

# Functional Neuroanatomy of Anxiety: A Neural Circuit Perspective

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**Abstract** Anxiety is a commonly experienced subjective state that can have both adaptive and maladaptive properties. Clinical disorders of anxiety are likewise also common, and range widely in their symptomatology and consequences for the individual. Cognitive neuroscience has provided an increasingly sophisticated understanding of the processes underlying normal human emotion, and its disruption or dysregulation in clinical anxiety disorders. In this chapter, I review functional neuroimaging studies of emotion in healthy and anxiety-disordered populations.

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A limbic-medial prefrontal circuit is emphasized and an information processing model is proposed for the processing of negative emotion. Data on negative emotion processing in a variety of anxiety disorders are presented and integrated within an understanding of the functions of elements within the limbic-medial prefrontal circuit. These data suggest that anxiety disorders may be usefully conceptualized as differentially affecting emotional reactivity and regulatory processes – functions that involve different neurobiological mechanisms. While the neural bases of several anxiety disorders are increasingly better understood, advances have lagged significantly behind in others. Nonetheless, the conceptual framework provided by convergent findings in studies of emotional processing in normative and anxiety-disordered populations promises to yield continued insights and nuances, and will likely provide useful information in the search for etiology and novel treatments.

**Keywords** Amygdala · Anterior cingulate · Anxiety · Circuit · Dorsomedial prefrontal · Emotion · Emotion regulation · Fear · GAD · Generalized anxiety disorder · Hippocampus · Hypothalamus · Insula · Limbic system · Medial prefrontal · Meta-analysis · Obsessive-compulsive disorder · OCD · Panic disorder · Periaqueductal gray · Posttraumatic stress disorder · PTSD · Social anxiety disorder · Social phobia · Specific phobia · Ventromedial prefrontal

## 1 Introduction

“Anxiety” describes a wide range of subjective, often unpleasant, sensations that likewise reflect responses to a wide range of inciting events or stimuli. Anxiety can be part of a contextually appropriate and adaptive response, as it alerts an organism to salient events in its environment or internal milieu. Anxiety, however, can also be triggered to an inappropriate degree or at inappropriate times, and when prolonged, severe enough, and disruptive to the individual, is then considered a clinical disorder of anxiety. In this chapter I will review the neural basis of anxiety in healthy and clinical populations, with primary focus on functional neuroimaging studies in humans. The goal of this chapter is not to provide a comprehensive review of all such studies, but rather to provide a coherent understanding of the functional neuroanatomy of anxiety in its various manifestations from a neural circuit perspective, through a selective review of the literature. While there are many ways in which to describe, categorize and compare mental states or psychiatric disorders, I have chosen to focus on a cognitive neuroscience approach, as this literature is sufficiently broad, both in healthy subjects and in those with anxiety disorders, to fuel a substantive discussion. Ultimately, however, the fullest view of anxiety will require simultaneous integration across multiple levels of investigation.

Fear and avoidance of trigger cues are common to many anxiety disorders (APA 1994) and resemble the arousal and avoidance responses shown by normal subjects to conditioned fear cues (Grillon 2002). Thus, a common element of anxiety

disorders may be an abnormally elevated fear response. Furthermore, some anxiety disorders appear to involve a more generalized dysregulation of negative affect, suggesting that a rich explanatory model of anxiety also has to take these factors into consideration. In order to understand the neurobiology of anxiety, we must therefore first elaborate on the neural circuitry underlying the normal response to negative emotional stimuli and the regulation of their effects. This broad field of study has seen a dramatic expansion over the last decade, attributable largely to a proliferation of functional neuroimaging methods, and very usefully informs interpretation of alterations in this circuitry in patients with anxiety disorders.

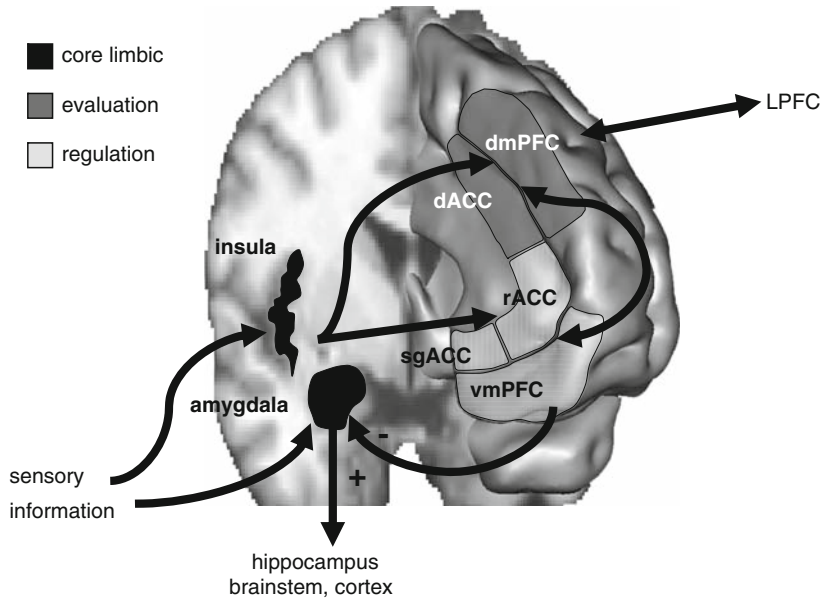
Moreover, though anxiety can be seen as a shared overriding category for diverse clinical situations, the attractiveness of that concept belies the complexity of clinical presentations and neural bases of anxiety disorders. I will explore both shared and disorder-specific features of anxiety disorders, and through that suggest a different way of understanding the neural basis of anxiety. Finally, I will review emerging knowledge on neurobiological changes associated with, or prognostic of, treatment-related improvement of symptoms in patients with anxiety disorders.

## ***1.1 Neural Circuitry of Anxiety-Relevant Negative Emotion: Reactivity and Regulation***

Human and animal studies of the processing of negative emotions, such as fear, have implicated a large number of cortical and subcortical areas, and these have been quantitatively summarized by a number of meta-analytic surveys of the literature (Kober et al. 2008; Phan et al. 2002; Wager et al. 2003). A simplified information-flow conceptual model of some of the regions and their functional interactions is shown in Fig. 1, and the details are given in the sections below. Central to a neural circuit of negative emotion are a set of core limbic structures, which include the amygdala and insula, as well as interconnected structures such as the periaqueductal gray (PAG) and hypothalamus. These regions interact with a number of cortical areas, amongst which are several medial prefrontal subregions. Finally, the processing of emotion modulates other cognitive systems involved in perception, motor planning, and memory.

