17.1 Introduction

In this chapter, a central idea we explore is that clinical anxiety involves changes in brain systems that are involved in the generation and regulation of normal emotion. In particular, a common element of anxiety disorders may be an abnormally elevated threat response, which appears to involve brain systems implicated in “fear” responses and “fear learning” in animals and healthy humans. However, some anxiety disorders, such as posttraumatic stress disorder (PTSD), generalized anxiety disorder (GAD), and panic disorder, appear to involve a more generalized dysregulation of negative affect. Interestingly, “fear-like” and “anxiety-like” behaviors in animal models may be different, and their brain substrates dissociable. Thus, a brain-based model of anxiety must also consider brain systems involved in negative affective states that extend beyond what has traditionally been labeled as “fear.” In this chapter, we will review the neural basis of anxiety in healthy and clinical populations, with a primary focus on functional neuroimaging studies in humans.

17.2 The “neural reference space” for emotion

“Emotion” – comprising a collection of specific thoughts, feelings, and action tendencies – is thought to emerge from one of two broad, interacting routes: (1) reactivity to a simple stimulus (such as seeing a spider) or (2) appraisal of one or more stimuli in a particular situational context. The neural reference space for emotion is thus, unsurprisingly, complex. A number of consistently activated regions from a recent meta-analysis of 163 studies are shown in Figure 17.1A. These include the amygdala; insula; ventral striatum and pallidum; periaqueductal gray (PAG); hypothalamus; medial prefrontal (mPFC), inferior frontal (IFC), and temporal cortices; and cerebellum – in short, many of the regions implicated in animal and human studies of emotional experience and emotional learning.

It is difficult to describe a particular region or set of regions with a simple label, such as “appraisal,” or even “fear.” Thus, instead we adopted a “bottom-up” approach to understanding how these regions assemble into functional networks by grouping them based on their patterns of co-activation. That is, if the studies that activated the right IFC were the same studies that activated the left IFC and the dorso-medial PFC (dmPFC), these regions were grouped into a functional network. The hope is that these networks may then be related to psychological concepts such as “appraisal” and “anxiety” or map onto physiological processes or action tendencies. Moreover, because our semantic labels may not correspond cleanly with specific brain systems, understanding the organization of brain systems in emotion is also a key step towards reformulation of psychological categories to better reflect brain processes.

Our analyses identified a number of networks, shown in Figure 17.1. Figure 17.1A shows an “unfolded” map of the key brain regions in two dimensions. Each dot is a brain region, and the different colors of the dots indicate the functional groups to which they belong. The closer two dots are, the more highly co-activated they are across studies. Lines connecting the dots indicate statistically significant co-activation of the pair of connected regions. These functional groups of regions provide a rudimentary organizational framework for understanding specific components of emotional processing. Shown in yellow and magenta in Figure 17.1A is a network involving occipital sensory and association and posterior cingulate cortices, which monitor and analyze the sensory environment. These networks provide input into amygdala and other “core”...
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17.3 Brain substrates of negative reactivity and regulation

17.3.1 Fear conditioning as a core model of negative emotional reactivity

Animal studies of fear learning have provided a solid and detailed body of evidence for understanding a particular type of negative emotional reactivity – learned “fear-like” responses to cues that have been paired with aversive events in a conditioning procedure.

limbic regions (red in Figure 17.1A) and paralimbic regions (green). An interconnected network of frontal regions (aqua) whose member regions are commonly activated in tasks involving cognitive control is connected to the paralimbic network. This frontal network provides a way for items to be held in the conscious “workspace” of working memory and to influence core limbic regions. Finally, the mPFC group (blue) is closely functionally related to the core limbic regions, suggesting that the mPFC is therefore in a position to govern, and be governed by, the core limbic regions.
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The behavioral expression of fear involves a pathway from the basolateral amygdala (BLA) to the central nucleus in the superior portion of the amygdala, which projects to the PAG and hypothalamus (Paxinos 2003). Stimulation of the PAG produces coordinated patterns of physiological and behavioral changes consistent with a whole-organism response mode (Bandler & Shipley 1994, Behbehani 1995). Its projections to the orbitofrontal cortex (OFC) and mPFC, the mediodorsal thalamic “association” nucleus, and neuromodulatory systems, such as the noradrenergic system, govern arousal and regulate behavior.

