygdala responses during extinction have been associated with higher trait anxiety (Barrett and Armony, 2009). Finally, extinction can be modulated by context (ie, the surroundings in which extinction takes place), and the hippocampus has a role in this process. In rodents, dorsal hippocampal lesions reduce the context-dependence of extinction (Bouton *et al*, 2006). In a recent fMRI study, hippocampal activation to the CS+ occurred in the extinction context but not in the conditioning context (Kalisch *et al*, 2006). Hippocampal activation was also positively correlated with vmPFC activation in this study (Kalisch *et al*, 2006), suggesting that hippocampal–vmPFC interactions may be important for the contextual modulation of extinction.

Fear States and Responses to Emotional Stimuli

Pharmacological challenge. Another way to examine the mediating functional neuroanatomy of fear or anxiety is to use specific pharmacological agents to provoke such states in healthy individuals during PET or fMRI scanning. For example, cholecystokinin-4 (CCK-4) is associated with increases in subjective states of fear and anxiety, as well as increased activation in the amygdala, insular cortex, claustrum, cerebellum, brain stem, and the ACC (Benkelfat *et al*, 1995; Eser *et al*, 2009; Javanmard *et al*, 1999; Schunck *et al*, 2006). In addition, two studies reported dACC increases during anticipatory anxiety preceding the CCK administration (Eser *et al*, 2009; Javanmard *et al*, 1999). It is important to keep in mind, however, that CCK-B receptor agonists like pentagastrin also have direct effects on stress axis stimulation independent of their effects on subjective experience of distress/fear (Abelson *et al*, 2005, 2008). Procaine administration has been associated with elevated subjective ratings of fear/anxiety, activation of the amygdala, ACC, and insular cortex (Ketter *et al*, 1996; Servan-Schreiber *et al*, 1998), and deactivation of neocortical structures (Servan-Schreiber *et al*, 1998). Furthermore, amygdala activity was positively correlated with subjective reports of anxiety (Ketter *et al*, 1996; Servan-Schreiber *et al*, 1998). Interestingly, those subjects who did not have a panic attack in response to procaine had greater activation in the rACC compared with those who did have a panic attack (Servan-Schreiber *et al*, 1998), consistent with the idea that the rACC may perform a regulatory or inhibitory function (Mayberg, 1997). The alpha-2 adrenergic antagonist yohimbine has likewise been associated with increased normalized blood flow in medial prefrontal cortex, insular cortex, and cerebellum in healthy individuals (Cameron *et al*, 2000). A major caveat in the interpretation of pharmacological challenge studies, however, is the difficulty in disentangling the effects that are specific to fear induction from the direct effect of a pharmacological agent on regional brain activity and from the non-specific effects of the pharmacological agent.

Emotional stimuli. Over the past two decades, functional neuroimaging studies have shown that a core set of brain

regions mediate responses to emotional stimuli in healthy humans. (For reviews, see Phan *et al*, 2002; Phan *et al*, 2004b). The relevance of these studies to fear/anxiety circuitry is two-fold: (1) A significant number of these emotional activation paradigms utilize stimuli that depict and/or elicit fear, and (2) these studies shed light on more general emotion-generating neurocircuitry. PET and fMRI studies have reported amygdala activation in response to emotionally negative photographs (Britton *et al*, 2006; Hariri *et al*, 2002; Irwin *et al*, 1996; Lane *et al*, 1997a; Paradiso *et al*, 1999; Phan *et al*, 2003b; Reiman *et al*, 1997; Taylor *et al*, 1998), odors (Zald and Pardo, 1997) and tastes (Zald *et al*, 1998). Several studies have reported amygdala activation to positive stimuli as well (Garavan *et al*, 2001; Hamann and Mao, 2002; Hamann *et al*, 1999, 2002; Liberzon *et al*, 2003), which suggests that the amygdala responds more broadly to emotionally arousing and/or salient stimuli (Phan *et al*, 2004b). Reappraisal of emotionally negative photographs is associated with reduced amygdala activation (Ochsner *et al*, 2002) and increased ventromedial prefrontal cortex activation (Urry *et al*, 2006). Finally, amygdala activation during encoding of emotionally arousing stimuli is correlated with the subsequent recollection of those stimuli (Cahill *et al*, 1996; Dolcos *et al*, 2004, 2005; Hamann *et al*, 1999).

Medial prefrontal cortex, including the rACC, also activates in response to emotional pictures (Lane *et al*, 1997a, b; Phan *et al*, 2003a, b, 2004a; Reiman *et al*, 1997) and may mediate self-referential processing (Kelley *et al*, 2002; Lane *et al*, 1997a; Zysset *et al*, 2002). Although the medial prefrontal cortex may activate regardless of task or valence, the rACC may be more likely to activate when a cognitive task is performed during scanning (Phan *et al*, 2002). Ventromedial PFC responses to fear-related images have been negatively associated with cortisol reactivity (Root *et al*, 2009). The dACC also activates in response to emotional photographs (Britton *et al*, 2006; Teasdale *et al*, 1999) and aversive tastes (Zald *et al*, 1998). Finally, the insular cortex is responsive to aversive stimuli (Phan *et al*, 2004a), internally generated sadness (Lane *et al*, 1997b; Reiman *et al*, 1997) and disgust-related stimuli (Britton *et al*, 2006).

Emotional facial expressions. Interestingly, the same neurocircuitry that has been implicated in fear/anxiety responses in humans is readily activated by stimuli that are not intrinsically threatening, but may convey information regarding the presence of threat in the environment or about the fearful emotional state of others. Responses in the amygdala are readily elicited by photographs of facial expressions, especially those of fear (Breiter *et al*, 1996a; Davis and Whalen, 2001; Fitzgerald *et al*, 2006; Morris *et al*, 1996; Vuilleumier and Pourtois, 2007; Whalen *et al*, 2001), even when presented below conscious awareness (Morris *et al*, 1998; Whalen *et al*, 1998, 2004). Emotional facial expressions have also been associated with activation in the dACC, rACC, medial frontal gyrus, and insular cortex (Fitzgerald *et al*, 2006; Gorno-Tempini *et al*, 2001; Morris *et al*, 1996; Phillips *et al*, 1997, 2004; Sabatini *et al*, 2009; Sprengelmeyer *et al*, 1998).

Brain responses to the relatively ambiguous facial expression of surprise have been shown, in some studies, to depend on the extent to which individual subjects interpreted these expressions as positive or negative; more negative interpretations were associated with greater amygdala and lower ventral medial prefrontal cortex activation (Kim *et al*, 2003). These findings are consistent with the notion that the amygdala and medial prefrontal cortex are reciprocally modulated (eg, Garcia *et al*, 1999). Furthermore, the experimental manipulation of the context in which surprise facial expressions are presented alters brain activation patterns in a similar way: surprise expressions associated with a negative context elicited more amygdala activation than those associated with a positive context (Kim *et al*, 2004). These amygdala activations were positively correlated with activation in the dACC (Kim *et al*, 2004).

Of relevance to our later discussion of anxiety disorders are findings that suggest that healthy individuals with high scores on anxiety measures have greater amygdala and insular cortex responses to emotional (angry, fearful, and happy) faces and less rACC activation than participants with normative scores on these measures (Bishop *et al*, 2004a, b; Stein *et al*, 2007). Similarly, trait anxiety has been positively correlated with amygdala responses to neutral faces (Somerville *et al*, 2004).

Summary

Studies of fear conditioning, pharmacologically induced fear, and responses to emotional stimuli and facial expressions have provided evidence that the human amygdala, although responsive to multiple salient stimuli, responds reliably and potentially preferably to stimuli that predict threat and can be involved in mediating fear/anxiety states. Given that patients with anxiety disorders experience fear and distress in response to possible predictors of threat, the amygdala has been hypothesized to be hyperresponsive in some anxiety disorders. In the next section, we will review the evidence related to this hypothesis.