## ***1.2 Core Limbic System***

The amygdala is a complex structure and is composed of multiple subnuclei, each with its own distinct pattern of afferent and efferent projections. Our understanding of the organization of the amygdala is derived largely from animal work investigating the functions of subnuclei within the amygdala, and the distinct brain networks that they take part in. Of particular interest for anxiety are the basolateral complex



**Fig. 1** A limbic-medial prefrontal circuit view of negative emotional processing. Relevant structures are separated into three functional groups. A core limbic group includes the amygdala, insula, as well as subcortical areas like the hypothalamus and periaqueductal gray (not depicted on this figure). These regions register emotional stimuli and initiate coordinated species-specific physiological and behavioral responses to them. A second group includes dorsal medial prefrontal structures including the dorsal anterior cingulate (dACC) and dorsomedial prefrontal cortex (dmPFC), and is involved in more extensive evaluation of emotion and may gate its access into conscious awareness. Finally, a third region, which includes the rostral and subgenual anterior cingulate (rACC, sgACC), and ventromedial prefrontal cortex (vmPFC), is involved in contextually appropriate regulation of emotion and core limbic processing. The processing of an emotional stimulus may lead to modulation of regions important in other cognitive functions (e.g., perception, motor planning, and memory) by core limbic regions. Additionally, lateral prefrontal (LPFC) executive regions may engage medial prefrontal emotion processing circuitry to aid in deliberate regulation of emotion

(BLA, a composite of the functionally related basal, lateral, and accessory basal nuclei) and the central nucleus, which is part of the centromedial amygdala (CMA) (Heimer et al. 1999). The BLA is the primary input site in the amygdala, receiving sensory information from the thalamic nuclei and sensory association cortices (Amaral et al. 1992), and also provides the majority of the thalamic and cortical projections from the amygdala. By contrast, the central nucleus is an output region that projects to the brain stem, hypothalamic and basal forebrain targets (Paxinos 2003), and is located dorsal to the BLA (Mai et al. 1997). In rodents, the basolateral amygdala encodes the threat value of a stimulus, while the central nucleus is essential for the basic species-specific defensive responses associated with fear (Davis and Whalen 2001).

Central to the circuit outlined above are anatomical connectivity findings in rodents and nonhuman primates, which differentiate the largely cortical connectivity pattern of the BLA from the largely subcortical connectivity pattern of the central nucleus or CMA (Amaral et al. 1992; Pitkanen 2000; Price et al. 1987). The anatomical connectivity of human amygdalar nuclei, however, is currently unknown. We recently examined the differential connectivity patterns of these amygdalar subregions in healthy subjects and patients with GAD to investigate the functional brain networks in which the amygdala is involved, and which underlie the distinct functions of these amygdalar subregions (Etkin et al. in press). Indeed, we found that the two key subregions of the amygdala can be dissociated using conventional human fMRI data, and that their patterns of connectivity closely matches those found in anatomical tract-tracing studies in nonhuman primates.

The human amygdala is activated by negatively valenced emotional stimuli (Phan et al. 2002; Wager et al. 2003). Lesions of the amygdala are associated with an inability to accurately label fearful facial expressions (Adolphs et al. 1994), and an inability to encode fear-based memories (Bechara et al. 1995). Invasive stimulation of the human amygdala with microelectrodes produces subjective reports of fear and anxiety (Lanteaume et al. 2007). Beyond its activation by negative emotional stimuli, the amygdala also responds to anxiety-provoking environmental cues that are themselves neutral in valence. Herry et al. (2007) compared the effects of predictable and unpredictable sequences of neutral tones in mice and humans and found that amygdala activation was increased in both species in response to the unpredictable sequence. Unpredictable tone sequences were also associated with increased anxiety-related behavior in mice and an attentional bias in response to emotional facial expressions in humans.

Activation of the amygdala can even occur in response to emotional stimuli processed outside of awareness, or under very limited attentional resources. We have found, for example, that activation in a region consistent with the basolateral amygdala to unconsciously presented fearful faces can be detected in healthy volunteers in a manner that varies with their baseline anxiety, such that activation is greatest for the most anxious subjects (Etkin et al. 2004). Along with amygdala activation, we found that individual differences in baseline anxiety predicted subjects' performance in a concomitant cognitive task. Others have found a similar relationship between amygdala activity and anxiety when evaluating the emotional content of fearful faces in the context of limited attentional resources (Bishop et al. 2004). The amygdala, therefore, plays an important role in both the subjective and attentional-vigilance aspects of threat processing, and thus abnormalities in this system may be associated with hyperarousal and hypervigilance to threat in anxiety disorders. Moreover, these data also suggest that there may be a conceptual overlap between amygdala activation observed in response to negative emotional stimuli presented outside of awareness, which cannot therefore be extensively consciously evaluated, and amygdala activation by anxiety-producing unpredictable or ambiguous stimuli. This is particularly important, since many anxiety disorders are associated with intolerance of uncertainty or ambiguity (Boelen and Reijntjes 2008;

Grillon et al. 2008; Holaway et al. 2006) and negative interpretations of ambiguous material (Bishop 2007; Eysenck et al. 1991).

The insula, another of the core limbic regions, is heavily interconnected with the amygdala, hypothalamus, and PAG matter (Paxinos 2003). The insula regulates the autonomic nervous system (Oppenheimer et al. 1992), and like the amygdala is activated during the processing of a variety of negative emotions (Phan et al. 2002). Though the insula has received less intense study than the amygdala in the context of negative emotional processing, its important role is suggested by its more frequent association with activation in the amygdala than with activation in other cortical regions, thereby suggesting a high degree of functional similarity to the amygdala (Kober et al. 2008). Studies have found, for example, that the insula plays a particularly important role in the monitoring and interpretation of internal physical sensations. 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). Similar to what has been noted for the amygdala, insular activation is greater in negative facial expression (e.g., disgust) than neutral expressions even in the context of limited attentional resources (Anderson et al. 2003).

The importance of both the amygdala and insula in anxiety-relevant negative emotion processes was investigated in a recent meta-analysis of human fear conditioning experiments (Etkin and Wager 2007). Current influential models of anxiety draw heavily on human and animal work on experimentally induced conditioned fear states, and enough of these studies have now been undertaken to allow for a quantitative meta-analysis of the results. Etkin and Wager examined ten well-controlled fear conditioning studies and found that consistent activation was seen, as predicted, in both the amygdala and insula, confirming a role for both of these regions in anxiety-relevant emotional processing. Finally, the PAG and hypothalamus are involved in the regulation of the autonomic nervous system, as well as characteristic species-specific motor response patterns, suggesting an important role for these regions in anxiety as well. Though the PAG and hypothalamus have not been the focus of studies on clinical anxiety, they likely play an important role by virtue of their normal functions in responses to negative emotional stimuli.