Substantial evidence corroborates the role of the human amygdalar complex in negative emotion-related reactivity, including numerous studies that have demonstrated conditioned responses in the amygdala to threat cues (Buchel & Dolan 2000, Etkin & Wager 2007, LaBar et al. 1998). While the amygdala appears to be a critical region for Pavlovian fear learning and an important component of fear responses, amygdala activity is by no means isomorphic with feelings of fear or anxiety. Amygdala activation is more commonly observed in response to perceiving stimuli that signal uncertainty or threat than in studies that elicit negative emotion (Phan et al. 2002, Wager et al. 2008a). It is reliably elicited by stimuli presented outside of conscious awareness (Etkin et al. 2004, Whalen et al. 2004) and that typically have no measurable impact on self-reported fear or anxiety. One way to think of amygdala activation is as a marker for vigilance for threat cues or for stimuli with behavioral relevance in the environment, which can be affected by anxiety. In our study, BLA activation to unconsciously presented fearful faces was greatest for those with the highest baseline anxiety (Etkin et al. 2004), suggesting that threat perception and learning mechanisms in the amygdala are particularly dominant in anxious individuals.

The insula is another region that is consistently responsive to negative affective states in humans, including conditioned fear cues (Etkin & Wager 2007). It is not directly involved in Pavlovian fear conditioning in animal models, but it is critical for learning and consolidating other types of anxiety-related behaviors, such as conditioned taste aversion (Eisenberg et al. 2003), highlighting the differential importance of various brain circuitry depending on the particular type of learning and emotional behavior. The insula is heavily interconnected with the amygdala, hypothalamus, and PAG (Paxinos 2003). Whereas the amygdala is particularly important for learning the affective value of isolated sensory cues, the insula is important for representing somatic and visceral information from the body. Its activation during a task in which subjects have to attend to their heartbeats, for example, was greater in individuals with greater interoceptive sensitivity and in those with higher levels of anxiety (Critchley et al. 2004). In humans, the amygdala and insula are also very commonly co-activated (Kober et al. 2008) (Figure 17.1), suggesting a prominent role for the insula in the representation of negative affective states. Thus, while the Pavlovian conditioning model has been tremendously useful in understanding fear elicited by simple cues, a broader set of systems is likely relevant for the range of negative affect involved in human anxiety.

17.3.2 Networks that support negative reactivity and regulation

The “core” limbic circuitry involved in negative emotional reactivity discussed above is probably an important component of anxiety in humans. However, other cortical and subcortical networks interact with this circuitry and can amplify, elaborate, or inhibit activity associated with behavioral and experiential aspects of negative emotion. Two large-scale networks that also can modulate fear and anxiety are shown at the right of Figure 17.2. One of these is a network of regions involved in executive working memory (aqua, top) that is broadly engaged when maintaining and manipulating information in the mind’s conscious workspace (Courtney et al. 1997, D’Esposito et al. 2000, Wager & Smith 2003). Another network, shown in yellow in Figure 17.2, involves the vmPFC, hippocampus, and posterior cingulate cortex (PCC). Both of these networks are thought to work in concert to provide context-based control over the generation and regulation of negative emotion.

17.4 The executive working memory system

Executive control is critical for goal-directed cognition, including controlling the focus of attention. In Gross’s influential theory of emotion regulation (Gross 1998), the earliest mechanism for regulating emotion when confronted with an adverse situation is to avoid attending to emotional, or “hot,” elements of a scene. Another key “leverage point” is cognitive reappraisal, or the generation of positive meaning in response to adverse events. The “cognitive control” network in Figure 17.1 (aqua) shows the subset of the executive
working memory system engaged most consistently during emotional processing. Numerous studies have now linked activity in multiple regions within the executive system to the cognitive reappraisal and suppression of emotion (Ochsner & Gross 2005). In a recent study of reappraisal of negative emotions elicited by aversive pictures, we found that multiple regions of the dorsomedial, superior and inferior lateral prefrontal, parietal, and temporal cortices were activated during reappraisal, and that their activity predicted greater success at reducing negative emotion (Wager et al. 2008b). Many of these regions correspond closely to regions reported in meta-analyses of executive working memory (Wager & Smith 2003) and controlled selection of semantic information and motor responses (Nee et al. 2007).

