Curr Psychiatry Rep (2015) 17: 49
DOI 10.1007/s11920-015-0586-9

ANXIETY DISORDERS (A PELISSOLO, SECTION EDITOR)

Neuroimaging and Anxiety: the Neural Substrates of Pathological and Non-pathological Anxiety

James M. Taylor[1] · **Paul J. Whalen**[1]

Published online: 10 May 2015

Abstract Advances in the use of noninvasive neuroimaging to study the neural correlates of pathological and non-pathological anxiety have shone new light on the underlying neural bases for both the development and manifestation of anxiety. This review summarizes the most commonly observed neural substrates of the phenotype of anxiety. We focus on the neuroimaging paradigms that have shown promise in exposing this relevant brain circuitry. In this way, we offer a broad overview of how anxiety is studied in the neuroimaging laboratory and the key findings that offer promise for future research and a clearer understanding of anxiety.

Keywords Anxiety · Neuroimaging · Amygdala · Prefrontal cortex · Anterior cingulate cortex · Insula

Introduction

Anxiety disorders remain the most prevalent of all psychiatric disorders comprising 18 % of all diagnoses in the USA (across a 12-month period; [1, 2]). This high prevalence, along with the associated costs of health care utilization, lost productivity, and lower health-related quality of life [3], highlights the importance of enhancing an overall understanding of how these disorders manifest. Anxiety disorder research has localized and highlighted neural correlates consistent across affected individuals, determined how these can be targeted by various treatments, and ascertained the extent to which these predict the efficacy of a given treatment prior to its initiation. Indeed, noninvasive techniques, such as functional magnetic resonance imaging (fMRI), continue to offer promise as a means to advance the neurobiological models of these disorders and identify the neural responses associated with symptoms of anxiety, to inform targeted pharmacological interventions, and to aid in the diagnosis or prediction of treatment responses [4, 5, 6•]. Further, these techniques may assist in the development of more personalized treatment options that take into account a given individual's likelihood of benefiting from one treatment strategy over another.

Anxiety disorders are a class of psychiatric disorders characterized by features of excessive fear and anxiety as well as behavioral disturbances [7]. In essence, anxiety can best be conceptualized as a sustained psychological state comprising the anticipation of a future threat, while fear is best thought of as the transient emotional reaction to specific stimuli or events [7, 8]. Even though anxiety and fear are normal states that can actually serve adaptive functions, disorders may develop when the symptoms of anxiety become disruptive and impair an individual's functioning [9]. As an example, it is adaptive to respond with fear to a threatening stimulus like a snake, however, that response would no longer be adaptive once realizing the snake is safely behind Plexiglass at the zoo [10].

The anxiety disorders differ in the types of external events or internal concerns that induce the behavioral and neural responses associated with each specific disorder [7]. Given the similarities across the disorders in terms of the induced anxiety reaction, this review will focus more broadly on anxiety disorders in general and not on differences between the various subtypes. In addition, although posttraumatic stress disorder (PTSD) is no longer listed under "Anxiety Disorders"

This article is part of the Topical Collection on *Anxiety Disorders*

✉ James M. Taylor
james.m.taylor.gr@dartmouth.edu

[1] Department of Psychological and Brain Sciences, Dartmouth College, 6207 Moore Hall, Hanover, NH 03755, USA

in DSM-5, this review will also discuss findings from research on PTSD as it involves many of the same regions and networks associated with other DSM-IV and DSM-5 anxiety disorders. Our purpose here is to offer a detailed account of the neural circuitry and major regions involved in the behavioral and cognitive manifestations of fear and anxiety, on both a clinical and nonclinical level.

The use of neuroimaging techniques, such as fMRI, to examine the neural underpinnings of anxiety disorders serves as a means to not only understand the neurocircuitry involved but also aid in the diagnosis and treatment of these disorders [5, 6•, 11•]. The neuroimaging findings reviewed here offer information about both structural and functional neural differences in anxiety. We will focus on neuroimaging studies that use stimuli comprising emotionally expressive faces, social threat and evaluation, and negative images to induce emotional responses in anxious subjects as well as "resting state" paradigms that capture neural differences in baseline functioning. Following a discussion of these paradigms, we will discuss findings consistent across studies that implicate distinct regions in the manifestation of anxiety disorders. Specifically, we will focus on the amygdala, the prefrontal cortex (especially the medial prefrontal cortex [mPFC] and anterior cingulate cortex [ACC]), and the insula. Although other brain regions are implicated in the behavioral and neural presentation of anxiety disorders, this review will focus discussion on these consistently and robustly activated regions. Finally, we will offer a summary of these findings and what they may mean for future research into the diagnosis and treatment of anxiety disorders.

Paradigms

Many fMRI studies assessing the differences in neural responding as a function of anxiety level or diagnosis present individuals with faces of various emotional expressions. This technique is largely based on findings that faces themselves serve as biologically relevant and predictive stimuli that consistently activate neural regions thought to be involved in fear and anxiety, most notably the amygdala [10, 12, 13]. Because facial expressions (e.g., fearful) can be both negative and ambiguous [10, 13], they inherently allow for the observer to draw inferences as to the message being conveyed by the face. In essence, negative facial expressions effectively trigger an "as if" emotional state, in terms of cognitive and physiological responding, in the observer.