Studies of extinction have highlighted the potential involvement of the vmPFC and hippocampus in the process of learning and remembering that stimuli that used to predict threat no longer do. One possible reason for exaggerated fear, anxiety, and distress in patients with anxiety disorders is that these emotional responses fail to extinguish or that extinction learning is not recalled even when specific cues no longer predict threat. Indeed, some studies have reported impaired extinction in several anxiety disorders, such as PTSD (Blechert *et al*, 2007; Milad *et al*, 2008; Orr *et al*, 2000; Peri *et al*, 2000; Wessa and Flor, 2007). Thus, the vmPFC and hippocampus are clear regions of interest in functional neuroimaging studies of anxiety disorders.

Finally, both the animal literature and studies reviewed above suggest that the dACC (and its likely homolog prelimbic cortex) and insular cortex respond to emotional

stimuli or those that predict threat. As with the amygdala, hippocampus, and vmPFC, these regions are involved in multiple other functions; however, they might also have important roles in specific aspects of anxiety. For example, the insular cortex is thought to mediate the monitoring of internal body states, and has been found to be hyperresponsive in anxiety-prone individuals (Paulus and Stein, 2006). In summary, research on healthy individuals has suggested that all of these brain regions are prime candidates to examine in patients with anxiety disorders.

STRESS

An important and often overlooked aspect of the fear/anxiety neurocircuitry is its overlap and interaction with the neurocircuitry that orchestrates the stress response. It is important to note that the concept of 'stress' used here is relatively specific. It does not encompass general concepts of 'subjective distress' or 'performance load.' Although these are useful concepts, they are heterogeneous by nature and are not likely to be associated with a specific neurocircuitry. On the other hand, the concept of a stress system that leads to activation of limbic–hypothalamo–pituitary–adrenal axis (LHPA) and secretion of stress hormones like corticotropin-releasing hormone (CRH), adrenocorticotropic hormone, and cortisol is quite specific and is likely to be highly relevant to the neurocircuitry of fear and anxiety. The neurocircuitry governing LHPA activation has been the focus of intense studies in rodents, primates, and humans because it has been repeatedly linked to the neurobiology of mood disorders (which is addressed in detail elsewhere in this volume), but the evidence linking LHPA axis abnormalities to anxiety disorders has been less consistent, sometimes confusing, and often oversimplified. At the same time, some of the same brain regions are implicated in both anxiety and stress responses, suggesting that these responses are interrelated and can influence each other. Furthermore, anxiety and mood disorders are highly comorbid, suggesting that some common abnormalities in neurocircuitry might be present in both disorders. In the following few paragraphs, we briefly address only the structural overlap in neurocircuits and the effects of stress system activation (or stress hormones) on anxiety/fear neurocircuitry.

Epidemiologically, major depression is highly comorbid with anxiety disorders like PTSD, panic disorder, and social phobia (Reiger *et al*, 1990), and anxiety symptoms are highly prevalent in depression (Frances *et al*, 1990). Furthermore, major subcortical components of the LHPA axis (eg, hypothalamus, hippocampus, amygdala, and BNST) have also been identified as key components of anxiety/fear neurocircuitry (albeit sometimes involving different subnuclei, for example paraventricular nuclei *vs* ventromedial hypothalamus for LHPA and fear neurocircuitry, respectively). More recently with the introduction of *in vivo* imaging methodologies in LHPA/stress research, the role of cortical structures like the insula and dorsal mPFC in the activation and inhibition of stress response, respectively, has been reported (Liberzon and Martis, 2006) as well as the role of subgenual ACC in self-induced sadness and depression (Mayberg *et al*, 1999). Together, these findings suggest a significant overlap in structures involved in the stress response and those involved in fear/anxiety responses (eg medial prefrontal cortex, insula, amygdala, hippocampus, and BNST). Finally, with respect to neurotransmitters involved, CRH is likely involved in the orchestration of both LHPA axis activity and many anxiety/fear responses. (For a review see Heim and Nemeroff, 2001.)

The activation of these overlapping regions in functional neuroimaging studies does not necessarily signify, however, activation of both the fear/anxiety response and the LHPA axis. As a matter of fact, activation of fear/anxiety does not necessarily activate an LHPA stress response, even in highly fearful (phobic) individuals (Curtis *et al*, 1976). In turn, activation of LHPA axis is not necessarily experienced subjectively as fear or anxiety. For example, morning awakening, food intake, and nausea all lead to LHPA axis activation without notable increases in subjective sense of fear. It is becoming increasingly clear that specific characteristics of experience (novelty, control, social support, etc.) are more salient for LHPA axis activation than degree of subjective distress or fear (Abelson *et al*, 2007). These facts help to better understand the findings of non-specific, or even sometimes counterintuitive, findings regarding the LHPA and stress responses in anxiety disorders such as panic disorder (Abelson *et al*, 2007) and PTSD (Yehuda, 2006; Yehuda *et al*, 1991). This also suggests that activation in specific cortical regions like mPFC or insula cannot be readily interpreted as a component of the fear response, and has to be considered within a context of a specific experiment, subjective report, symptoms, neuroendocrine profile, etc.

With these caveats in mind, important findings about stress exposure and LHPA axis activation affecting fear/anxiety responses have been accumulating. These can be seen in two general categories: (1) the immediate effects of stress or of stress hormones on fear/anxiety responses (eg, stress or stress hormone exposure immediately precedes, or is present during the fear/anxiety responses), and (2) delayed or developmental effects, (eg, stress exposure during developmentally sensitive periods, like early childhood, modulates fear/anxiety responses later in life). In the former category, it has been reported that exposure to acute stress in healthy individuals potentiates the anxiety response (Grillon *et al*, 2007). In addition, stress exposure (Trier Social Stress Test) led to enhanced galvanic skin responses to conditioned stimuli (CS+) during fear conditioning (Jackson *et al*, 2006). Interestingly, stress modulates fear responses differentially in men and women. Differential effects of stress on fear/anxiety in females *vs* males also have been demonstrated in animal studies.

Chronic stress exposure led to impaired extinction recall of fear conditioning in male but not female rats (Baran *et al*, 2009). Stress exposure in animal studies also led to enhancement in contextual fear conditioning (Cordero *et al*, 2003). The effects of stress hormone exposure are somewhat more difficult to interpret because higher endogenous cortisol levels were associated with higher skin conductance responses (SCR) (Jackson *et al*, 2006), whereas administration of exogenous cortisol led to decreased SCR (Stark *et al*, 2006).

With respect to delayed effects of stress during the vulnerable developmental period, the findings are somewhat complex. Studies of early maternal separation in rodents (Plotsky and Meaney, 1993) and variable foraging in primates (Coplan *et al*, 1996) have revealed long-term alteration in stress axis responses and key neurotransmitter systems (for review see Heim and Nemeroff, 2001). In addition, recent findings of gene-by-environment interactions in PTSD (Binder *et al*, 2008) also point toward the possibility that early childhood experience might modify fear/anxiety neurocircuitry and contribute to the development of anxiety disorders. Direct evidence of these effects on fear/anxiety behavior is less convincing, however, as maternal separation in rat pups, which did alter relevant neurotransmitter systems, did not result in significantly enhanced startle response or decreased open field exploration as compared with non-separated animals (Caldji *et al*, 2000). Similarly, mixed results have been obtained in other studies where rats exposed to severe sporadic stress spent more time in open arms of an elevated plus maze but displayed increases in defensive probe burying behavior. Furthermore, animals exposed to milder chronic stress showed opposite changes (Pohl *et al*, 2007).

The character of the stress exposure (mild *vs* severe, prolonged *vs* short, predictable *vs* non-predictable) and the sex of the individual emerge as important variables that can define the long-term effects of stress exposure, but more experimental data are clearly needed. Similarly, little is known about the specific mechanisms by which stress exposure modulates fear/anxiety circuitry. It has been suggested, as stated above, that early developmental stress exposure alters fear/anxiety circuitry via altered sensitivity and responsivity of the CRH and adrenergic systems, and recent advances in morphological work had suggested a potential mechanism for the effects of stress on fear conditioning and extinction. Chronic stress decreases dendritic branching in the hippocampus (McEwen, 2001) and mPFC (Liston *et al*, 2006; Radley *et al*, 2004), but increases dendritic branching in the amygdala (Mitra *et al*, 2005; Vyas *et al*, 2006). This pattern could lead to increased conditioning and impaired extinction, and both of these processes could contribute changes in anxiety/fear-related behaviors. Future research addressing these important questions will be needed to fully understand the impact of stress/LHPA axis activation on fear/anxiety and the underlying neurocircuitry.