The amygdala is the emotion-related region most consistently downregulated during reappraisal (Ochsner & Gross 2005, 2008). In our recent study (Wager et al. 2008b), reappraisal success was positively and independently correlated with both reduced amygdala responses to aversive pictures and greater responses in the nucleus accumbens and ventral striatum. In analyzing frontal “cognitive control” regions that predicted these subcortical responses, we focused on the ventrolateral prefrontal cortex (VLPFC), which is particularly important for controlled information-selection processes. The VLPFC was positively correlated with both amygdala and accumbens activation, suggesting a prefrontal role in both the generation and regulation of emotion. Our interpretation was that viewing the pictures requires two kinds of appraisals. Most of the aversive pictures in the standardized set we used do not elicit automatic negative reactions. Rather, they require cognitive interpretation to generate a negative response. For example, a picture of a crying elderly woman requires filling in some critical background details before it is aversive: the woman may appear to be sick, or she may be sad because a loved one has died. When participants were asked to reappraise the pictures, they were asked to generate a second, more positive appraisal: the woman is crying because her grandson has just been accepted to college and has a bright future. The idea is that of controlled information selection and memory retrieval, a process of cognitive contextualization. This cognitive control network can both increase and decrease negative emotion. Bilateral VLPFC is activated by both positive and negative emotion-induction tasks, often in tandem with subcortical activation (Kober et al. 2008).

A role for the executive attention system in fear conditioning has not been intensively explored, in part because fear conditioning is a very simple process at a cognitive level of analysis. However, Delgado and colleagues (2008) reported lateral PFC activity during the cognitive regulation of conditioned fear responses. The implication is that conditioned fear, like other types of
negative emotional responses, can be regulated by the executive control system.

17.5 The affective appraisal network

The group of regions that we have termed the “affective appraisal network" includes the rostral mPFC, including both dorsal (dmPFC) and ventral (vmPFC) subdivisions, the hippocampus, and the posterior cingulate cortex (PCC). These regions are shown in yellow in Figure 17.2. This triad of regions, along with the inferior parietal cortex, has received much attention recently because of its role in a number of self-evaluation-related processes. The vmPFC is activated robustly even with relatively minimal manipulations of attention to the self or internal state (Northoff et al. 2006), and the PCC has a similar profile of activation and is often co-activated with vmPFC (Buckner & Carroll 2007, Kober et al. 2008). These regions have some of the highest levels of resting metabolism in the brain (Raichle et al. 2001). What is striking about these areas, however, is that they are robustly deactivated in a wide variety of cognitive tasks (Gusnard & Raichle 2001). These features have led to the labeling of the vmPFC and PCC, along with other temporal areas, as the “default mode network” (Raichle et al. 2001).

Interestingly, there is one kind of difficult cognitive task that reliably increases activity in the default mode network, the hippocampus, and medial temporal lobes: long-term memory retrieval. Recently, Buckner and Carroll (2007) have highlighted the striking similarity in activation patterns across the default mode network when no explicit task is performed: these similarities include long-term memory-related activations, prospection or prediction of future states, and processes of self-evaluation and representing others’ knowledge. Thus, an integrative view of the human vmPFC and interconnected areas is that they comprise a system for retrieving information from memory about the current situation, combining it with information about the internal state of the body, and prospection about the implications of the context for the future self. This process is precisely what is captured by the term “emotional appraisal," which refers to the integration of the environmental context with an assessment of one’s internal needs, goals, and capabilities.