Masked presentations of facial expressions, in which an emotionally salient face is presented briefly and immediately followed by a non-expressive face, allow for these stimuli to be shown to the observer without their explicit knowledge of having seen them. Further, these paradigms activate the same regions involved in fear and anxiety and may minimize the likelihood of top-down regulation of implicitly driven emotional responses [9, 14, 15]. Because negative facial expressions can also predict the presence or future appearance of a threat, they may also trigger another core component of anxiety disorders, i.e., the anticipation of later threats. Thus, the use of negative facial expressions, such as fear, builds upon findings pointing to the importance of the amygdala in aversive conditioning [16–18] with the idea that these faces, in and of themselves, are usefully thought of as conditioned stimuli (CSs) [10].

Indeed, the amygdala and prefrontal cortex (PFC) are critically implicated in classical conditioning and extinction [18, 19•], a process that may be aberrant in anxiety disorders. Early rodent work (discussed in more detail later) has demonstrated the extent to which the amygdala and PFC are involved in the acquisition, extinction, and recall of extinction of conditioned fear responses [20, 21], findings that have been observed in humans with similar results [22]. These classical fear-conditioning studies involve the pairing of previously neutral stimuli (CS) with aversive stimuli (UCS) such that during fear acquisition, the acquired response, be it neural or physiological, to the CS (now called the CR) approximates the response to the UCS (UCR) [23]. Extinction occurs when the CR is no longer observed to the CS because the UCS is no longer presented with the CS [19•, 23, 24]. Interestingly, spontaneous recovery of the previously extinguished response can occur when time elapses after extinction [23]. Recent work suggests that the extent of this recovery is positively correlated with an individual's self-reported level of intolerance of uncertainty [25•] and highlights the extent to which individual differences in self-reported measures can contribute to fear learning and memory.

Human functional neuroimaging allows for a measure of responses in regions thought to be involved in the acquisition and extinction of responses to CSs that predict aversive noises [26], images [27], or shocks [22]. Since anxiety disorders involve both transient reactions to and sustained psychological anticipation of threat, studies of aversive conditioning and extinction allow for direct assessment of the underlying neural correlates of these two main components of the disorder.

Other methods seek to assess differences in neural functioning that manifest when participants are not engaged in instructed tasks. This work focuses on the functioning of the brain's default network—a specific system engaged preferentially when individuals are not focused on the external environment or any explicit tasks [28]. Of particular interest is the finding that some of the same regions that comprise this default mode network are also engaged in processing self-

related, compared to other-related, character traits [29]. Being that generalized anxiety disorder (GAD) involves excessive worry about various domains outside of the individual's control [7], it is useful to consider how the regions and networks involved in self-focus and self-awareness can lead to the onset and exacerbation of anxiety disorders and their symptoms.

Although this is certainly a modest overview of the number of paradigms employed to study anxiety disorders, it serves as a starting point for this review and offers a considerable representation of paradigms utilized by numerous research studies in this domain.

Brain Regions Implicated in Anxiety

Amygdala

The amygdala is a critical component of the neural circuitry involved in the detection of biologically relevant cues [5, 12, 30], aversive conditioning [16–18], and the acquisition and expression of aversive memories [31]. Broadly, the amygdala can be thought of as being made up of two subdivisions, the centrocorticomedial and basolateral divisions, with approximately 12 distinct nuclear divisions in total [32]. Work from nonhuman primates shows that this region also has widespread connectivity with a variety of subcortical and cortical regions [33]. The human literature has also shed light on the extensive connectivity of the amygdala. Although the detailed neurocircuitry of the amygdala is beyond the scope of this review ([32, 33] for a more comprehensive description), it is critical to keep in mind that the etiology of anxiety disorders implicates not only the amygdala but also reciprocally connected brain regions. Indeed, the function of these circuits will be as critical to the understanding anxiety as the function of any one given neural region.

The amygdala responds robustly to a number of experimental stimuli including fearful faces [10, 13, 14], aversive images [27], and cues that predict aversive outcomes such as shocks [22, 26]. Given the number of stimuli to which the amygdala activates, it is possible to design various paradigms all aimed at targeting this critical structure [16–18].

Amygdala and the Anxiety Disorders Amygdala hyperresponsivity is one of the more consistent findings across studies of the anxiety disorders [34•]. Hariri and colleagues [35] found that amygdala reactivity to environmental threat is modulated by a regulatory variant (5-HTTLPR) in the human serotonin transporter gene. Specifically, their work shows that hyperreactivity in the amygdala is short allele driven [35]. Additional work by Furmark and colleagues [36] found that heightened amygdala responsivity to social provocation was modulated by one or two short alleles in the promoter region of the human serotonin transport system. Furthermore, individuals homozygous for the short allele appear to engage neural systems that enhance fear and arousal to a greater degree than those carrying the long allele in response to an acute laboratory stressor [37•]. Together, these findings offer a genetic basis for variations in amygdala responding and argue that amygdala excitability can serve as an endophenotype for the analysis of neuropsychiatric disorders [36].