ANXIETY DISORDERS

Posttraumatic Stress Disorder

PTSD can develop in individuals who (1) were exposed to an event or events that involved the threat of death or serious injury and (2) reacted with intense fear, helplessness or horror (APA, 2000). Individuals with PTSD reexperience the traumatic event in the form of nightmares, intrusive recollections, flashbacks, and physiological arousal and distress in response to reminders of trauma. These patients may attempt to avoid reminders of the trauma and may experience a restricted range of effect, especially positive effect. Finally, patients with PTSD report hyperarousal symptoms, such as hypervigilance, exaggerated startle, and difficulty sleeping or concentrating (APA, 2000).

Neurocircuitry models of PTSD implicate the amygdala, mPFC, and hippocampus (Rauch *et al*, 1998b, 2006). According to some models, the amygdala is hyperresponsive in PTSD, which may account for exaggerated fear responses and the persistence of traumatic memories. In addition, portions of the vmPFC (including the rACC) are hyporesponsive and fail to inhibit the amygdala. It is not clear which of the two regions 'drives' the overall outcome, but a hyperresponsive amygdala and hyporesponsive mPFC may potentially lead to deficits in extinction, emotion regulation, attention, and contextual processing (Liberzon and Sripada, 2008). Abnormal hippocampal function may contribute to deficits in contextual processing, as well as impairments in memory and neuroendocrine dysregulation. Although not originally included in early neurocircuitry models, the dACC and insular cortex may have a role in PTSD as well. Recent studies have suggested that the dACC is hyperresponsive in PTSD, perhaps underlying exaggerated fear learning. Finally, the insular cortex appears to be hyperresponsive in PTSD and other anxiety disorders, consistent with the notion that the insula may mediate anxiety proneness (Paulus and Stein, 2006; Simmons *et al*, 2006). (For other models, see Elzinga and Bremner, 2002; Hamner *et al*, 1999; Layton and Krikorian, 2002.)

Amygdala. Several studies have reported increased amygdala activation in PTSD relative to comparison groups in response to trauma-related imagery (Shin *et al*, 1997; Shin *et al*, 2004a), combat-related sounds or smells (Liberzon *et al*, 1999; Pissiota *et al*, 2002; Vermetten *et al*, 2007), trauma-related photographs or words (Driessen *et al*, 2004; Hendler *et al*, 2003; Morey *et al*, 2009; Protopopescu *et al*, 2005), fear conditioning (Bremner *et al*, 2005), and fearful facial expressions (Bryant *et al*, 2008b; Rauch *et al*, 2000; Shin *et al*, 2005; Williams *et al*, 2006). Exaggerated amygdala activation in PTSD has also been found at rest (Chung *et al*, 2006; Semple *et al*, 2000) and during the completion of neutral attention and memory tasks (Bryant *et al*, 2005; Shin *et al*, 2004b). Several studies, however, have found no differential response in the amygdala in PTSD (eg, Bremner *et al*, 1999a; Lanius *et al*, 2001) or even decreased responsivity to negative stimuli (Phan *et al*, 2006a). Interestingly, resilience to PTSD may be associated with

relatively decreased amygdala activation (Britton *et al*, 2005; Osuch *et al*, 2008), and amygdala lesions may reduce the occurrence of PTSD (Koenigs *et al*, 2008). In support of the potential role of amygdala in PTSD, some studies have reported that amygdala activation is positively correlated with PTSD symptom severity (Armony *et al*, 2005; Dickie *et al*, 2008; Pissiota *et al*, 2002; Protopopescu *et al*, 2005; Rauch *et al*, 2000; Shin *et al*, 2004a). Similarly, response to cognitive-behavioral treatment is associated with a decrease in amygdala activation (Felmingham *et al*, 2007; Peres *et al*, 2007), and relatively higher pre-treatment amygdala activation is predictive of a less favorable response to cognitive-behavioral therapy (Bryant *et al*, 2008a).

Relatively few studies have examined amygdala structure and neurochemistry in PTSD. Two studies have reported trends for smaller amygdala volumes in PTSD (Bremner *et al*, 1997; Wignall *et al*, 2004), but several others have not (Bonne *et al*, 2001; De Bellis *et al*, 2001a; Fennema-Notestine *et al*, 2002; Gilbertson *et al*, 2002; Gurvits *et al*, 1996; Lindauer *et al*, 2004b). One recent study using PET and ^{11}C-carfentanil has reported diminished mu-opioid receptor binding in the extended amygdala in trauma-exposed individuals with *vs* without PTSD (Liberzon *et al*, 2007b). Another study has found decreased [^{11}C]flumazenil binding in the left amygdala in PTSD subjects compared with trauma-exposed control participants, consistent with altered GABAergic function in this disorder (Geuze *et al*, 2008a), although two other studies have not reported this finding (Bremner *et al*, 2000a; Fujita *et al*, 2004).

Medial prefrontal cortex. Functional neuroimaging studies of PTSD have reported decreased activation or failure to activate the mPFC (including the rACC, medial frontal gyrus, and subcallosal cortex) during traumatic script-driven imagery (Bremner *et al*, 1999a; Britton *et al*, 2005; Lanius *et al*, 2001; Lindauer *et al*, 2004a; Shin *et al*, 1999, 2004a), the presentation of trauma-related stimuli (Bremner *et al*, 1999b; Hou *et al*, 2007; Yang *et al*, 2004), and negative, non-traumatic stimuli (Kim *et al*, 2007; Lanius *et al*, 2003; Phan *et al*, 2006a; Shin *et al*, 2005; Williams *et al*, 2006). Relatively diminished activation of the mPFC in PTSD also has been shown during extinction (Bremner *et al*, 2005), emotional Stroop interference (Bremner *et al*, 2004; Shin *et al*, 2001), emotional word retrieval (Bremner *et al*, 2003b), non-emotional cognitive tasks (Bryant *et al*, 2005; Semple *et al*, 2000) and at rest (Semple *et al*, 2000). Furthermore, mPFC activation appears to be inversely correlated with PTSD symptom severity (Britton *et al*, 2005; Dickie *et al*, 2008; Hopper *et al*, 2007; Kim *et al*, 2007; Shin *et al*, 2004a, 2005; Williams *et al*, 2006) and positively correlated with pre-scan cortisol levels (Liberzon *et al*, 2007a). Finally, increased mPFC activation following treatment has been positively associated with symptomatic improvement (Felmingham *et al*, 2007; Lansing *et al*, 2005; Peres *et al*, 2007; Seedat *et al*, 2004), although not all studies have shown this, perhaps due to paradigm-related methodological differences (Bryant *et al*, 2008a).

Most of the findings summarized above reflect activation peaks in rostral ACC and *ventral* portions of the mPFC. In contrast, more *dorsal* regions of the ACC (ie, the dACC) appear to have either normal or exaggerated responsivity in PTSD during fear conditioning, interference tasks, an auditory oddball task, and at rest (Bremner *et al*, 2005; Bryant *et al*, 2005; Felmingham *et al*, 2009; Pannu Hayes *et al*, 2009; Shin *et al*, 2001, 2007, in press).

The findings of several studies suggest diminished volumes or gray matter densities in the ACC in PTSD (Corbo *et al*, 2005; Kasai *et al*, 2008; Rauch *et al*, 2003; Woodward *et al*, 2006; Yamasue *et al*, 2003), and smaller ACC volumes have been associated with greater PTSD symptom severity (Woodward *et al*, 2006; Yamasue *et al*, 2003). In a study of monozygotic twins discordant for trauma exposure, diminished gray matter densities in pregenual ACC were not found in the identical twins of the PTSD participants, suggesting that this gray matter density decrease is likely an acquired sign of the disorder rather than a familial risk factor (Kasai *et al*, 2008).