### ***1.3 Medial PFC***

Consistent cortical activations to emotional stimulation are found throughout the medial wall of the PFC, including the anterior cingulate cortex (ACC), as well as in parts of the lateral PFC. In the largest and most recent meta-analysis of neuroimaging studies of emotion, Kober et al. (2008) used multivariate clustering methods to discriminate between groups of coactivated regions. This data-driven approach identified two distinct medial prefrontal groups of activation clusters. The first group consisted of the presupplemental motor area in the posterior medial PFC, and was associated with coactivation in several lateral PFC structures. This pattern

of coactivation suggests that this group, labeled by the authors as “cognitive/motor” in function, is likely to reflect attentional or executive processes involved in emotion, but not specific to it. The second group was more anterior and consisted of the dorsal ACC, overlying regions of the dmPFC, and extended into the rostral (pregenual) ACC and portions of the subgenual ACC (together labeled the “medial prefrontal” group). Regions within this group consistently coactivated with the amygdala and PAG, suggesting an important role in emotion. Interestingly, the ventromedial PFC (including the medial orbitofrontal cortex), another region commonly implicated in the processing of emotion, did not appear in this meta-analysis. There may have been various reasons for this, including the frequent loss of signal in this region due to magnetic susceptibility artifacts in functional magnetic resonance imaging (fMRI) studies, or the limited contexts in which it is activated during emotion processing (e.g., only when certain types of emotion regulation are engaged, see below).

It has, however, become increasingly apparent that the large area of activation in the “medial prefrontal” group, along with the ventromedial PFC, can be functionally divided into meaningful subregions, though the precise roles of these subregions are not fully clear. One influential view, derived from studies of the ACC, holds that the dorsal regions are “cognitive” in function, in part through their connectivity with “cognitive” regions in the lateral PFC involved in cognition and executive functioning. Ventral regions, meanwhile, are argued to be “affective” in nature (Bush et al. 2000), in part through their connectivity with core limbic structures such as the amygdala. The meta-analysis results above, however, argue against this view, as both dorsal and ventral medial prefrontal regions appear to be similarly engaged in emotion processing. Indeed, while cognitive (i.e., nonemotional) processing appears to engage the dorsal more than the ventral regions of the medial PFC and ACC (Ridderinkhof et al. 2004), affective processing appears to be more widespread. Consistent activation is seen in the dorsal ACC, for example, during fear conditioning (Etkin and Wager 2007). An informative alternative view comes from studies of evaluation and regulation of emotion.

Converging work suggests that the dorsal ACC and overlying dorsomedial PFC are involved in appraising and monitoring emotion, and may be important for the conscious subjective experience of emotion. Kalisch et al. (2006a) induced anxiety in healthy volunteers by signaling that they may receive a shock and found that increased anxiety was associated with activation of the dorsomedial PFC. If subjects, however, also simultaneously carried out a challenging working memory test, activation in the dorsomedial PFC diminished, likely reflecting the role of this structure in higher level emotional appraisal, which can be interrupted when attentional load was high enough. Consistent with this, another recent meta-analysis found that dorsomedial PFC activation was more commonly noted in studies in which subjects were induced to experience emotion, rather than just perceiving it (e.g., through judgments about attributes of an image) (Wager et al. 2008).

Etkin et al. (2006) recently developed an emotional analog to the color-word Stroop task to test how individuals respond to and regulate the impact of emotional conflict. They showed subjects images of fearful or happy facial expressions and



asked them to identify the affect. Written across the faces were the words “fear” or “happy,” which were either of the same affect (congruent) or of a different affect (incongruent) as the facial expression. As in the color-word Stroop task, subjects were to ignore the text but were unable to avoid involuntarily reading the word and extracting its meaning. The emotional meaning of the words thus led to direct conflict with interpretation of the facial affect. As a result, incongruent stimuli interfered with affect identification, and were associated with dorsomedial PFC activation.

During conflict tasks, however, the degree of behavioral interference by an incongruent trial varies in a predictable manner based on previous trial history. It has been found that there is less reaction time interference (i.e., less conflict) for incongruent trials if they are preceded by an incongruent trial than if they are preceded by a congruent trial – a phenomenon termed conflict adaptation (Botvinick et al. 1999; Egner and Hirsch 2005a, b; Gratton et al. 1992; Kerns et al. 2004). These findings suggest that the conflict generated by an immediately prior incongruent trial activates a regulatory mechanism, which leads to improved handling of conflict on the next trial (Botvinick et al. 2001). Incongruent trials can thus be separated depending on whether they are associated with high conflict regulation and consequently less conflict (an incongruent trial preceded by an incongruent trial) or low conflict regulation and thus more conflict (an incongruent trial preceded by a congruent trial). Neural activity in regions responsible for either generating or monitoring conflict should reflect the amount of behavioral conflict, resulting in higher activity for low conflict regulation than for high conflict regulation trials in these regions (i.e., low > high conflict regulation trials). By contrast, for brain regions implicated in conflict resolution, reduced conflict should be associated with increased neural activity (i.e., high > low conflict regulation trials).

Activation in the dorsomedial PFC decreased during high conflict regulation trials, confirming a role for this region in the monitoring and evaluation of negative emotion. Interestingly, a follow-up study, which compared the emotional conflict paradigm above to a matched nonemotional conflict task, found that activation in the nearby dorsal ACC was common to the monitoring or evaluation of both emotional and nonemotional conflict (Egner et al. 2008), suggesting that aspects of dorsomedial PFC function in emotion may be part of a greater role for this region in monitoring ongoing processing demands for the purpose of recruiting context-appropriate control processes. Along these lines, activation of the dorsomedial PFC or dorsal ACC is seen during interpretation of affective ambiguity (Simmons et al. 2006), and is similarly also engaged during interpretation of nonemotional ambiguity.

More ventral portions of the ACC however, show a different pattern of activation from the dorsomedial PFC and dorsal ACC, suggesting that while they may be part of the “medial prefrontal” group in the Kober et al. meta-analysis (Kober et al. 2008), they can be functionally dissociated from the more dorsal structures. Activation of the rostral ACC was associated with regulation of emotional conflict in the task of Etkin et al. 2006, described above. Activation of the rostral ACC was also accompanied by a simultaneous and correlated reduction in amygdala activity.