Many studies aimed at understanding the neural correlates of social anxiety disorder (SAD) or generalized social anxiety disorder (gSAD) have incorporated emotionally salient images of a social nature. These include negative and threatening facial expressions, which activate the amygdala in SAD [38] and in generalized social phobia [39] as well as other images imbued with a social context. For instance, when presented with negative images from the International Affective Picture System (IAPS) [40], individuals with gSAD displayed heightened bilateral amygdala activity compared to controls, and the extent of this activation was associated with the severity of the disorder [41]. Using images of fearful faces, Blair and colleagues [42] found elevated amygdala responsivity in individuals with generalized social phobia. Additionally, increased right amygdala activation was also observed in patients with SAD in response to angry, compared to neutral, schematic facial expressions [43]. Taken together, these studies highlight the consistency of a heightened amygdala response to social stimuli in anxiety disorders in which socially relevant stimuli trigger the symptom response profile.

Exaggerated amygdala activity in response to the anticipation of giving a speech, a type of social evaluative threat, has also been found in patients with generalized social phobia [44]. In addition, amygdala activation was exaggerated in response to spider pictures in subjects with spider phobia [45]. Though this argues for a domain specific response in certain phobias, these same spider-phobic patients also expressed greater amygdala activation to general fear and disgust-inducing photos suggesting a more general response to disgust-inducing stimuli [45].

In a group of patients with acute PTSD, the amygdala response to masked fearful faces, compared to masked happy faces, positively correlated with symptom severity [46]. Studies of subjects with generalized anxiety disorder (GAD) report similar findings of exaggerated amygdala responsivity. Whalen and colleagues [5], for example, found that the extent of amygdala reactivity to fearful faces observed in a patient group before starting venlafaxine treatment, predicted the magnitude of a treatment response (reduction in HAM-A scores) following 8 weeks of treatment. Specifically, greater

amygdala activation coupled with decreased activation in rostral ACC (rACC) prior to treatment predicted a poorer treatment response. This study also highlights the delicate interplay between the amygdala and prefrontal regions in anxiety disorders, a point that we will discuss in more detail later.

Amygdala and Developmental Anxiety Disorders Amygdala findings in anxiety disorders, including SAD, are also present in youth and adolescent subjects. Indeed, most adult anxiety disorders tend to be preceded by adolescent disorders [47]. As is true of the findings discussed thus far, anxiety disorders in adolescence are also characterized by heightened amygdala reactivity to threat cues, e.g., fearful faces [47]. Similar findings were also observed in youth with GAD when exposed to masked angry faces. Specifically, Monk and colleagues [48] found greater right amygdala activation that also positively correlated with disorder severity. Of note, initial enhanced amygdala activity may be a typical and important characteristic of normal adolescent development, helping individuals learn the emotional and social significance of objects in their environment; however, failure of this response to subside over time when it is no longer warranted may be indicative of psychopathology [49, 50•].

Amygdala and Non-pathological Anxiety Subjects who report higher levels of trait anxiety also show heightened amygdala activation to emotional faces [11•, 51]. Presentions of masked fearful faces also produced activity in the amygdala, specifically the basolateral amygdala, which was predicted by individual differences in trait anxiety levels [52]. Work by Bishop and colleagues [53] shows that subjects with higher levels of state anxiety show a heightened amygdala response to fearful, compared to neutral faces, even when they are instructed not to attend to presented face stimuli. Using a classical fear-conditioning paradigm, Barrett and Armony [26] found that individuals with higher anxiety-related traits displayed not only a more resistant response during extinction, but also that this was accompanied by a hyperresponsive amygdala. These studies highlight the extent to which normal variations in self-reported anxiety levels can offer insight into how the systems implicated in the manifestation of anxiety disorders vary and leave some individuals susceptible to disorder development.

Prefrontal-Amygdala Connectivity

Nonhuman primate anatomy has shown that, in addition to its many subcortical connections, the amygdala is reciprocally connected with the frontal, insular, cingulate, and temporal cortices [33]. Interestingly, the projections to the cortex are heavier than the return projections [33, 54]. Work examining fear extinction recall in rats found that lesions of the infralimbic cortex did not prevent the acquisition of extinction learning, but rather, impaired later recall of that extinction learning [20]. Further, neurons in the infralimbic cortex were found to fire only when rats effectively recalled their extinction training on the following day [24]. These findings are relevant for patients with PTSD who hypercondition to traumatic events and sensory cues and show deficits in fear extinction [19•, 55, 56]. Furthermore, in patients with PTSD, failure to recall extinction learning was associated with hypoactivation in the ventromedial prefrontal cortex (vmPFC) [57]. These data are consistent with studies of subjects with PTSD who show reduced activation of vmPFC during script-driven imagery recall [58], recollection of personal trauma [59], and when presented with fearful faces [60].

Taken together, these data led Milad and Quirk [19•] to suggest that this vmPFC region might be a human homolog of rodent infralimbic cortex. Supporting this assertion, use of a two-day protocol to examine extinction recall in humans [22] found that activation of the vmPFC increased during extinction recall in healthy participants. Clearly, the vmPFC is strongly implicated in the consolidation, retention, and expression of extinction memories [61].