Magnetic resonance spectroscopy (MRS) studies have revealed diminished *N*-acetyl aspartate (NAA) levels in the ACC in PTSD (De Bellis *et al*, 2001b, b; Ham *et al*, 2007a; Mahmutyazicioglu *et al*, 2005; Schuff *et al*, 2008). Furthermore, NAA levels in the pregenual ACC were negatively correlated with the severity of reexperiencing symptoms (Ham *et al*, 2007a). Two recent studies have reported decreased benzodiazepine receptor binding in the mPFC in PTSD (Bremner *et al*, 2000a; Geuze *et al*, 2008a), although one other study failed to find this effect (Fujita *et al*, 2004).

Hippocampus. Some functional neuroimaging studies have reported decreased hippocampal activation during symptomatic states (Bremner *et al*, 1999a) and during memory tasks that involve neutral or emotional stimuli (Astur *et al*, 2006; Bremner *et al*, 2003a, b; Moores *et al*, 2008; Shin *et al*, 2004b). One study found reduced glucose metabolic rate in the hippocampus at rest (Molina *et al*, 2007), and another reported that successful treatment was related to increased hippocampal activation (Peres *et al*, 2007). Other studies, however, have reported increased activation in the hippocampus in PTSD (Geuze *et al*, 2007, 2008b; Sachinvala *et al*, 2000; Semple *et al*, 2000; Thomaes *et al*, 2009; Werner *et al*, 2009) or a positive correlation between hippocampal activation and PTSD symptom severity (Osuch *et al*, 2001; Shin *et al*, 2004b). The direction of hippocampal functional abnormalities appears to depend in part on the type of task and the type of statistical analysis used.

Hippocampal volumes appear to be diminished in PTSD in some (Bossini *et al*, 2008; Bremner *et al*, 1995, 1997, 2003a; Gilbertson *et al*, 2002; Gurvits *et al*, 1996; Karl *et al*, 2006; Kitayama *et al*, 2005; Smith, 2005; Stein *et al*, 1997; Villarreal *et al*, 2002a; Wignall *et al*, 2004; Winter and Irle, 2004; Woon and Hedges, 2008), but not all studies (Bonne *et al*, 2001; Carrion *et al*, 2001; De Bellis *et al*, 1999, 2002; Fennema-Notestine *et al*, 2002; Golier *et al*, 2005; Pederson *et al*, 2004). Hippocampal volumes have been inversely associated with verbal memory deficits (Bremner *et al*, 1995), combat exposure severity (Gurvits *et al*, 1996), dissociative symptom severity (Bremner *et al*, 2003a; Stein *et al*, 1997), depression severity (Villarreal *et al*, 2002a), and

PTSD symptom severity (Bremner *et al*, 2003a; Gilbertson *et al*, 2002; Villarreal *et al*, 2002a). Spectroscopy studies of hippocampus have reported decreased NAA in the hippocampus, often interpreted as consistent with decreased neuronal integrity (Brown *et al*, 2003; Freeman *et al*, 1998; Ham *et al*, 2007a; Mohanakrishnan Menon *et al*, 2003; Schuff *et al*, 2001; Villarreal *et al*, 2002b). The results of two studies suggest that hippocampal volumes may increase following treatment with serotonin reuptake inhibitors (Bossini *et al*, 2007; Vermetten *et al*, 2003).

Whether decreased volumes can explain abnormal hippocampal activation in PTSD is not entirely clear, although the findings of at least two studies suggest that functional abnormalities might be still present even if the volumetric differences are controlled statistically (Bremner *et al*, 2003a; Shin *et al*, 2004b). The origin of decreased hippocampal volumes is not known, although the results of one twin study suggest that diminished hippocampal volumes may be a familial risk factor for developing PTSD following psychological trauma (Gilbertson *et al*, 2002).

With regard to neurochemistry, one recent PET study found decreased [^{11}C]flumazenil binding in the hippocampus (as well as thalamus and cortical areas) suggesting diminished benzodiazepine–$GABA_A$ function in the hippocampus in PTSD (Geuze *et al*, 2008a).

Insular cortex. Relative to comparison groups, increased activation in the insular cortex has been found in PTSD during script-driven imagery (Lanius *et al*, 2007; Lindauer *et al*, 2008), fear conditioning and extinction (Bremner *et al*, 2005), the anticipation of negative images (Simmons *et al*, 2008), the retrieval of emotional or neutral stimuli (Bremner *et al*, 2003b; Werner *et al*, 2009; Whalley *et al*, 2009), aversive smells and painful stimuli (Geuze *et al*, 2007; Vermetten *et al*, 2007), and the performance of an emotional Stroop task (Shin *et al*, 2001). Insular cortex activation has been found to be positively correlated with measures of symptom severity (Carrion *et al*, 2008; Hopper *et al*, 2007; Osuch *et al*, 2001) and post-scan plasma adrenocorticotropic hormone levels (Liberzon *et al*, 2007a). Although greater insular activation in PTSD has been confirmed by a recent voxel-wise meta-analysis (Etkin and Wager, 2007), a few studies have reported either no group differences in insular activation or relatively decreased activation in PTSD (Bremner *et al*, 1999a, 2004; Molina *et al*, 2007; Moores *et al*, 2008; Phan *et al*, 2006a; Shin *et al*, 1999).

Voxel-based morphometry studies of PTSD have reported reduced gray matter density in the insular cortex (Chen *et al*, 2006; Corbo *et al*, 2005; Kasai *et al*, 2008). In one study, gray matter density in the insular cortex was negatively correlated with reexperiencing; that is, lower gray matter density was associated with greater reexperiencing (Kasai *et al*, 2008).

One recent PET-[^{11}C]flumazenil study has reported decreased benzodiazepine–$GABA_A$ receptor binding in bilateral insular cortex in PTSD (Geuze *et al*, 2008a).

Summary. In general, the functional neuroimaging findings in PTSD support the hypothesis that the amygdala is hyperresponsive and ventral portions of medial prefrontal cortex are hyporesponsive, at least in some groups of PTSD patients. Indeed, the latter finding appears to be one of the most robust in the literature (Etkin and Wager, 2007) (Table 1). In addition, albeit in a small number of studies, reduced volumes and gray matter densities in the ACC have been fairly consistently reported. Furthermore, emerging evidence suggests that the dACC and insular cortex may be hyperresponsive in PTSD, although insular cortex hyperresponsivity does not appear to be specific to PTSD (Etkin and Wager, 2007). Finally, the majority of studies have found diminished hippocampal volumes in PTSD patients. Hippocampal function appears to be abnormal as well, although the direction of the abnormality seems to depend on the type of task completed during neuroimaging.

Panic Disorder

Panic disorder patients experience recurrent, unexpected panic attacks, along with a persistent concern about having future attacks, or worry about the implications of the attacks, or a significant change in behavior related to the attacks (APA, 2000). A panic attack is a discrete episode of intense fear, discomfort, and sympathetic nervous system arousal that occurs in the absence of true danger (APA, 2000). According to one of the neurocircuitry models of panic disorder, the 'fear network,' which includes the

Table 1 Summary of the Direction of Functional Neuroimaging Findings in Anxiety Disorders

	Amygdala	rACC	dACC	Hippocampus	Insular cortex
Posttraumatic stress disorder	↑	↓	↑*	↑↓	↑↓
Panic disorder	↑↓*	↑*	—	↑↓	—
Social phobia	↑	↑↓*	↑↓	—	↑
Specific phobia	↑	↑↓*	↑	—	↑
Generalized anxiety disorder	↑↓*	↑*	↑*	—	—

rACC = rostral anterior cingulate cortex; dACC = dorsal anterior cingulate cortex.
↑ = increased function in the disorder (relative to control groups).
↓ = decreased function in the disorder (relative to control groups).
↑↓ = mixed findings.
* = based on a very small number of studies.
— = too little information available.

amygdala, hippocampus, thalamus, and brain stem structures, is hypersensitive. Furthermore, frontal cortex fails 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 (Coplan and Lydiard, 1998; Gorman *et al*, 2000). This type of model is similar to the models proposed for other anxiety disorders such as PTSD. Indeed, PTSD patients often suffer from comorbid panic attacks (Falsetti and Resnick, 1997). Although it is quite possible that PTSD and panic disorder indeed share similar pathophysiological components, it will be important in the future to identify abnormalities that are disorder specific and are responsible for disorder-specific symptomatology.