These results are consistent with a recent study of the extinction of conditioned fear responses, in which subjects evaluate and override expectations for aversive stimuli. Fear extinction involved increased activity in the rostral and subgenual ACC, and the ventromedial PFC, along with decreased activity in the amygdala (Phelps et al. 2004). Likewise, rostral ACC activation has also been observed during placebo anxiety reduction, a process in which control over an emotional stimulus (an aversive picture) is recruited to diminish the effect of the emotional stimulus (Petrovic et al. 2005). These data suggest that the ventromedial PFC and rostral/subgenual portions of the ACC may have an important role in the regulation of emotion, which is different from the evaluation and monitoring role of the dorsomedial PFC and dorsal ACC.

Beyond functionally differentiating between core limbic and medial prefrontal subregions, evidence indicates that these regions communicate with each other in a coherent and meaningful way. Emotional evaluation by the dorsomedial PFC and dorsal ACC is mediated through direct projections from core limbic regions (Ghashghaei et al. 2007) and indirectly through limbic-ventromedial prefrontal projections (Stein et al. 2007). Emotion generation or evaluation signals are in turn able to recruit emotional control processes. Emotional conflict-related activation during incongruent trials in the amygdala and dorsomedial PFC, for example, predicted conflict regulation-related activation in the rostral ACC on subsequent trials (Etkin et al. 2006). Activation by ventral ACC and ventromedial PFC regions in turn modulated activity in areas such as the amygdala, which are involved in generating aspects of the emotional response of the individual. This model of emotional reactivity and regulation is consistent as well with studies in the likely rodent homologs of these areas, which suggest that amygdala activity can be dampened by stimulation of the medial PFC due to activation of top-down inhibitory projections from the medial PFC to the amygdala (Quirk et al. 2003). Moreover, lesions of the medial PFC in rodents impair extinction of conditioned fear, leading to persistent fear responses in the absence of an aversive stimulus (Morgan et al. 1993). Drawing on the data presented above, Fig. 1 summarizes the flow of information processed within the limbic-medial prefrontal circuit.

#### ***1.4 Explicit and Implicit Emotion Regulation***

Where do these data fit into the current understanding of emotion regulation circuitry? Gross (Gross 2002) has proposed a framework for classifying different emotion regulation strategies. One important distinction is between “antecedent-focused” strategies, which aim to alter emotional responses before they begin, and “response-focused” strategies, which suppress the expression of emotion. Antecedent-focused strategies include willful detachment, distraction, and cognitive reappraisal; response-focused strategies include voluntary suppression of positive or negative emotional reactions. Orthogonal with this framework is the idea that a given emotion regulation strategy may be “deliberate,” requiring conscious top-down

intentionality, or may be “implicit,” engaging top-down regulation of emotional processes without requiring conscious intentionality.

Several recent neuroimaging studies of the neural circuitry associated with deliberate efforts at emotion regulation (Beauregard et al. 2001; Kalisch et al. 2005; Kalisch et al. 2006b; Levesque et al. 2003; Ochsner et al. 2004) found that deliberate emotion regulation involves consistent activation of the dorsolateral PFC, an area associated with top-down cognitive control, regardless of whether an antecedent-focused or a response-focused strategy was being employed. These findings suggest that some of the same regulatory circuitry is involved in the cognitive control of emotion as in nonemotional forms of cognitive control. Consistent with this view, adaptation to nonemotional conflict, even if in the context of task-irrelevant emotional stimuli, involves activation of lateral prefrontal control mechanisms (Egner et al. 2008). This pattern of activation was dissociable from the one described above in which rostral/ventral ACC activation was associated with the regulation of emotional conflict, and dampening of amygdalar reactivity (Egner et al. 2008). Thus, it appears that the role in emotion regulation of the limbic-medial prefrontal circuit described above and depicted in Fig. 1 is different from the role of the dorsolateral PFC in deliberate, instructed forms of emotion regulation.

Insight about the nature of emotion regulation by the limbic-medial prefrontal circuit is suggested by the details of the tasks which trigger it, none of which involved a deliberate instruction to regulate emotion. It is highly unlikely, for example, that subjects in the emotional conflict task of Etkin et al. 2006 were aware of the effect of previous trial emotional incongruence on their response to an emotionally incongruent stimulus on the current trial. Thus, emotion regulation by the limbic-medial prefrontal circuit may represent an implicit and reflexive form of emotion regulation, dissociable both psychologically and neurobiologically from explicit and instructed strategies for emotion regulation. Thus, implicit emotion regulation may be based on an individual's expectation or anticipation of emotional stimuli, which may operate outside of their awareness, and be independent of an explicit goal of emotion regulation. This view would therefore predict that abnormalities in the circuitry mediating implicit emotional regulation may be demonstrated in psychiatric disorders with prominent emotional dysregulation, but in which no concurrent dorsolateral PFC deficits are observed.

Though the circuit in Fig. 1 describes the limbic-medial PFC circuit as recurrent, or feedback, in nature, it is likely that it is not entirely inhibitory with respect to effects on emotion generating limbic structures. In fact, there may be instances when increasing negative emotion, through positive ventral frontal-limbic interactions, is more contextually appropriate than decreasing it. One such example is a recent study in which subjects played a video game in which they were chased, and if captured would receive a shock to their hand (Mobbs et al. 2007). When the threat was relatively distal, it would seem appropriate to activate and enhance fear or threat responses in order to better shape behavior to avoid the threat. Consistent with this idea, this phase of the chase was associated with coactivation of the ventromedial PFC and basolateral region of the amygdala. Increased confidence of escape was associated with increased ventromedial PFC activation. By contrast,

when threat was near and defensive responses might be hypothesized to take precedence over fear-motivated avoidance responses, activation shifted to the dorsal region of the amygdala, where the central nucleus is located, and the PAG, an important brainstem target of the central nucleus. Likewise, engaging in contextually appropriate negative emotion-relevant behavior (shooting an aggressive assailant or healing a wounded bystander) resulted in greater activity in the ventromedial PFC, amygdala, and insula than matched contextually inappropriate behavior (shooting the bystander or healing the assailant)(King et al. 2006).