Though it is difficult to directly examine the connectivity between PFC and amygdala in humans [8, 19•], it has been suggested that the PFC exerts "top-down" control over the amygdala to attenuate a fear response that is no longer valid (i.e., the threat is no longer present or does not actually pose any danger to the viewer) [4]. Although there is evidence to suggest that subregions of the vmPFC function differentially [62], various studies offer strong support that the PFC plays a critical role in the regulation of the initial call to alarm triggered by the amygdala in response to any possible threat. Further, differences within the PFC can contribute to variations in anxiety levels in both clinical and nonclinical populations.

In youth with GAD, who showed increased right amygdala activation to masked angry faces, weaker negative coupling between the right amygdala and right ventrolateral PFC (vlPFC) was observed compared to controls in response to the angry faces [48]. Here, the heightened amygdala response without the increase in vlPFC activation, which likely serves as a compensatory mechanism to regulate the amygdala's response, appears to be a key feature of GAD in youth [48]. In adults with GAD, resting-state data suggest an abnormally coupled network comprised of the amygdala and dorsolateral PFC (dlPFC) with stronger connectivity appearing in the least anxious of these patients [63]. The connectivity between lPFC, vmPFC, and the basolateral amygdala consequently may be important for emotion regulation [63].

Using a resting-state paradigm to study whole-brain functional connectivity, Ding and colleagues [64] found aberrant connectivity in patients with SAD. Particularly, weaker negative correlations between the frontal lobe, mainly involving the right mPFC and occipital lobe, were positively correlated

with symptom severity [64]. Another resting-state study of participants with SAD found altered neural activity in bilateral angular gyrus as well as left mPFC [65]. These perturbations follow the consistent findings of decreased activity in both ACC and PFC in patients with SAD, which may represent a decreased ability for cognitive processing [66].

Using structural scans to examine gray matter volumes in the brain, Schienle and colleagues [67] found a positive correlation between volumes of dorsomedial PFC (dmPFC) and ACC and self-reports of symptom severity in patients with GAD. Patients in their study also displayed greater gray matter volumes in bilateral amygdala. Of note, dmPFC has previously been implicated in both worry states and anticipatory anxiety, offering a possible mechanism for some of the behavioral manifestations in GAD [67]. Also in patients with GAD, increased lateral frontal responses to angry faces were related to self-reported anxieties [42]. This study argues that this frontal pathology may be more important in the behavioral manifestation of GAD and that any amygdala dysfunction in this disorder may represent broader amygdala-frontal circuitry disruptions [42]. In other work, elevated resting-state activity in the vlPFC has been interpreted as a compensatory response rather than a cause of GAD itself [66]. Patients with GAD also show elevated activity in the ACC, and dmPFC when worry was triggered by mood inducing sentences [68]. This activation persisted in later resting-state scans and was positively correlated with symptom severity [68]. Paulus [11•] suggests that the GAD phenotype involves an altered top-down modulation of anxiety circuitry wherein the prefrontal cognitive control system attempts to downregulate limbic structures through cognitive activity, i.e., the worrying seen in GAD.

Indeed, psychotherapeutic treatments for patient with anxiety disorders generally lead to an increase in prefrontal activity and decreased activity in the amygdala wherein, if the treatments are successful, activity in the fear network more closely resembles healthy subjects [69]. For treatment responders, cognitive-behavioral therapy in particular appears to modify the neural circuits involved in emotion regulation and fear extinction, specifically reducing the dysfunction in the PFC [70].

Prefrontal-Amygdala Connectivity and Non-pathological Anxiety Findings highlighting the extent to which prefrontal regions are engaged when participants are asked to reappraise the meaning or context of emotionally evocative images [71] put forth the argument that the ability to regulate emotional responses may preferentially involve cognitive control regions such as PFC, orbito-frontal cortex (OFC), and cingulate control systems [72]. Indeed, the pattern of activation by which vmPFC is activated and amygdala activity is attenuated during emotion regulation is similar to the pattern of activation observed in rats during fear extinction recall [73]. Consequently, the extent to which an individual is able to engage these regions to attenuate their emotional responses appears to be a compensatory mechanism through which anxiety symptoms are mitigated [63]. Imbalanced activity in this network has also been observed in child and adolescent mood and anxiety disorders where increased responses in the vmPFC that are inversely correlated with amygdala responding predict fear extinction, attenuation of autonomic responses, and more positive interpretations of ambiguous stimuli [50•].

Resting-state work examining the functional connectivity between amygdala and regions of mPFC shows that individuals with higher levels of self-reported anxiety do not display the positive correlation between amygdala and ventral mPFC observed at rest in low-anxious subjects (vmPFC; [74•]). We interpret this finding to mean that a positive correlation between amygdala and vmPFC is a healthy functional relationship where these two brain structures are "on the same page" and in this way can communicate more adaptively in reaction to an emotional stressor, whereas if these two brain areas show uncorrelated activity at rest, perhaps amygdala reactions to emotional challenges are not as easily regulated by the prefrontal cortex. Indeed, Milad and colleagues [75] showed that amygdala and vmPFC activity at rest predicted activity in the other structure (respectively) during extinction training. These functional data fit nicely with previous structural diffusion tensor imaging (DTI) data showing that a stronger white matter connection between the amygdala and PFC predicts lower trait anxiety levels [76].