Amygdala. Hyperactivation of the amygdala in panic disorder has been reported in response to panic-related words (van den Heuvel *et al*, 2005b) and neutral faces (Pillay *et al*, 2007). One recent PET study found greater resting glucose metabolism in the amygdala (Sakai *et al*, 2005), although amygdala glucose metabolism did not change after effective treatment with cognitive-behavioral therapy (Sakai *et al*, 2006). The possibility that amygdala hyperactivation is present in a subgroup of panic disorder patients has been supported by recent studies examining the effect of genotypes within patients with panic disorder. These have revealed greater amygdala activation in carriers of the COMT 158val allele (Domschke *et al*, 2008), the 5-HT1A x1019 GG allele, and the short allele of the serotonin transporter polymorphism (Domschke *et al*, 2006). In contrast, two studies found relatively decreased amygdala activation during anticipatory anxiety (Boshuisen *et al*, 2002) and in response to fearful facial expressions (Pillay *et al*, 2006), although the latter finding may be attributed to the fact that panic disorder patients were taking antidepressants, which have been found to decrease amygdala activation (Harmer *et al*, 2006).

The volumetric findings in the amygdala of panic disorder patients are very sparse. One study reported smaller bilateral amygdala volumes in panic disorder compared with healthy participants (Massana *et al*, 2003). The same group reported reduced levels of creatine and phosphocreatine in the right medial temporal lobe (including the amygdala and part of the hippocampus) in panic disorder. This was interpreted as potentially representing a hypermetabolic state in the right medial temporal region (Massana *et al*, 2002), which would be consistent with the findings of Sakai *et al* (2005). Finally, with respect to relevant neurotransmission findings, SPECT and PET studies have reported decreased GABA–benzodiazepine receptor binding in the medial temporal lobes (Kaschka *et al*, 1995; Malizia *et al*, 1998) and decreased 5-HT1$_A$ receptor binding in the amygdala in panic disorder (Nash *et al*, 2008).

Medial prefrontal cortex. Consistent with the literature on pharmacologically induced fear and panic in healthy volunteers, studies of panic disorder have revealed increased rACC activation during imagery of high *vs* low anxiety situations (Bystritsky *et al*, 2001), anticipatory anxiety (Boshuisen *et al*, 2002), and in response to happy faces in panic disorder (Pillay *et al*, 2007), although medication was a potential confound in the latter study. Dorsal ACC hyperresponsivity has also been reported in panic disorder in one study (Pillay *et al*, 2007). Panic disorder patients who are carriers of the COMT 158val allele appear to have less medial prefrontal deactivation and greater orbitofrontal activation in response to emotional facial expressions (Domschke *et al*, 2008). In contrast, panic disorder subjects with the 5-HT1A x1019 GG allele had less ACC, medial prefrontal cortex, and orbitofrontal activation in response to fearful facial expressions (Domschke *et al*, 2006).

Volumetric evidence is again sparse, but it appears that both dACC and rACC might be exhibiting similar types of change. Gray matter volumes appear to be reduced in the rACC (Asami *et al*, 2008; Uchida *et al*, 2008) and dACC (Asami *et al*, 2008), and white matter integrity, as measured by DTI, appears to be enhanced in the rACC in panic disorder (Han *et al*, 2008).

Two studies have reported decreased GABA$_A$–benzodiazepine receptor binding in the ACC and medial prefrontal cortex, including in the dACC (Hasler *et al*, 2008; Malizia *et al*, 1998), and one study found a negative correlation between panic attack symptom severity and benzodiazepine receptor binding in dorsal medial frontal gyrus (Bremner *et al*, 2000b). An MRS study reported increased lactate and choline levels in the rACC (Ham *et al*, 2007b), and two PET studies have reported decreased 5-HT1$_A$ receptor binding in the anterior cingulate in panic disorder (Nash *et al*, 2008; Neumeister *et al*, 2004).

Hippocampus. The evidence for hippocampal involvement in panic disorder comes mainly from studies of metabolism and perfusion. Two PET studies of panic disorder have reported abnormalities in the laterality of hippocampal resting glucose metabolic rates (Nordahl *et al*, 1990, 1998), and two PET studies have found greater resting glucose metabolism in the hippocampus in patients with panic disorder (Bisaga *et al*, 1998; Sakai *et al*, 2005). In contrast, a SPECT study has reported reduced perfusion in the hippocampus in panic disorder (De Cristofaro *et al*, 1993). Two studies have reported decreased GABA$_A$–benzodiazepine receptor binding in the hippocampus (Bremner *et al*, 2000b; Malizia *et al*, 1998), and one study has reported the opposite finding (Hasler *et al*, 2008).

Insular cortex. With regard to the insular cortex in panic disorder, studies have reported decreased activity during anticipatory anxiety (Boshuisen *et al*, 2002), increased gray matter volume (Protopopescu *et al*, 2006; Uchida *et al*, 2008), decreased 5-HT1$_A$ receptor binding (Nash *et al*, 2008), and decreased GABA$_A$–benzodiazepine receptor binding (Malizia *et al*, 1998).

Brain stem. Functional neuroimaging studies have reported increased glucose metabolic rates (Sakai *et al*, 2005) and increased activity during anticipatory anxiety (Boshuisen *et al*, 2002) in the brain stem in panic disorder. Gray matter

volume appears to be increased in the midbrain and pons (Protopopescu *et al*, 2006; Uchida *et al*, 2008). Decreased $GABA_A$–benzodiazepine receptor binding was reported in the pons (Malizia *et al*, 1998), and two studies have found decreased 5-$HT1_A$ receptor binding in the raphe nucleus in panic disorder (Nash *et al*, 2008; Neumeister *et al*, 2004).

Summary. Several studies have provided evidence consistent with amygdala and brain stem hyperresponsivity in panic disorder. Activation in rACC and dACC appears to be increased, and gray matter volumes in these regions appear to be decreased. Several studies have reported decreased $GABA_A$–benzodiazepine and 5-HT_{1A} receptor binding in the amygdala, medial prefrontal cortex, insular cortex, and brain stem in panic disorder. A common limitation seen in several neuroimaging studies of this disorder is the inclusion of participants taking psychiatric medications (Domschke *et al*, 2006, 2008; Han *et al*, 2008; Pillay *et al*, 2006, 2007; Uchida *et al*, 2008). Thus, the findings of such studies should be interpreted cautiously pending replication in medication-free participants.

Social Phobia

Social phobia (or social anxiety disorder) is characterized by a marked and persistent fear of social or performance situations involving possible scrutiny by others (APA, 2000). The fear of embarrassment and distress can lead to avoidance of social situations and impairment in social, occupational, and academic functioning. The amygdala and medial prefrontal cortex have been considered important regions of interest in this disorder (Amaral, 2002; Liebowitz *et al*, 2005; Mathew *et al*, 2001; Stein *et al*, 2002a; Stein, 1998).