## ***1.5 Hippocampus***

Though the hippocampus is not commonly considered to be a central region in human emotional processing, apart from the relevance of its mnemonic role in emotional modulation of memory, a growing body of animal work implicates it in anxiety, and is thus worth a brief discussion. Studies in rodents differentiate between the function of the dorsal hippocampus, which is primarily involved with memory and other cognitive functions, and the function of the ventral hippocampus. Unlike the dorsal hippocampus, the ventral hippocampus is heavily interconnected with the amygdala and the hypothalamus (Bannerman et al. 2004). Lesions or inactivation of the ventral hippocampus results in a reduction of endogenous anxiety-like behavior in rodents, an effect that is not seen if similar manipulations are made of the dorsal hippocampus (Bannerman et al. 2004; Kjelstrup et al. 2002). In humans, a nonmnemonic role for the hippocampus in emotional processing has not clearly emerged, nor has its relevance for anxiety disorders been delineated. Thus, unlike limbic and medial prefrontal circuitry, the lack of a significant role for the hippocampus in human anxiety currently stands in contrast to the relative conservation of fear- and anxiety-related circuitries across phylogeny.

## ***1.6 Summary***

In the preceding sections I have outlined the neural circuitry central to the processing of negative emotional material in humans, focusing on the specific functions of each region and how information flows within the circuit. The focus on negative emotion and its regulation reflects an assumption that this material is of special relevance to anxiety, and also benefits from the broad wealth of neuroimaging and related studies in this area. As shown in Fig. 1, registration and reactivity to a negative emotional stimulus is carried out in the amygdala and insula, two core limbic structures. These regions can direct and modulate activity in a range of target regions, including the PAG, hypothalamus, hippocampus, and sensory cortex. Further monitoring and evaluation of the negative stimuli is carried out by the dorsal ACC and dorsomedial PFC, which are informed directly by core limbic

regions, and indirectly through projections from ventral frontal regions which receive innervation from core limbic regions. Engagement of these dorsal structures leads to a detailed appraisal of the emotional stimulus not possible by the amygdala and insula, and can involve conscious awareness of that emotional appraisal. Information on the stimulus is relayed to regulatory regions in the ventral ACC (rostral and subgenual) and ventromedial PFC, either through direct projections from core limbic regions, or through projections from dorsal ACC and dorsomedial PFC, which likely reflect different aspects of the emotional reaction to a stimulus. These regulatory regions in turn provide feedback onto core limbic areas, resulting in context-appropriate regulation, which may take the form of either inhibition or enhancement of limbic processing.

I have also emphasized that this limbic-medial prefrontal loop appears to result in the regulation of emotion in the absence of a specific goal for emotion regulation and likely outside of subjects' awareness. This model stands in contrast to the prevailing view of deliberate emotion regulation, wherein lateral prefrontal circuitry important in cognitive control in nonemotional contexts is thought to mediate the cognitive control of emotion. Since lateral prefrontal structures have little direct projections to core limbic regions, indications are that cognitive control of emotion by the lateral PFC is achieved by its engagement of medial prefrontal areas within the limbic-medial prefrontal loop described above (Johnstone et al. 2007; Urry et al. 2006). Thus, understanding the differences between implicit and explicit emotion regulation processes may be an important avenue for interpreting neural abnormalities in anxiety disorders and the mechanisms of their treatment.

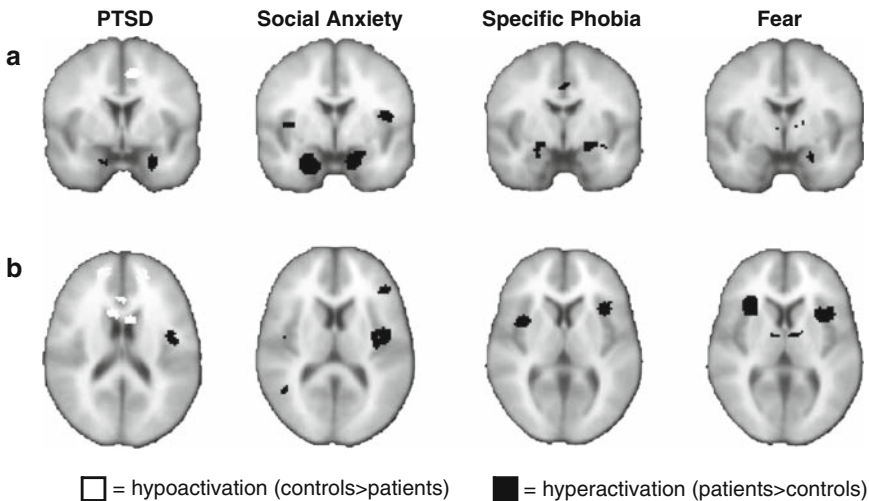
While informative and helpful in understanding anxiety, the model above remains simplistic, and narrow in its focus. I have neglected other functions of some of these regions, including in reward (amygdala and ventromedial PFC), and in self-related processing (throughout the medial PFC). Basic research in these areas is generally not as well detailed as for negative emotional processing, and few investigations exist in these areas in anxiety disorders. Others have recently emphasized a unifying role for the medial PFC in functions such as reward or self-referential processing, with particular relevance to understanding the neural bases of anxiety disorders (Liberzon and Sripada 2008). Thus, understanding these aspects of anxiety will be a topic for future research.

## ***1.7 Negative Emotional Processing in Anxiety Disorders: A Meta-Analytic Framework***

The number of functional neuroimaging studies of negative emotion in clinical anxiety disorders have accumulated 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, was carried out on 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,

which are 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 across-study variability. In addition, robust meta-analytic findings can help define the regions of greatest interest and support specific hypotheses for future studies, such that these studies can approach their questions in the most direct and nuanced manner possible. Etkin and Wager (2007) have recently reported a meta-analysis of negative emotional processing in posttraumatic stress disorder (PTSD), social anxiety disorder (SAD), and specific phobia, and compared these findings to 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. I will review these findings and then highlight other relevant findings in each anxiety disorder, including those that were not part of the meta-analysis.