Using a letter-search task, Bishop [77] showed that individuals with high trait anxiety had reduced prefrontal activity when the task did not fully occupy attention, i.e., a low cognitive load condition. More specifically, the observed deficit in the recruitment of dlPFC in this study may represent a processing style that makes these individuals vulnerable to anxiety, perhaps through difficulties disengaging from task-irrelevant stimuli when attention is not fully captured by current tasks [77].

Although the majority of this section focused on the contributions of medial and lateral PFC to anxiety disorders, the remainder of this discussion on prefrontal contributions will concentrate on the role of anterior cingulate cortex (ACC). The functions of the ACC in emotion and anxiety have been summarized in terms of conflict resolution during the processing of emotional content [78, 79]. As mentioned in the section on the amygdala, Whalen and colleagues [5] found that responses in the amygdala and rACC to fearful faces correlated with reductions in anxiety severity in GAD patients. Specifically, increased rACC and decreased amygdala before treatment predicted better outcomes with venlafaxine [5]. Similar results were observed when participants with GAD were exposed to anticipatory cues signaling neutral or aversive scenes. Here, responses in the pregenual ACC (pgACC) predicted treatment success following venlafaxine treatment [80]. Specifically, increased activity in pgACC prior to

treatment correlated with a greater decrease in self-reported anxiety symptoms [80]. Taken together, these studies suggest that ACC activity may be useful for the differentiation of patients with GAD who may or may not respond to certain pharmacological treatments [81]. Using a version of the Stroop conflict task, Etkin and colleagues [82] demonstrated that activity in rACC was associated with the resolution of emotional conflict and offers that the rACC seems to inhibit amygdala responding to resolve this conflict. Consequently, this offers support to the idea that the extent of rACC activity may serve as an informative marker for an individual's ability to respond effectively to certain anxiety treatments.

Volumetric analyses also show neural differences in ACC in individuals with GAD. Specifically, self-reports of symptom severity in GAD patients were positively correlated with ACC volume [67]. Other work demonstrates a reduction in ACC volume in anxiety disorders without a correlation with symptom severity [83]. However, this latter study included patients with panic disorder, SAD, and GAD, which could contribute to the inconsistent findings. In recently diagnosed patients with PTSD, rACC volume, similar to functional findings in GAD, predicted cognitive behavioral therapy (CBT) response with greater volumes yielding a better treatment response [66]. Other work notes a reduction in ACC volume and activation with the reexperiencing of trauma in PTSD [1].

In terms of treatment, the ACC appears to be one of the main target structures that normalizes following successful CBT; however, different subregions of the ACC appear to be differentially affected as a function of disorder type [69]. For example, results from diffusion tensor imaging studies examining functional anisotropy values in GAD and PTSD patients found lower values in right anterior cingulate gyrus in PTSD compared to GAD [84], which suggests that different disorders do not act homogeneously on all affected structures. Furthermore, hypoactivation in both dorsal and rostral regions of ACC has been found in PTSD [85].

The ACC has also been implicated in the manifestation of specific phobia where processing of phobic threats is associated with increased ACC activation [70]. This response was attenuated, as were phobic symptoms, following successful CBT [70]. Panic patients also displayed decreased activation in the left ventral ACC following successful CBT [70]. Patients with general social phobia and GAD show difficulties engaging dorsal ACC (dACC) during tasks requiring them to reappraise emotionally evocative images [86]. Although these results conflict with other findings of enhanced ACC activation, the authors note that this deactivation may reflect a reduced capacity to engage these regions as a function of task demands, i.e., reappraise the meaning of emotionally salient images [86].

Patients with social phobia show a significant increase in rACC activity when viewing disgust faces [78]. Patients with generalized social phobia show reduced activity in prefrontal regions (such as dACC) during anticipation of giving a speech [44]. These studies highlight the ways in which these subregions of ACC respond to disorder specific tasks. In patients with gSAD, ACC activation was reduced, compared to controls, when the task required a shift of attention away from emotional faces, a finding which may indicate difficulty disengaging from emotionally salient faces [87•].

As is true of other regions of PFC, activation in ACC shows a differential response pattern as a function of anxiety-relevant traits. Specifically, using a classic fear-conditioning paradigm, Barrett and Armony [26] found heightened ACC activation to extinction compared to acquisition trials and that those with higher trait anxiety displayed a greater differential response between extinction and acquisition in the ACC. Given their amygdala findings (discussed above), the authors conclude that this activity may reflect a compensatory mechanism in the high trait anxious group by which the amygdala activity is attenuated [26].