17.5.1 Dissociable roles for the dmPFC and vmPFC in reactivity and regulation

If the mPFC is important for context-based appraisal, it should be important for both the generation and regulation of negative emotions, and ample evidence suggests that this is the case. Recent neuroimaging and animal evidence converges to suggest that the dorsal regions are most involved in generating negative appraisals, whereas the most ventral regions may play a preferential role in generating positive appraisals that reduce anxiety and negative emotion. In our meta-analysis (Wager et al. 2008a) and others (Kringelbach & Rolls 2004), vmPFC and medial OFC show a preference for positive emotional experiences, whereas the dmPFC shows a preference for negative experiences. This vmPFC region does not appear in the overall network analysis shown in Figure 17.1 because its activation was not consistent enough across all types of emotion.

The distinction between dorsal and ventral regions of the mPFC also is seen in animal studies of fear learning and human studies of more complex behaviors (Quirk et al. 2000, Milad & Quirk 2002, Milad et al. 2004, Vertes 2004, Gabbott et al. 2005). In humans, vmPFC activity is correlated with extinction memory during delayed extinction tests (Phelps et al. 2004, Kalisch et al. 2006). The dmPFC shows increased responses to conditioned cues, whereas the vmPFC shows deactivation (Phelps et al. 2004, Delgado et al. 2008). These studies suggest that dorsal portions of mPFC are important for generating fear responses, or more generally for generating negative appraisals, and ventral regions are important for representing contextual information that reduces fear expression. Combined with findings from human studies implicating mPFC in the controlled retrieval of information from memory, the overall impression is that the mPFC region is involved in the integration of sensory, interoceptive, and mnemonic information into an overall representation of the self in context.

The link between mPFC, episodic memory, and context processing may help explain the role of mPFC in fear learning and extinction. If mPFC and the hippocampus together form part of a memory-guided appraisal system, then simple forms of fear learning should not require mPFC or hippocampus. This appears to be the case. The hippocampus’s role in fear learning is limited to consolidation of contextual fear (Kim et al. 1993, Maren et al. 1997), and the mPFC is not critical for fear learning or immediate fear extinction. However, in more complex learning situations the mPFC may be necessary.

Some aspects of extinction memory also appear to require the “context-based appraisal”
mPFC–hippocampal circuit as well. Extinction learning, for example, is impaired by hippocampal inactivation (Corcoran et al. 2005). Expressing extinction behavior in the correct context also requires an intact hippocampus (Corcoran et al. 2005). In humans, extinction recall co-activates both vmPFC and hippocampus (Kalisch et al. 2006, Milad et al. 2007). Studies have implicated the mPFC in the generation and regulation of emotion in contexts beyond fear learning and extinction as well. In our recent emotion regulation study (Wager et al. 2008b), vmPFC activity was associated with increases in nucleus accumbens, which in turn predicted successful regulation of negative emotion.

Another example that extends the role of mPFC beyond the study of fear conditioning is a recent series of papers on emotional conflict. Etkin and colleagues (2006) showed subjects images of fearful or happy facial expressions and asked them to identify the emotion. Written across the faces were the words “fear” or “happy,” which were either of the same emotion type as the facial expression (congruent) or a different type (incongruent). This paradigm can shed light on the brain mechanisms involved in processing affective valence and those used to ignore competing affect-related information. Emotion identification was poorer in the incongruent condition, and dmPFC activation was higher. In addition, incongruent trials produced a regulatory effect on processing in the next trial, reducing dmPFC activity to subsequent incongruent trials. This type of trial-to-trial regulation has been taken as an indication that conflict increases control mechanisms, which then reduce conflict in subsequent trials (Gratton et al. 1992, Botvinick et al. 1999, Kerns et al. 2004, Egner & Hirsch 2005a, 2005b). Importantly, this type of emotion regulation, unlike the reappraisal process described earlier, occurs spontaneously and without the explicit awareness of subjects, hence an “implicit” form of emotion regulation. Together, the results implicate dmPFC in processing affective conflict. A follow-up study found that activation in the nearby dorsal cingulate was common to the monitoring or evaluation of both emotional and non-emotional conflict (Egner et al. 2008), suggesting a broader role for dmPFC in processing competing types of information. Along these lines, activation of the dorsomedial PFC or dorsal ACC is seen during interpretation of affective ambiguity (Simmons et al. 2006).