The studies included for each disorder were a combination of symptom-provocation studies, in which scripts, images, or sounds were used to specifically evoke disorder-specific anxiety symptoms, and 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 (see Fig. 2). A similar pattern of activation was noted during fear conditioning, suggesting that amygdala and insula hyperactivation in patients reflects excessive engagement of fear- or negative emotion-related circuitry. This finding is important because it identifies a core phenotype for at least these three

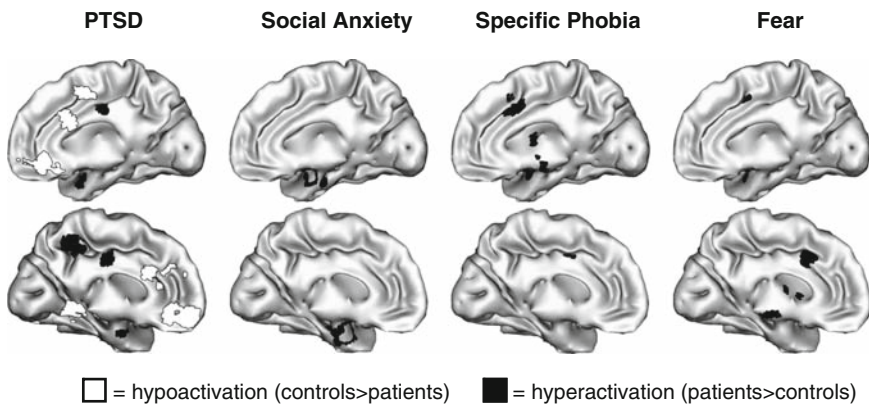


**Fig. 2** Clusters in which significant hyperactivation or hypoactivation was found in patients with PTSD, Social Anxiety Disorder (SAD), and Specific Phobia relative to comparison subjects and in healthy subjects undergoing fear conditioning. Notable is common hyperactivation in the amygdala and insula. Adapted from Etkin et al. (2007)

anxiety disorders and supports an understanding of anxiety derived from animal fear conditioning studies. Moreover, it settles debate in the literature about whether, as hypothesized, amygdalar hyperactivity is a hallmark of at least some common forms of clinical anxiety. 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, for SAD and specific phobia, only clusters showing greater activity in patients compared to controls were noted. By contrast, for PTSD, there were large regions of both hyper- and hypoactivation in patients. Extensive hypoactivation was found in the dorsal ACC and dorsomedial PFC as well as in ventral portions of the ACC and the ventromedial PFC (see Fig. 3). These hypoactivations were significantly more common in PTSD than in the other two anxiety disorders. There was also a small cluster of hypoactivation in the dorsal part of the amygdala, spatially distinct from the more ventral cluster showing hyperactivity in patients. Interestingly, no differences between anxiety disorder patients and matched controls were found in lateral prefrontal regions involved in cognitive control. The results above also held true when only symptom provocation studies were used in the analysis.

Of the three disorders, PTSD is considered to be more severe, and has more 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 exuberant 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



**Fig. 3** Clusters in which significant hyperactivation or hypoactivation was found in patients with PTSD, SAD, and Specific Phobia relative to comparison subjects and in healthy subjects undergoing fear conditioning. Notable are PTSD-specific hypoactivations in the dorsal and ventral portions of the medial prefrontal cortex. Adapted from Etkin et al. (2007)

and memories, rumination, affective instability (e.g., anger outbursts), anhedonia, and a sense of negative foreboding (APA 1994).

In the light of the previous discussion on emotional processing and implicit regulation by the limbic-medial prefrontal circuit, Etkin and Wager (2007) proposed that the robust hypoactivation in the medial PFC in PTSD reflects a deficit in implicit emotion regulation occurring in the absence of deliberate attempts at emotional control. This neural abnormality would therefore be reflected clinically in symptoms of emotion dysregulation and anxiety generalization. In the framework provided by the information processing model for the limbic-medial prefrontal emotion circuit shown in Fig. 1, patients with PTSD appear to have dysfunction in both the dorsal monitoring/evaluation and the ventral regulation components.

Others have recently proposed that medial PFC deficits in PTSD reflect a core abnormality in extinction of learned fear (Milad et al. 2006; Rauch et al. 2006). It would seem, however, that dysfunction of a more general implicit evaluation and regulation system for negative emotional stimuli by the medial PFC would more readily explain the range of emotion dysregulation symptoms in PTSD, and may subsume within it a deficit in fear extinction. Much work, however, needs to be done in this area before any firm conclusions can be drawn. In particular, theoretical and experimental attention must also be paid to the distinction between dorsal medial frontal regions involved in the monitoring, evaluation, or experiencing of emotion, and ventral regions involved in emotion regulation, as this distinction is growing clearer in the basic science literature.

An important role for the medial PFC in PTSD is supported as well by results from structural imaging studies. A number of these studies have reported decreased gray matter volumes in patients with PTSD in both the dorsal and ventral portions of the ACC or medial PFC (Karl et al. 2006; Kasai et al. 2008; Yamasue et al. 2003). One study examined variation in ACC volume as a function of trauma exposure or a putative genetic vulnerability for PTSD, assessed by comparing identical twin pairs discordant for combat exposure or PTSD, and found that decreased ACC volumes reflected the presence of PTSD symptoms rather than simply exposure to trauma without resulting symptoms or a genetic vulnerability to PTSD (Kasai et al. 2008). Interestingly, studies in rodents suggest that exposure to an uncontrollable stressor, which may reflect some aspects of the effects of traumas on patients with PTSD, resulted in dendritic retraction in a rodent analog of human medial PFC, potentiated fear conditioning, and interfered with fear extinction (Amat et al. 2005; Izquierdo et al. 2006). Thus, medial prefrontal dysfunction may be an important factor maintaining the symptoms of PTSD, and may to some degree have resulted from long-lasting effects of the trauma on basic aspects of medial prefrontal neuronal architecture.

### ***1.8 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 afford an



opportunity to 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, presentation of faces with different expressions can trigger limbic system activation in healthy subjects, and can thus be used as a probe for emotional processing in disorders where abnormal social signaling is not a central feature (i.e., not SAD, in which face stimuli are disorder-specific symptom triggers). 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 likewise also resulted in amygdalar hyperactivity in PTSD (Shin et al. 2005). Patients with specific phobia, meanwhile, showed similar amygdalar responses to emotional faces as controls (Wright et al. 2003). These data suggest that dysregulation within the limbic-medial prefrontal circuit during the processing of disorder nonspecific negative stimuli may be characteristic of states of generalized emotional dysregulation, such as those seen in PTSD, and does not merely reflect the presence of anxiety *per se*. Comparable experiments, however, have not yet been reported in other anxiety disorders, and will be important for further testing of this hypothesis.

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 analysis of emotional processing within and outside of awareness. Several recent studies have shown that elevated generalized anxiety (e.g., trait anxiety) in nonpsychiatric populations is associated with exaggerated amygdalar activation, most sensitively detected when emotional stimuli are processed outside of awareness or in 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 (Bryant et al. 2008b; Rauch et al. 2000). 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. By extension, this information will also be useful in understanding the interplay between emotional reactivity and regulation processes in shaping symptomatology.