Insula

In addition to the amygdala and PFC, the insula is a consistently implicated region in the etiology of anxiety disorders [1]. This region, activated during the anticipation of uncertain, aversive events [27], has also been separately found to correlate with subjective ratings of uncertainty [1, 88]. Anatomically speaking, as was true with the amygdala and PFC, the insula too has been found to maintain connections with both the amygdala and prefrontal regions [11•, 33, 89]. The insula also appears to contribute, through connections with other regions like the hypothalamus, to the regulation of activity in the autonomic nervous system [85]. Engel and colleagues [89] note that the insular cortices are involved in anxiety disorders by initiating and maintaining inputs modulating prefrontal and limbic structures. Further, it has been argued that the insula functions in awareness, the ability to maintain a sense of self, interoception, and subjective feelings states [11•, 90].

Insula and the Anxiety Disorders In gSAD, the insula shows a hyperactive response pattern to probes of social threat, and the extent of this activation correlates with levels of trait anxiety [41]. Enhanced insula activation was also observed when patients with gSAD attended to emotional faces [87•]. During an emotional word-encoding task, patients with anxiety disorders showed increased insula activation to negative words [91]. Indeed, insula activity during negative emotion processing seems to be a consistent finding [85]. In a resting-state study of patients with SAD, insula again showed a hyperactive response pattern [92]. Even in healthy subjects, heightened insula activation is associated with heightened levels of trait anxiety [89].

Insula and Non-pathological Anxiety In a healthy subject sample, Critchley and colleagues [93] found insula activation modulated by perceptual awareness of a threat stimulus. By pairing masked and unmasked faces with the delivery of an aversive tone, the authors showed a difference between amygdala activation, which responded to masked and unmasked faces, and insula activation, which was observed as a function of awareness of the threat stimuli, i.e., the unmasked condition only [93]. In another non-patient sample presented with ambiguously affective faces, insula activation has also been shown to correlate with individual levels of intolerance of uncertainty, i.e., the affective response to situations where outcomes are uncertain [88]. Insula activation to emotional faces was also heightened in a group of individuals with higher levels of trait anxiety [51].

Paulus [11•] argues that the relationship between the amygdala, mPFC, and insula involves the recognition, anticipation, and representation of self-relevant emotions. Given the role of the insula in subjective awareness and conditions of uncertainty, the aberrant functioning of this system in anxiety may lead to an over prediction of aversive outcomes by the insula or a system whereby the heightened arousal in the amygdala causes stimuli to be inaccurately categorized by the insula [11•]. What is clear is that although most of the literature on anxiety disorders seems to target limbic and prefrontal regions, Engel and colleagues' [89] argument that the insula, with its role in the perception of body states, warrants more attention is certainly valid.

Conclusions

In this review, we sought to highlight the neural regions and networks commonly implicated in the anxiety disorders. Although there are certainly other regions involved (e.g., the hippocampus has been implicated in stress, and the development of mood and anxiety disorders [66]), we attempted to focus on those showing some of the most consistent results. With this in mind, it is easy to see the extent to which observed results are malleable as a function of task type and the individual nuances of each anxiety disorder. The functional inconsistencies observed across tasks and disorder subtypes serve to highlight the heterogeneous nature of this class of psychiatric disorders.

We have described the importance of the amygdala, PFC (particularly the vmPFC and ACC), and insula in the etiology and manifestations of the behavioral correlates of anxiety disorders. We have shown not only how these regions may function atypically, but also how a disruption in one region may influence a larger circuit (e.g., amygdala-prefrontal circuitry). Although we discussed the potential benefits of focusing on aberrant functioning in a given region as a marker of a disorder, it is clear that treatment strategies must take into account the role of these regions within the broader circuit. Paulus [11•] nicely encapsulates this point by addressing how different anxiety phenotypes can be the result of hyperactive bottom-up processes or hypoactive top-down processes. Consequently, although the neural and behavioral signatures of these disorders may be similar, the target of treatment, and even the type of treatment chosen, will be very different. As neuroimaging continues to advance and fine-tune its methods, it will be important to continue to assess the relationship between the interplay of these regions and anxiety symptoms, both normal and pathological.

Compliance with Ethics Guidelines

Conflict of Interest James M. Taylor and Paul J. Whalen have received a grant from the NIMH (Grant No. MH080716).

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance

1. Damsa C, Kosel M, Moussally J. Current status of brain imaging in anxiety disorders. Curr Opin Psychiatry. 2008;22(1):96–110. doi:10.1097/YCO.0b013e328319bd10.
2. Kessler RC, Chiu WT, Demler O, Walters EE. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry. 2005;62(6):617–27. doi:10.1001/archpsyc.62.6.617.
3. Comer JS, Blanco C, Hasin DS, Liu SM, Grant BF, Turner JB, et al. Health-related quality of life across the anxiety disorders. J Clin Psychiatry. 2011. doi:10.4088/JCP.09m05094blu.
4. Rauch SL. Neuorimaging and the neurobiology of anxiety disorders. In: Handbook of affective sciences. Oxford: University Press; 2003. p. 963–75.
5. Whalen PJ, Johnstone T, Somerville LH, Nitschke JB, Polis S, Alexander AL, et al. A functional magnetic resonance imaging predictor of treatment response to venlafaxine in generalized anxiety disorder. Biol Psychiatry. 2008. doi:10.1016/j.biopsych.2007.08.019.
6.• Shin LM, Rauch SL, Pitman RK, Whalen PJ. The human amygdala in anxiety disorders. In: Whalen PJ, Phelps EA, editors. The human amygdala. New York: Guilford Press; 2009. p. 321–43. **A comprehensive review of the findings and approaches that comprises the field of neuroimaging the anxiety disorders**.
7. American Psychiatric Association. DSM 5. American Psychiatric Association; 2013.
8. Kim MJ, Loucks RA, Palmer AL, Brown AC, Solomon KM, Marchante AN, et al. The structural and functional connectivity of the amygdala: from normal emotion to pathological anxiety. Behav Brain Res. 2011;223(2):403–10. doi:10.1016/j.bbr.2011.04.025.