Amygdala. Exaggerated amygdala responses in social phobia have been observed during public speaking (Tillfors *et al*, 2001), the anticipation of public speaking (Lorberbaum *et al*, 2004; Tillfors *et al*, 2002), negative comments (Blair *et al*, 2008a), and in response to neutral, angry, contemptuous, happy, and schematic angry facial expressions (Birbaumer *et al*, 1998; Blair *et al*, 2008b; Cooney *et al*, 2006; Evans *et al*, 2008; Gentili *et al*, 2008; Guyer *et al*, 2008; Phan *et al*, 2006b; Schneider *et al*, 1999; Stein *et al*, 2002b; Straube *et al*, 2004a, 2005; Veit *et al*, 2002; Yoon *et al*, 2007). One study found temporally delayed amygdala responses to faces in a social phobia group compared with a healthy control group (Campbell *et al*, 2007). In addition, amygdala responses in social phobia have been positively correlated with self-reported fear increases (Tillfors *et al*, 2001), severity of social anxiety symptoms (Blair *et al*, 2008b; Evans *et al*, 2008; Guyer *et al*, 2008; Phan *et al*, 2006b), and state-trait anxiety scores (Cooney *et al*, 2006). The genetic predisposition for social phobia has been supported by the finding that social phobia patients with a short allele of the serotonin transporter polymorphism had greater amygdala responses during public speaking compared to those with long alleles (Furmark *et al*, 2004). Finally, amygdala activation during public speaking in social phobia appears to decrease with successful treatment (Furmark *et al*, 2002, 2005). In contrast, one recent study found decreased amygdala activation during script-driven imagery of anxiety-provoking social situations and a mental arithmetic task in social phobia (Kilts *et al*, 2006). One study has reported reduced 5-HT_{1A} receptor binding in the amygdala in this disorder (Lanzenberger *et al*, 2007).

Medial prefrontal cortex. Exaggerated rACC activation in social phobia has been found in response to facial expressions of fear (Blair *et al*, 2008b) and disgust (Amir *et al*, 2005), and in response to pictures of peers with whom patients did not want to interact (Guyer *et al*, 2008). One study reported greater orbitofrontal cortex activation to angry *vs* neutral prosody (Quadflieg *et al*, 2008). In contrast, other studies have found decreased activation (Van Ameringen *et al*, 2004) and decreased glucose metabolic rates in the ventromedial prefrontal cortex (Evans *et al*, 2009), which increased following treatment with tiagabine (Evans *et al*, 2009). Glutamate/creatine and NAA/creatine ratios appear to be elevated in the rACC and are correlated with symptom severity (Phan *et al*, 2005).

Studies of dACC function in social phobia also have been somewhat mixed. Greater dACC activation has been reported in response to negative comments (Blair *et al*, 2008a) and harsh or disgusted facial expressions (Amir *et al*, 2005; Phan *et al*, 2006b). Another study reported greater dorsal medial frontal activation in response to harsh faces (Stein *et al*, 2002b). Treatment with nefazodone-decreased activation in dACC (Kilts *et al*, 2006). In contrast, other studies have found decreased dACC activation to schematic angry faces (Evans *et al*, 2008) and in anticipation of public speaking (Lorberbaum *et al*, 2004), as well as decreased glucose metabolism at rest (Evans *et al*, 2009). One study found temporally delayed medial prefrontal cortex/dACC responses to faces in social phobia, which may help to account for the heterogeneity of findings in the literature regarding this structure (Campbell *et al*, 2007). Finally, one study reported reduced 5-HT_{1A} receptor binding in the anterior cingulate in social phobia, although whether this finding occurred in the dorsal or rostral ACC was not specified (Lanzenberger *et al*, 2007).

Insular cortex. Insular cortex activation appears to be elevated in social phobia during the anticipation of public speaking (Lorberbaum *et al*, 2004) and in response to emotional facial expressions (Amir *et al*, 2005; Gentili *et al*, 2008; Straube *et al*, 2004a, 2005; Yoon *et al*, 2007), including schematic facial expressions (Evans *et al*, 2008; Straube *et al*, 2004a). Two studies, however, found decreased insular cortex activation during public speaking (Tillfors *et al*, 2001) and during an implicit sequence-learning task in social phobia (Sareen *et al*, 2007). One study has found reduced 5-HT_{1A} receptor binding in the insular cortex in this disorder (Lanzenberger *et al*, 2007).

Striatum. One recent study has found reduced caudate activation during an implicit sequence-learning task in generalized social phobia (Sareen *et al*, 2007). Other studies have found reduced D_2 receptor binding and dopamine transporter densities in the striatum in social phobia (Schneier *et al*, 2000; Tiihonen *et al*, 1997), although a

recent study failed to replicate these findings (Schneier *et al*, 2009).

Summary. Exaggerated amygdala activation has been the most consistent functional neuroimaging finding in the social phobia literature. Although several studies have reported exaggerated rACC and insular cortex activation as well, a number of other studies have reported contradictory findings. Future research will have to: (1) address questions regarding ACC/mPFC and insular involvement, potentially utilizing cognitive activation tasks to probe ACC function, and (2) attempt to identify the neurocircuitry specific to social phobia (eg, the regions that contribute to the perception/interpretation of social stimuli as particularly anxiety/fear inducing).

Specific Phobia

Specific phobias are marked by excessive, unreasonable and persistent fear of specific objects or situations such as small animals, flying, enclosed places, heights, and blood/injury (APA, 2000). The fear and avoidance causes significant distress and/or impairment in occupational, academic, or social functioning. Specific phobia is a relatively common disorder, with a lifetime prevalence of 7–11% (APA, 2000). Early models of the etiology of phobias centered on fear conditioning and extinction, and therefore implicated the amygdala and medial prefrontal cortex. Admittedly, such fear conditioning models are likely to be incomplete given that (1) many individuals with phobias cannot recall a conditioning event, and (2) only a small number of common stimuli or situations are the objects of phobias (Fyer, 1998). Nevertheless, fear conditioning and extinction models have been useful in guiding neuroimaging researchers toward examining amygdala, medial prefrontal cortex, and insular cortex function in this disorder.

Amygdala. Exaggerated amygdala activation in individuals with specific phobia has been observed in response to phobia-related pictures (Dilger *et al*, 2003; Goossens *et al*, 2007a, b; Schienle *et al*, 2005, 2007; Straube *et al*, 2006b; Veltman *et al*, 2004; Wendt *et al*, 2008). In addition, treatment has been associated with decreased amygdala activation (Goossens *et al*, 2007b; Schienle *et al*, 2007). However, numerous studies have not reported exaggerated amygdala activation in specific phobia (Hermann *et al*, 2007; Larson *et al*, 2006; Paquette *et al*, 2003; Straube *et al*, 2004b, 2007; Wik *et al*, 1996, 1997; Wright *et al*, 2003), perhaps in part due to methodological differences, such as the use of different imaging modalities, type of stimuli (verbal *vs* pictorial), mode of presentation (video clips *vs* stills), or phobia-unrelated facial expressions. Preliminary findings assessing the NK1 receptor have suggested enhanced levels of endogenous neuropeptide substance P (commonly associated with stress and negative affect) in the amygdala in phobics when presented with phobia-relevant pictures (Michelgard *et al*, 2007).

Medial prefrontal cortex. The findings with regard to the rACC in specific phobia are mixed, with two studies showing less rACC activation in phobia groups in response to phobia-related *vs* neutral pictures (Hermann *et al*, 2007; Schienle *et al*, 2007), and two studies reporting enhanced rACC activation to phobia-related stimuli (Britton *et al*, 2009; Pissiota *et al*, 2003). Activation in the rACC appears to be positively correlated with anticipatory anxiety in phobia patients (Straube *et al*, 2007). The rACC has been shown to be thicker in participants with specific phobias relative to control participants without phobias (Rauch *et al*, 2004).

In contrast, the results of functional neuroimaging studies are much more consistent with regard to the dACC, which has been found to be hyperresponsive to phobia-related stimuli (Goossens *et al*, 2007a, b; Straube *et al*, 2006a, b) or the anticipation of such stimuli (Straube *et al*, 2007). In addition, dACC activation in specific phobia decreases after habituation (Veltman *et al*, 2004) and cognitive-behavioral treatment (Goossens *et al*, 2007b; Straube *et al*, 2006a).