## 2 Generalized Anxiety Disorder

Despite its prevalence, generalized anxiety disorder (GAD) has not been a focus of neuroimaging studies on anxiety, and thus very little is known about the neural abnormalities associated with it. The data discussed above can establish several hypotheses about the neurobiology of GAD, and a handful of studies have recently emerged which can begin to address these hypotheses. Several recent GAD studies

have used fearful expression faces to probe amygdalar activity, and found that consciously presented fearful faces do not result in amygdalar hyperactivation in GAD patients (Blair et al. 2008; Whalen et al. 2007). In fact, in one study, angry faces were even associated with amygdalar hypoactivation in patients (Blair et al. 2008). Of note, in one of these studies, a cohort of subjects with SAD were scanned using the same task and, as expected, showed exaggerated amygdalar responses to fearful faces, providing a positive control (Blair et al. 2008).

While no study has as yet been reported using unconsciously presented threat in adults with GAD, one such study has recently been published in children and adolescents (Monk et al. 2008). In this study, subjects were presented with fearful face stimuli presented only outside of awareness, and thus a direct comparison of conscious to unconscious threat processing was not possible. As predicted, however, patients with pediatric GAD showed exaggerated amygdalar responses to unconsciously processed disorder nonspecific threat (Monk et al. 2008). It will be important in future work to extend this paradigm to adults and to directly compare neural responses to conscious and unconscious threat.

We recently found evidence of the involvement of the amygdala in several ways in adult GAD (Etkin et al. in press), by analyzing the differential connectivity of the BLA and CMA, as described earlier. This analysis revealed an intra-amygdalar abnormality at the subregional level in GAD, which was accompanied by abnormal amygdalar coupling with a several brain networks.

Finally, Etkin et al. 2008 have recently reported preliminary data on GAD using the emotional conflict task described above. They found that patients with GAD failed to regulate emotional conflict, and as a consequence displayed exaggerated responses to conflict. At a neural level, patients failed to activate the ventral ACC and, failed to modulate the dorsomedial PFC. If these results hold up for a larger group, they would suggest that the similar dorsal monitoring/evaluation and ventral regulation PFC deficits seen in GAD and PTSD reflect a generalized dysfunction in implicit emotion regulation. Indeed, an essential part of the DSM-IV criteria for GAD is difficulty controlling worry (APA 1994), suggesting that dysfunction in general emotion regulation systems may be central to this disorder. There is also considerable controversy regarding the nature of GAD: whether it reflects an extreme temperament or a distinct psychiatric condition, and what its relationship with major depression is, given their high degree of comorbidity. Neuroimaging studies of GAD will be in an important position to address these issues.

### **3 Panic Disorder**

Very little is currently known about the neurobiology of panic disorder, in part because neuroanatomical models of panic disorder have been in flux, and in part due to a lack of sufficient neuroimaging data. Earlier models have emphasized abnormal brainstem responsiveness to carbon dioxide, termed the “false suffocation

alarm” (Klein 1993). Subsequent models have employed the fear conditioning paradigm just as other anxiety disorders like PTSD have (Gorman et al. 2000). Spontaneous panic attacks have been hypothesized to arise from overly sensitive fear circuitry that either inappropriately reacts to minor stimuli, or cannot restrain minor anxiety responses, which then develop into severe panic attacks (Gorman et al. 2000). Evidence of this and related hypotheses is largely lacking, though a recent imaging study of a single subject who had a spontaneous panic attack during fMRI scanning reported increased amygdala activity during the attack (Pfleiderer et al. 2007). Previous studies have induced panic attacks through pharmacological means during PET scanning, producing mixed results. These studies are also difficult to interpret in the context of global cerebral vascular perfusion changes during a panic attack, which can confound neural activity-related regional blood flow changes.

More conceptually clear is the phobic avoidance of reminders and possible triggers or exacerbating stimuli for panic attacks, which may be more readily understood within the context of a traditional fear conditioning model, though this too remains largely theoretical. The generalization of fear and anxiety beyond specific stimuli in panic disorder suggests some similarity to PTSD and GAD. A medial prefrontal deficit may therefore account for the persistence of free-floating anxiety and emotional dysregulation in these disorders, which is not seen in SAD or specific phobia – disorders in which medial prefrontal function appears to be largely intact.

## 4 Obsessive-Compulsive Disorder

Unlike the anxiety disorders discussed above, obsessive-compulsive disorder (OCD) appears to have a distinct neural basis. In fact, many features of OCD differ from those of the other anxiety disorders, suggesting that it may no longer be part of the anxiety disorder category in revisions for DSM-V (Hollander et al. 2008). While amygdala activation has been reported in OCD (van den Heuvel et al. 2005), this appears to be the exception, rather than the rule. More prominently, abnormalities have been identified in cortico-striato-thalamic-cortical circuits that mediate motor planning and learning, as well as habits, but also play a role in a variety of cognitive and affective functions. The striatum receives input from a wide range of cortical regions, and projects to the thalamus, which gates neurotransmission back to the cortex. A particular focus for OCD has been on the lateral orbitofrontal cortex, anterior cingulate, and caudate nucleus. Abnormalities in the orbitofrontal cortex and ACC have been proposed to relate to obsessions in OCD, while striatal abnormalities have been suggested to lead to stereotyped or ritualistic behavior (Graybiel and Rauch 2000; Menzies et al. 2008; Saxena and Rauch 2000). Early resting metabolism studies demonstrated increased activity in the orbitofrontal cortex and caudate, an effect that has also been observed in symptom provocation studies (Menzies et al. 2008). A recent meta-analysis of performance of patients with OCD on a wide range of fMRI tasks found support for elevated orbitofrontal

and caudate activity in OCD, but also found involvement of several other regions in the ACC, medial and lateral PFC, as well as regions of striatal hypoactivation (Menzies et al. 2008). Neurosurgical interventions for severe OCD also reflect some of the regions consistently identified as abnormally engaged in imaging studies of OCD, with promising results reported for dorsal ACC lesions and deep brain stimulation in the striatum (Aouizerate et al. 2004; Dougherty et al. 2002). Abnormalities in OCD, therefore, do not readily fit into the limbic-medial PFC emotional processing circuit described above, further supporting its differentiation from the other anxiety disorders.