9. Rauch SL, Shin LM, Wright CI. Neuroimaging studies of amygdala function in anxiety disorders. Ann N Y Acad Sci. 2003;985(1):389–410. doi:10.1111/j.1749-6632.2003.tb07096.x.
10. Whalen PJ, Davis FC, Oler JA, Kim H, Kim MJ, Neta M. Human amygdala responses to facial expressions of emotion. In: Whalen PJ, Phelps EA, editors. The human amygdala. New York: Guilford Press; 2009. p. 265–88.
11.• Paulus MP. The role of neuroimaging for the diagnosis and treatment of anxiety disorders. Depress Anxiety. 2008;25(4):348–56. doi:10.1002/da.20499. **Where the current review focuses on the paradigms that helped identify relevant brain circuitry, Paulus offers a view based on outcomes**.
12. LeDoux J. The emotional brain: the mysterious underpinnings of emotional life. New York: Simon & Schuster Paperbacks; 1996.
13. Whalen PJ. Fear, vigilance, and ambiguity: initial neuroimaging studies of the human amygdala. Curr Dir Psychol Sci. 1998;7(6):177–88. doi:10.2307/20182537?ref=no-x-route:70ee559cf7b83a6038ec85d41c596aa2.
14. Whalen PJ, Rauch SL, Etcoff NL, McInerney SC, Lee MB, Jenike MA. Masked presentations of emotional facial expressions modulate amygdala activity without explicit knowledge. J Neurosci. 1998;18(1):411–8.
15. Rauch SL, Whalen PJ, Shin LM, McInerney SC, Macklin ML, Lasko NB, et al. Exaggerated amygdala response to masked facial stimuli in posttraumatic stress disorder: a functional MRI study. Biol Psychiatry. 2000;47(9):769–76. doi:10.1016/S0006-3223(00)00828-3.
16. Davis M. The role of the amygdala in fear and anxiety. Annu Rev Neurosci. 1992;15:353–75.
17. Kapp BS, Whalen PJ, Supple WF, Pascor JP. Amygdaloid contributions to conditioned arousal and sensory information processing. In: Aggleton JP, editor. The amygdala: neurobiological aspects of emotion, memory, and mental dysfunction. New York: Wiley-Liss; 1992. p. 229–54.
18. LeDoux JE. The amygdala and emotion: a view through fear. In: Aggleton JP, editor. The amygdala: a function analysis. 2nd ed. New York: Oxford University Press; 2000. p. 289–310.
19.• Milad MR, Quirk GJ. Fear extinction as a model for translational neuroscience: ten years of progress. Annu Rev Psychol. 2012. doi:10.1146/annurev.psych.121208.131631. **A review of the regions and networks involved in fear extinction that makes a compelling case that findings from animal literature can be translated to neuroimaging work in humans**.
20. Morgan MA, Romanski LM, LeDoux JE. Extinction of emotional learning: contribution of medial prefrontal cortex. Neurosci Lett. 1993;163(1):109–13. doi:10.1016/0304-3940(93)90241-C.
21. Quirk GJ, Russo GK, Barron JL, Lebron K. The role of ventromedial prefrontal cortex in the recovery of extinguished fear. J Neurosci. 2000;20(16):6225–31.
22. Phelps EA, Delgado MR, Nearing KI, LeDoux JE. Extinction learning in humans: role of the amygdala and vmPFC. Neuron. 2004. doi:10.1016/j.neuron.2004.08.042.
23. Bouton ME. Learning and behavior: a contemporary synthesis. Massachusettes: Sinauer Associates, Inc. Publishers; 2007.
24. Milad MR, Quirk GJ. Neurons in medial prefrontal cortex signal memory for fear extinction. Nature. 2002. doi:10.1038/nature01144.
25.• Dunsmoor JE, Campese VD, Ceceli AO, LeDoux JE, Phelps EA. Novelty-facilitated extinction: providing a novel outcome in place of an expected threat diminishes recovery of defensive responses. Biol Psychiatry. 2014. **This paper examines extinction in both a human and animal model and offers interesting implications for what these findings may mean for the use of extinction in clinical settings**.
26. Barrett J, Armony JL. Influence of trait anxiety on brain activity during the acquisition and extinction of aversive conditioning. Psychol Med. 2008;39(02):255. doi:10.1017/S0033291708003516.
27. Sarinopoulos I, Grupe DW, Mackiewicz KL, Herrington JD, Lor M, Steege EE, et al. Uncertainty during anticipation modulates neural responses to aversion in human insula and amygdala. Cereb Cortex. 2010. doi:10.1093/cercor/bhp155.