More ventral areas of the mPFC, by contrast, were more active on incongruent trials that followed incongruent trials, suggesting a role in implementing the control processes that reduce affective ambiguity and conflict. Activation in the vmPFC during the regulation of conflict was associated with simultaneous and coordinated reduction in amygdalar activity – a relationship that predicted the behavioral success of emotion regulation.

17.6 Clinical neuroimaging studies of anxiety disorders: a meta-analytic framework

The number of functional neuroimaging studies of negative emotion in clinical anxiety disorders has grown at a rapid pace, now reaching a point at which a quantitative meta-analytic review is feasible. Much of the clinical neuroimaging literature, particularly in its earlier periods, reports studies of small groups of subjects, with significant sample heterogeneity between studies and methodologies. This has led to inconsistencies of findings across studies, even for the brain regions most heavily hypothesized to be important for anxiety. One advantage of a meta-analysis is that it allows for a quantitative summary of the findings by accounting for cross-study variability. In addition, robust meta-analytic findings can help define the regions of greatest interest and support specific hypotheses for future studies so that these studies can approach their questions in the most direct and nuanced manner possible.

In a recent meta-analysis (Etkin & Wager 2007), we compared negative emotional processing in posttraumatic stress disorder (PTSD), social anxiety disorder (SAD), and specific phobia, as well as experimentally induced anxiety to discrete cues in healthy individuals through fear conditioning. These disorders were chosen as they were the only anxiety disorders for which a sufficient number of relatively homogeneous publications were available to allow for a reliable meta-analysis. The studies included for each disorder were a combination of (1) symptom-provocation studies, in which scripts, images, or sounds were used to evoke disorder-specific anxiety symptoms, and (2) studies using generally negative, but not disorder-specific, emotional stimuli. The latter were most often pictures of aversive scenes or emotional facial expressions.

Common to all three anxiety disorders was consistent hyperactivation of the amygdala and insula in patients, compared to matched controls, as shown in Figure 17.3. A similar pattern of activation was noted during fear conditioning, suggesting that amygdala and
insula hyperactivation in patients shares common features with fear conditioning. This finding is important because it identifies a core phenotype for at least these three anxiety disorders and supports an understanding of anxiety derived from animal fear-conditioning studies. Moreover, it helps to settle debate in the literature about whether, as hypothesized, amygdalar hyperactivity is a hallmark of at least some common forms of clinical anxiety. In our meta-analysis there was also a small cluster of hypoactivation in the dorsal part of the amygdala in PTSD specifically, which was spatially distinct from the more ventral cluster showing hyperactivity. Finally, it brings the insula, which had not been a central part of previous neural circuitry conceptualizations of anxiety, into prominence alongside the amygdala.

In addition to the shared findings across disorders, there are also important differences between disorders. Most strikingly, PTSD was characterized by extensive hypoactivation in the mPFC, including the pre-SMA region, which forms part of the executive working memory system, and the rostral cingulate and vmPFC regions associated with context-based control of emotion (Figure 17.4). Hypoactivation of the vmPFC proper is significant, given the increasingly well-documented relationship between this region and fear extinction that we reviewed above. These hypoactivations were significantly more common in PTSD than in the other two anxiety disorders.

Converging evidence comes from structural imaging studies, which have reported decreased gray-matter volumes in patients with PTSD in both dorsal and ventral mPFC (Yamasue et al. 2003, Karl et al. 2006, Kasai et al. 2008). One particularly well-controlled study assessed anterior cingulate volumes in identical twin pairs with similar combat trauma exposure but with only one twin diagnosed with PTSD (Kasai et al. 2008). Decreased ACC volumes were associated specifically with the presence of PTSD symptoms.

Of the three disorders, PTSD is considered to be most severe, and it has the most diverse symptomatology. In addition to symptoms of hyperarousal and hypervigilance to trauma-related cues, and avoidance of trauma reminders, all of which may be consistent with a model of anxiety based on inappropriately exaggerated fear conditioning, PTSD also presents with a range of symptoms reflecting generalized emotional dysregulation. The latter include emotional numbing, generalization of anxiety reactions to stimuli not closely related with the trauma, intrusive thoughts and memories, rumination, affective instability (e.g., anger outbursts), anhedonia, and a sense of negative foreboding (American Psychiatric Association 2000).