Insular cortex. Recent research has reported exaggerated insular cortex activation in specific phobia *vs* control cohorts in response to phobia- or fear-related pictures, videos, and words (Dilger *et al*, 2003; Goossens *et al*, 2007a, b; Schienle *et al*, 2005; Straube *et al*, 2004b, 2006b, 2007; Wendt *et al*, 2008), as well as fearful facial expressions (Wright *et al*, 2003). In addition, treatment studies have reported decreased insula activation following cognitive-behavioral treatment (Goossens *et al*, 2007b; Schienle *et al*, 2007; Straube *et al*, 2006a). Insular cortex also appears to be thicker (bilaterally) in participants with specific phobia as compared with healthy control participants (Rauch *et al*, 2004).

Summary. The amygdala, dACC and insular cortex all appear to be hyperresponsive to phobia-related stimuli in specific phobia. These abnormalities tend to normalize with successful treatment. The findings are few and mixed with regard to the rACC.

Obsessive–Compulsive Disorder

Patients with obsessive–compulsive disorder (OCD) experience recurrent, unwanted thoughts or images (obsessions) that cause distress, and engage in excessive ritualistic behaviors or mental acts (compulsions) that are typically carried out in response to the obsessions (APA, 2000). Because OCD is covered more extensively in another chapter, we only very briefly discuss it here (see also Friedlander and Desrocher, 2006; Menzies *et al*, 2008). In general, abnormalities in thalamo-cortico–striatal loops have been posited to account for the repetitive quality and the cognitive and motor content of the obsessions and compulsions in OCD. One neurocircuitry model of OCD posits that the striatum (caudate nucleus) functions abnormally, leading to inefficient gating in the thalamus (Graybiel and Rauch, 2000; Rauch *et al*, 1998a). This may lead to hyperactivity in the orbitofrontal cortex and the anterior cingulate cortex, which may mediate intrusive thoughts and anxiety, respectively. Compulsions may serve to recruit the striatum and to achieve thalamic gating,

thereby neutralizing the obsessions and reducing anxiety. Thus, the fear/anxiety-related brain regions that we have focused on so far (eg, amygdala, mPFC, insula, and hippocampus) do not appear to mediate the core OCD symptomatology. It is interesting to note here that the neurocircuitry model of OCD is much further developed (eg, nodes, links, and directionality are better specified) than the models of other anxiety disorders. There could be a number of factors contributing to this: (1) OCD has been studied longer than other anxiety disorders; (2) The nature of OCD symptoms (for example the predominant cognitive component) implicated neurocircuitry that is better understood or is organized in a way that renders itself easier for the development of circuitry-based models. Whatever the reason might be, one of the goals for future research in other anxiety disorders should be to strive to develop neurocircuitry hypotheses that are comparable in detail and specifications to the models that are already available for OCD.

Although some functional neuroimaging studies have found elevated amygdala activation in OCD (Breiter *et al*, 1996b; van den Heuvel *et al*, 2004; Van Laere *et al*, 2006), the majority have not, even with facial expression paradigms that are known to activate the amygdala in healthy subjects and patients with other anxiety disorders (Cannistraro *et al*, 2004). The preponderance of neuroimaging studies have identified functional and/or structural abnormalities in the components of thalamo–cortico–striatal loops: striatum (Bartha *et al*, 1998; Baxter *et al*, 1987, 1988; Chen *et al*, 2004; Rauch *et al*, 1994, 1997; Remijnse *et al*, 2006; Robinson *et al*, 1995; Rosenberg *et al*, 1997; van den Heuvel *et al*, 2005a), thalamus (Atmaca *et al*, 2006; Chen *et al*, 2004; Fitzgerald *et al*, 2000; Gilbert *et al*, 2000), orbitofrontal cortex (Baxter *et al*, 1987, 1988; Chamberlain *et al*, 2008; Chen *et al*, 2004; Kang *et al*, 2004; Rauch *et al*, 1994; Remijnse *et al*, 2006; Valente *et al*, 2005), and the ACC (Ebert *et al*, 1997; Fitzgerald *et al*, 2005; Rauch *et al*, 1994; Valente *et al*, 2005). In addition, recent receptor imaging studies in OCD have revealed reduced serotonin transporter availability in the thalamus and midbrain (Reimold *et al*, 2007), as well as reduced 5-HT_{2A} receptor availability in the ACC and other frontal cortical areas (Perani *et al*, 2008). One interesting and unanswered question remains: If OCD is indeed associated with very high anxiety states, especially linked to specific worries or compulsions, why doesn't the circuitry associated with other anxiety disorders or state anxiety in healthy controls have a more prominent role in the expression of this anxiety?

Generalized Anxiety Disorder

Generalized anxiety disorder (GAD) is characterized by excessive diffuse anxiety and worry that is difficult to control. Patients with GAD may experience restlessness, fatigue, irritability, muscle tension, and sleep and concentration difficulties (APA, 2000). Relatively few neuroimaging studies of GAD exist in the literature and some of the findings are conflicting; however, some studies have implicated the amygdala and medial prefrontal cortex in this disorder.

Amygdala. Exaggerated amygdala activation in response to fearful (McClure *et al*, 2007b) and masked angry facial expressions (Monk *et al*, 2008) and during the anticipation of aversive photographs (Nitschke *et al*, 2009) has been reported in patients with GAD. In a mixed cohort of subjects with GAD and social phobia, subjects who had a low tolerance for uncertainty had elevated amygdala activation during a decision-making task (Krain *et al*, 2008). In a study of adolescents with GAD, amygdala responses were positively correlated with GAD symptom severity (Monk *et al*, 2008). However, other studies have not found exaggerated amygdala activation in GAD (Blair *et al*, 2008b; Whalen *et al*, 2008). In a recent treatment study, greater pre-treatment left amygdala activation to fearful faces was associated with a less favorable response to venlafaxine (Whalen *et al*, 2008); in contrast, a different study on a pediatric GAD sample found that greater pre-treatment left amygdala activation to fearful faces was associated with a more favorable response to cognitive-behavioral treatment (McClure *et al*, 2007a). One study has reported larger amygdala volumes in pediatric GAD (De Bellis *et al*, 2000a).

Medial prefrontal cortex. Although the literature is currently very small, it appears that medial prefrontal cortex activation may be elevated in GAD. Activation in dACC and rACC appears to be elevated in response to fearful facial expressions in adolescents with GAD (McClure *et al*, 2007b). In a mixed cohort of subjects with GAD and social phobia, those with higher intolerance for uncertainty had elevated rACC and subgenual ACC activation during a decision-making task (Krain *et al*, 2008). In addition, dorsal ACC activation in response to worry *vs* neutral statements declined significantly after treatment with citalopram (Hoehn-Saric *et al*, 2004). Finally, greater pre-treatment rACC activation in response to fearful facial expressions (Whalen *et al*, 2008) and the anticipation of emotional stimuli (Nitschke *et al*, 2009) was associated with a more favorable response to venlafaxine. Regions in lateral prefrontal cortex also appear to show exaggerated activation (Monk *et al*, 2006) and elevated NAA/creatine ratios in GAD (Mathew *et al*, 2004).

Summary. Although there is some evidence for exaggerated amygdala and medial prefrontal cortex responses in GAD, there are too few studies to form conclusions about the role of these structures in the pathophysiology of GAD. Future functional neuroimaging studies using fearful facial expressions and tasks that probe medial prefrontal cortex function (eg, extinction, emotion regulation, or interference tasks) might be able to contribute the much needed additional information regarding amygdala and medial prefrontal cortex function in GAD.