## 5 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 controls. Nonetheless, there are several suggestive studies that open the way to increasingly better designed and more sophisticated approaches. In one such study, Furmark et al. (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 waiting-list control subjects. Comparing treatment groups with a control group of waiting-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 1 year later. Along similar lines, though using resting brain metabolic imaging, Baxter et al. (1992) noted normalization of caudate hyperactivity in OCD after treatment with either fluoxetine or CBT (nine subjects per group).

Finally, Straube et al. (2006) examined subjects with spider phobia, and compared the effects of symptom provocation in a group randomized to receive brief, intensive CBT (two 4–5 h 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. Much, however, 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 et al. (2007) reported that increased rostral ACC and decreased amygdala activation to fearful faces at baseline predicts a better response to venlafaxine. Meanwhile, Bryant et al. (2008a) 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. 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 treatment strategy. Second, a common brain region (e.g., rostral ACC) may be broadly predictive of the likelihood of a patient to respond 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 aspect of implicit emotion regulation mediated by the medial PFC may be the ultimate predictor of treatment response, across varied treatments and disorders.

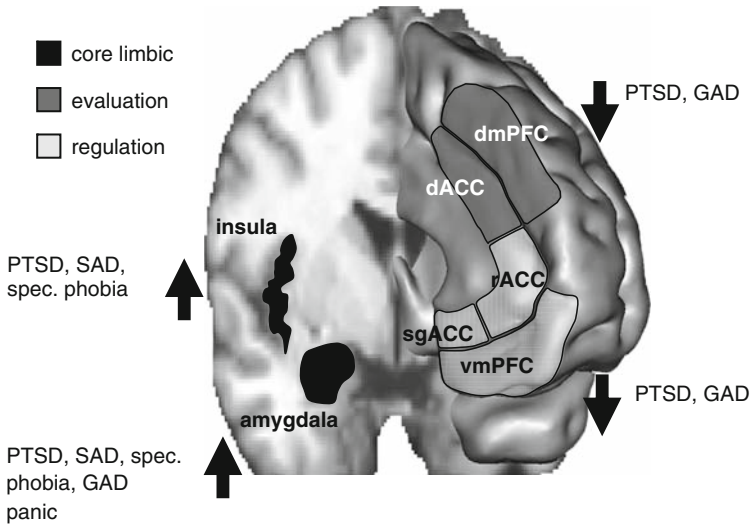
## 6 Conclusion

In this chapter I have outlined a limbic-medial prefrontal neural circuit involved in the reactivity to and regulation of negative emotional stimuli. Figure 1 presents an information flow conceptual model of this circuit in which it is argued that a set of core limbic regions (amygdala, insula, hypothalamus, PAG) perform the initial evaluation of an emotional stimulus, and are critical for generating a coordinated physiological and subjective response to that stimulus indicative of emotional activation. Information about the emotional stimulus is conveyed to ventral prefrontal regions including the rostral ACC and ventromedial PFC, as well as to dorsal prefrontal regions including the dorsal ACC and dorsomedial PFC. The latter structures may get information about the emotional nature of the stimulus either through the direct influence of limbic regions or indirectly through projections from ventral prefrontal structures. Activation of the dorsal ACC and dorsomedial PFC enables more extensive evaluation of the emotional stimulus, and may gate the

access of that information into conscious awareness. Recruitment of the rostral ACC and ventromedial PFC either through the direct influence of limbic regions or through information flow from the dorsal ACC or dorsomedial PFC then results in context-appropriate feedback regulation of limbic structures involved in the emotional response. This feedback may take the form of inhibition or activation, depending on the context and goal of the organism with regard to the emotional stimulus.

As described, the limbic-medial prefrontal circuit appears to play an important role in emotion regulation occurring in the absence of deliberate efforts at regulation, thus implying that it underlies certain forms of “implicit” emotion regulation. By contrast, explicit emotion regulation appears to consistently involve activation of lateral prefrontal structures important in nonemotional forms of cognitive control. Deliberate emotion regulation, however, may be achieved through access to the medial PFC by lateral prefrontal structures.

Strikingly, abnormalities in clinical anxiety disorders are frequently and consistently noted within elements of the limbic-medial prefrontal circuit. Across most or all anxiety disorders, with the exception of OCD, which involves alterations outside of the limbic-medial prefrontal circuit, patients have been found to activate the amygdala and/or insula more than controls (see summary in Fig. 4). The apparent overlap between these effects and activation in healthy subjects of the amygdala and insula during the processing of negative emotional stimuli, including during



**Fig. 4** Summary of functional alterations within nodes of the limbic-medial prefrontal circuit outlined in Fig. 1 for several anxiety disorders (PTSD, SAD), panic disorder, generalized anxiety disorder (GAD), and specific phobia). While all of these disorders appear to have in common abnormalities in the amygdala or the insula, only those in which anxiety is generalized and emotion is more widely dysregulated (PTSD and GAD), have prominent dysfunction in both medial prefrontal nodes of the circuit

fear learning, suggests that hyperactivation of these structures in anxiety disorder patients is related to symptoms of hyperarousal and hypervigilance – symptoms shared across anxiety disorders.

Disorders in which generalization of anxiety or profound dysregulation of emotion are prominent, however, appear to additionally be associated with hypoactivation in both the dorsal and ventral regions of the medial PFC (see Fig. 4). An understanding of how dorsal medial prefrontal structures evaluate emotional stimuli and recruit emotion regulation mechanisms in the ventral medial PFC is thus essential to better comprehend the neural bases of the generalized symptoms of PTSD and GAD. Moreover, preliminary indications are that the response of anxious individuals to treatment is positively predicted by pretreatment levels of activity in the medial PFC. These extremely preliminary findings suggest that some of the same emotion evaluation and regulation mechanisms that may underlie aspects of emotion dysregulation symptomatology in PTSD, and GAD may also determine the capacity of a patient to benefit from treatment.

The data discussed in this chapter, along with the information flow circuit model proposed, are intended to provide an integrated account of the functional neuroanatomy of normal negative emotional processing and its dysfunction in clinical anxiety disorders. While it is clear that certain domains have been well investigated and the literature now allows for the creation of specific neuroanatomical hypotheses for future experiments, it is also readily apparent that a great deal of work is needed in several of these disorders and in the study of treatment interventions. Importantly, the limbic-medial prefrontal neural circuit perspective outlined in this chapter may allow for exciting future directions in the development of novel therapeutics, identification of genetic or environmental vulnerability factors through the use of an endophenotype approach, improvements in diagnosis and disorder classification, and in the prognostication and tracking of the success of treatment.

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