In light of the previous discussion of emotional processing and implicit regulation by the limbic–medial prefrontal circuit, we proposed that the robust hypoactivation in the mPFC in PTSD reflects a deficit in implicit context-based emotion regulation occurring in the absence of deliberate attempts at emotional control (Etkin & Wager 2007). This neural abnormality would therefore be reflected clinically in symptoms of emotion dysregulation and anxiety generalization, rather than being specifically a deficit of fear extinction (Etkin & Wager 2007). Moreover, in the context of the previous discussion of the affective appraisal system, patients with PTSD appear to have dysfunction in both the dorsal affect monitoring/generation and ventral regulation components.
17.7 Generalization of anxiety beyond disorder-related material: PTSD and specific phobia

As discussed above, functional neuroimaging studies of anxiety have employed both disorder-specific and generally negative stimuli. These experiments help determine the extent to which specific types of anxiety manifest through abnormal responses to any negatively valenced stimulus, or whether a response is only elicited to disorder-specific stimuli. For example, different facial expressions can trigger limbic system activation in healthy subjects and can thus be used as a probe of emotional processing in disorders where abnormal social signaling is not a central feature. Patients with PTSD displayed the characteristic pattern of medial prefrontal hypoactivity when viewing fearful compared to neutral or happy faces (Shin et al. 2005, Williams et al. 2006), counting emotionally negative compared to neutral words (Shin et al. 2001), recalling anxious or sad autobiographical events using script-guided imagery (Lanius et al. 2003), or viewing pictures of aversive compared to neutral visual scenes (Phan et al. 2006). Viewing fearful-expression faces also resulted in amygdalar hyperactivity in PTSD (Shin et al. 2005). Patients with specific phobia, meanwhile, showed amygdalar responses to emotional faces similar to those of controls (Wright et al. 2003). These data suggest that dysregulation within the limbic–medial prefrontal circuit during the processing of non-disorder-specific negative stimuli may be characteristic of states of generalized emotional dysregulation, such as seen in PTSD, and does not merely reflect the presence of anxiety per se.

It is now also clear, based on a number of imaging studies in healthy subjects, that understanding disorder-related alterations in amygdalar functioning requires separate analyses of emotional processing within and outside of awareness. Several recent studies have shown that elevated generalized anxiety (e.g., trait anxiety) in non-psychiatric populations is associated with exaggerated amygdalar activation, most sensitively detected when emotional stimuli are processed outside of awareness or under the presence of limited attentional resources (Bishop et al. 2004, Etkin et al. 2004). In PTSD, fearful faces can activate the amygdala even when processed outside of awareness (Rauch et al. 2000, Bryant et al. 2008a). While similar manipulations of attention or awareness have not been reported in other anxiety disorders, this type of approach will be useful to probe the level at which vigilance or hypersensitivity to threat is already evident in each anxiety disorder.

17.8 Treatment studies

Compared to depression, relatively few neuroimaging-coupled intervention studies have been reported for each anxiety disorder. Of these, most are difficult to interpret because of an absence of important experimental controls. Nonetheless, there are several suggestive studies that open the way to increasingly better designed and more sophisticated approaches. In one such study, Furmark and colleagues (2002) examined patients with SAD treated with either citalopram or cognitive–behavioral therapy (CBT), measuring brain activity in response to having to give a prepared speech in the scanner while in the presence of others, a potent symptom provocation paradigm (Tillfors et al. 2001). Improvement in symptoms with treatment was accompanied by decreased activity in the amygdala and the medial temporal lobe. No such changes were seen in wait-list control subjects. Comparing treatment groups with a control group of wait-list patients who received no treatment allowed the authors to rule out changes...
related only to subject rescanning or simply to the passage of time. Decreases in the activity of the amygdala were seen in both the CBT and the citalopram groups, supporting an important role for this region in the symptoms of SAD. The two treatment groups, however, differed with respect to neural changes outside the amygdala, though interpretation of these findings is hampered by the very small sample sizes (six subjects per group). Interestingly, the degree to which amygdala activity decreased as a result of therapy predicted patients’ reduction in symptoms one year later. Along similar lines, though using resting brain metabolic imaging, Baxter and colleagues (1992) noted normalization of caudate hyperactivity in OCD after treatment with either fluoxetine or CBT (nine subjects per group).