Summary

Overall, the findings of functional neuroimaging studies are consistent with the notion of exaggerated amygdala

activation to specific stimuli in a number of anxiety disorders, especially social phobia, specific phobia, and PTSD. Facial expressions have been especially effective probes of amygdala responses in social phobia and PTSD. Interestingly, the data regarding amygdala function in panic disorder are still inconclusive, and given that relatively few studies have examined amygdala function in GAD, additional research is needed to make meaningful comparisons of amygdala responses between various anxiety disorders. Although increased amygdala activation has been observed in a few studies of OCD, the overall pathophysiology of OCD appears to be localized to a different brain circuit. One potential conceptualization of these findings is that amygdala hyperactivation is a common pathway for exaggerated anxiety/fear that is triggered by specific stimuli. Thus anxiety disorders that manifest increased fear/anxiety that is associated with specific identifiable stimuli (eg, PTSD, social phobia, and specific phobia) will have evidence of exaggerated amygdala reactivity. Panic attacks, on the other hand, can occur in the absence of such stimuli and might thus involve activation of other structures within fear/anxiety neurocircuitry (such as brain stem nuclei, periaqueductal gray, and mPFC). If this is the case, it can explain why the degree of amygdala activation in panic disorder may vary depending on the presence of identified panic-related stimuli and/or other brain regions activated. Conceptually, the hyperresponsivity of amygdala and brain stem is consistent with cognitive and somatic manifestation of panic attacks; however, hyperactivation of the anterior cingulate is probably more consistent with compensatory/regulatory roles rather than reflecting panic-specific pathophysiology.

Consistent with the findings of the meta-analysis of Etkin and Wager (2007), relatively diminished rACC activation has been reported fairly consistently in PTSD, but not in other anxiety disorders. Thus, relatively diminished rACC function may be specific to PTSD and could reflect abnormalities in recall/contextualization of fear memories. Activation in other regions like the dACC and insular cortex appears to be elevated in PTSD and in several of the other anxiety disorders. Exaggerated activation in these regions may reflect various aspects of anxiety/fear response, such as anticipatory anxiety, interoceptive components, autobiographic memory, or anxiety proneness (Paulus and Stein, 2006; Shin *et al*, in press; Simmons *et al*, 2006). Together these findings can be conceptualized as an evidence of hyperresponsive threat detection, autobiographic memory, and somatic/physiological reactivity systems in PTSD, accompanied by the failure in regulatory regions responsible for safety signaling, fear extinction, and stimulus appraisal, together leading to aberrant contextual processing of the threat-related stimuli.

The hippocampus was studied most frequently in PTSD and panic disorder, but rarely in the other disorders. Thus, whether similar structural and functional abnormalities in the hippocampus occur in other anxiety disorders is uncertain. Although the evidence for hippocampal involvement in memory and contextual processing is strongly supported by animal studies, and deficits in hippocampal function (eg, contextual processing) are consistent with the PTSD model outlined above, more information is needed to understand the role of the hippocampus in anxiety disorders.

However, neuroimaging studies of anxiety disorders are not without limitations. On the technical side, the spatial resolution of functional neuroimaging techniques is limited, and even those techniques with the best spatial resolution (fMRI) cannot accurately differentiate between very small adjacent structures (such as subnuclei of the amygdala). This, in addition to the presence of susceptibility artifacts (in the case of fMRI studies), makes resolution of potentially important structures, such as the hypothalamus and brain stem nuclei, particularly problematic for studies of fear/anxiety neurocircuitry. In addition, the temporal resolution of some of the imaging techniques used (ie, PET and SPECT) makes it difficult to detect quick and transient responses to stimuli. On the clinical side, the use of medications (ie, antidepressants or benzodiazepines) in patient groups can affect brain activation and represent a confounding factor. However, for regions such as the amygdala, medications tend to normalize amygdala responses rather than exaggerate them (Harmer *et al*, 2006; Paulus *et al*, 2005). Comorbidity represents a challenge as well. The majority of patients with anxiety disorders have comorbid conditions, such as depression. Although it is tempting to exclude from neuroimaging studies those anxiety disorder patients with comorbid conditions, this procedure raises concerns about the ability to generalize findings to the larger population of individuals with anxiety disorders. Recent studies have attempted to deal with this issue by separating anxiety disorder patients into groups with and without comorbidity (Kemp *et al*, 2007; Lanius *et al*, 2007).

FUTURE RESEARCH DIRECTIONS

Although much information that is relevant to the pathophysiology of anxiety disorders has been gained over the last two decades, many research questions remain to be answered. As we have noted previously, questions remain regarding the specific roles of the amygdala, medial prefrontal cortex, insula, and hippocampus in the anxiety disorders. In addition, one of the more general and basic questions is whether the functional abnormalities identified in anxiety disorders represent acquired signs of the disorders or vulnerability factors that increase the risk of developing the disorders. For example, does amygdala hyperresponsivity occur after the symptoms of social phobia, specific phobia, or PTSD appear? Or does the amygdala hyperresponsivity precede the development of symptoms and increase the risk for developing them? Two types of studies could be used to try to address these

questions. First, longitudinal studies that include functional neuroimaging could assess functional activation before the onset of anxiety symptoms (or before trauma exposure in the case of PTSD) to determine whether baseline amygdala activation predicts (or increases the risk for) subsequent anxiety disorder diagnoses. One recent study using a variant of this longitudinal design has yielded findings suggesting that amygdala activation may represent a vulnerability factor. In this study, amygdala activation in response to novel faces was studied in adults who were categorized in childhood as either behaviorally inhibited or uninhibited (Schwartz *et al*, 2003). Behavioral inhibition in childhood is a known risk factor for the development of social anxiety later in life (Biederman *et al*, 2001; Schwartz *et al*, 1999). Amygdala activation was greater in the inhibited group as compared with the uninhibited group, and this finding remained even when inhibited subjects with social phobia were removed from the analyses. Although this study does not provide definitive proof that exaggerated amygdala activation is a vulnerability factor for the development of social phobia, it does lend some support to the idea.

The second type of study that can help determine whether functional abnormalities are acquired characteristics or vulnerability factors involves studying the identical twins of probands with *vs* without the disorder in question. With regard to PTSD, Roger Pitman and colleagues have studied combat veterans with PTSD and their combat-unexposed identical co-twins without PTSD, as well as combat veterans who never had PTSD and their identical combat-unexposed co-twins without PTSD. Structural and functional abnormalities that are observed in both the individuals with PTSD and their identical trauma-unexposed co-twins likely represent familial vulnerability factors, whereas abnormalities that are observed only in the individuals with PTSD would be consistent with acquired characteristics. Using this type of design, diminished hippocampal volumes (Gilbertson *et al*, 2002) and dACC hypermetabolism (Shin *et al*, in press) appear to be familial vulnerability factors, whereas diminished gray matter volumes in the rACC appear to be acquired characteristics (Kasai *et al*, 2008).

This twin design, however, is unable to determine whether familial vulnerability is attributable to genetic *vs* environmental factors. Future studies will be needed to determine whether the functional abnormalities that appear to be familial vulnerability factors are associated with specific genotypes. For example, dACC hypermetabolism has been reported in healthy carriers of the short allele of the serotonin transporter polymorphism (Graff-Guerrero *et al*, 2005). The prevalence of the short allele appears to be elevated in PTSD (Lee *et al*, 2005), and the finding of dACC hypermetabolism in individuals with PTSD and their identical co-twins could be at least in part attributable to the presence of this short allele. Future studies will evaluate this possibility. Studies that examine links between specific genotypes and endophenotypes (eg, neuroimaging or neuroendocrine measures) that may predispose individuals to various anxiety disorders following environmental modulation (during development or in adulthood) are likely to prove very valuable in future research.

Much more progress is urgently needed in examining *in vivo* neurochemistry in anxiety disorders. SPECT, PET, and MRS studies are needed to link functional neuroimaging data with cellular and molecular changes that might be driving these abnormalities. Finally, another major future direction would entail using functional neuroimaging to predict treatment response in patients with anxiety disorders. This type of research has recently begun, and some studies have reported that greater amygdala activation at a pre-treatment baseline predicts a less favorable response to (1) cognitive-behavioral therapy in PTSD (Bryant *et al*, 2008a), and (2) venlafaxine in GAD (Whalen *et al*, 2008). Future studies will be needed to determine whether specific pre-treatment functional neuroimaging profiles can distinguish between those who will respond to medication *vs* cognitive-behavioral treatments. One ultimate goal of this research would be to determine whether functional neuroimaging measures can be used to guide treatment choice for individual patients.

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The authors have no conflicts or disclosures.

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APPENDIX

Introduction

I. Fear neurocircuitry in healthy humans
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IV. Future research directions