Finally, Straube and colleagues (2006) examined subjects with spider phobia and compared the effects of symptom provocation in a group randomized to receive brief, intensive CBT (two four- to five-hour sessions) to a wait-list control group. At baseline, spider phobics hyperactivated the insula and dorsal ACC in response to video clips of spiders. After treatment, the CBT group no longer showed these abnormalities, but they persisted in the wait-list control group. Together, these studies demonstrate that the neural abnormalities associated with symptomatology in anxiety disorders (e.g., amygdala and insula hyperactivation) are corrected after successful clinical interventions. However, much remains unclear, including a more thorough understanding of which neural abnormalities persist after treatment, whether they reflect trait or vulnerability markers, and by what neurobiological mechanisms treatment-related change comes about. It is likely that an understanding of the circuits mediating emotional reactivity and regulation, as outlined above, will be useful in this respect as well. It is interesting in this regard that another study of CBT for spider phobia noted an increase in ventromedial prefrontal activation during symptom provocation after therapy but not in a wait-list control group (Schienle et al. 2007).

Another important aspect of understanding the mechanisms of treatments for anxiety is an appreciation of which subjects are most likely to respond to treatment, whether they respond differentially to various treatments, and why. To this end, two studies have reported results of correlations of pretreatment brain activation during emotional processing with treatment outcome in two anxiety disorders. Whalen and colleagues (2008) reported that increased rostral ACC and decreased amygdala activation to fearful faces at baseline predicted a better response to venlafaxine, a serotonin–norepinephrine reuptake inhibitor commonly used as an antidepressant, in patients with GAD. Meanwhile, Bryant and colleagues (2008b) reported that increased activation in both the rostral ACC and amygdala in response to unconsciously presented fearful faces at baseline was predictive of a favorable response to CBT in patients with PTSD. While these results are preliminary and have not yet been replicated, they raise several interesting possibilities. First, the same brain region (e.g., amygdala) may differentially predict treatment outcome, depending on either the diagnosis or the treatment strategy. Second, a common brain region (e.g., rostral ACC) may be broadly predictive of the likelihood of a patient responding to any treatment. Indeed, treatment-outcome prediction studies in depression have consistently and similarly implicated the rostral ACC across different treatments and imaging modalities (reviewed in Etkin et al. 2005). Even more intriguing, these data suggest that individual differences in the aspects of implicit emotion regulation mediated by the medial PFC may be the ultimate predictor of treatment response across varied treatments and disorders.

17.9 Conclusion

In this chapter, we have outlined limbic–prefrontal neural circuits involved in the reactivity to and regulation of negative emotional stimuli. We focus on a core circuit for negative affective reactivity identified in animal and human studies of fear conditioning. Activity in these regions appears to be modulated by two large-scale, distributed systems. One, the executive working memory system, is a set of cortical networks that comprise a system for goal-directed, flexible control over attention and memory. The other, the affective appraisal system, is a set of paralimbic cortical and subcortical regions involved in emotion generation and regulation, self-related cognition, long-term memory retrieval, and context-based modulation of conditioned fear.

While it is clear that certain domains have been well studied and that the literature now provides a basis for specific neuroanatomical hypotheses for future experiments, it is also readily apparent that a great deal more work on anxiety disorders and treatment interventions is needed to map basic findings onto clinical conditions. The systems reviewed in this chapter provide a
basis for testable outcome measures for therapeutic interventions and provide some guiding principles for establishing the neural circuitry that underlies both vulnerability and resilience to several types of anxiety disorders. This research is in its early stages, and it ultimately may lead to the identification of endophenotypes for genetic vulnerability and other intermediate phenotypes that can be used to both classify disorders and understand individual variability in treatment responses.

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References


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