28. Buckner RL, Hanna JA, Schacter DL. The brain's default network. Ann N Y Acad Sci. 2008. doi:10.1196/annals.1440.011.
29. Kelley WM, Macrae CN, Wyland CL, Caglar S, Inati S, Heatherton TF. Finding the self? An event-related fMRI study. J Cogn Neurosci. 2002;14(5):785–94. doi:10.1162/08989290260138672.
30. Davis M, Whalen PJ. The amygdala: vigilance and emotion. Mol Psychiatry. 2001;6:13–34.
31. Knight DC, Nguyen HT, Bandettini PA. The role of the human amygdala in the production of conditioned fear responses. NeuroImage. 2005. doi:10.1016/j.neuroimage.2005.03.020.
32. LeDoux JE, Schiller D. The human amygdala: insights from other animals. In: Whalen PJ, Phelps EA, editors. The human amygdala. New York: Guilford Press; 2009. p. 43–60.
33. Freese JL, Amaral DG. Neuroanatomy of the primate amygdala. In: Whalen PJ, Phelps EA, editors. The human amygdala. New York: Guilford Press; 2009. p. 3–42.
34.• Shin LM, Liberzon I. The neurocircuitry of fear, stress, and anxiety disorders. Neuropsychopharmacology. 2010;35(1):169–91. doi:10.1038/npp.2009.83. **Explains the roots of anxiety research, i.e. the study of fear while also discussing those circuits commonly implicated in stress and anxiety disorders**.
35. Hariri AR, Drabant EM, Munoz KE. A susceptibility gene for affective disorders and the response of the human amygdala. Arch Gen Psychiatry. 2005;62:146–52. doi:10.1016/S0006-3223(02)01543-3.
36. Furmark T, Tillfors M, Garpenstrand H, Marteinsdottir I, Långström B, Oreland L, et al. Serotonin transporter polymorphism related to amygdala excitability and symptom severity in patients with social phobia. Neurosci Lett. 2004;362(3):189–92. doi:10.1016/j.neulet.2004.02.070.
37.• Drabant EM, Ramel W, Edge MD, Hyde LW, Kuo JR, Goldin PR, et al. Neural mechanisms underlying 5-HTTLPR-related sensitivity to acute stress. Am J Psychiatry. 2012;169(4). doi:10.1176/appi.ajp.2011.10111699. **Highlights the extent to which advances in using genetics to understand individual differences in behaviors and responses to stress continue to better inform our understanding of how different disorders may manifest**.
38. Fouche J-P, van Der Wee NJA, Roelofs K, Stein DJ. Recent advances in the brain imaging of social anxiety disorder. Hum Psychopharmacol Clin Exp. 2012;28(1):102–5. doi:10.1002/hup.2281.
39. Stein MB, Goldin PR, Sareen J, Zorrilla LTE, Brown GG. Increased amygdala activation to angry and contemptuous faces in generalized social phobia. Arch Gen Psychiatry. 2002;59(11):1027–34. doi:10.1001/archpsyc.59.11.1027.
40. Lang PJ, Bradley MM, Cuthbert BN. International affective picture system (IAPS): technical manual and affective ratings. Gainesville: NIMH Center for the Study of Emotion and Attention, University of Florida; 1997.
41. Shah SG, Klumpp H, Angstadt M, Nathan PJ, Phan KL. Amygdala and insula response to emotional images in patients with generalized social anxiety disorder. J Psychiatry Neurosci. 2009;34(4):296-302
42. Blair K, Shaywitz J, Smith B, Rhodes R, Geraci M, Jones M, et al. Response to emotional expressions in generalized social phobia and generalized anxiety disorder: evidence for separate disorders. Am J Psychiatry. 2008;165:1193-202.
43. Evans KC, Wright CI, Wedig MM, Gold AL, Pollack MH, Rauch SL. A functional MRI study of amygdala responses to angry

schematic faces in social anxiety disorder. Depress Anxiety. 2008;25(6):496–505. doi:10.1002/da.20347.
44. Lorberbaum JP, Kose S, Johnson MR, Arana GW, Sullivan LK, Hamner MB, et al. Neural correlates of speech anticipatory anxiety in generalized social phobia. NeuroReport. 2004;15(18):2701.
45. Schienle A, Schäfer A, Walter B, Stark R, Vaitl D. Brain activation of spider phobics towards disorder-relevant, generally disgust- and fear-inducing pictures. Neurosci Lett. 2005;388(1):1–6. doi:10.1016/j.neulet.2005.06.025.
46. Armony JL, Corbo V, Clément MH, Brunet A. Amygdala response in patients with acute PTSD to masked and unmasked emotional facial expressions. Am J Psychiatr. 2005;162(10):1961–3.
47. Beesdo K, Lau JYF, Guyer AE, McClure-Tone EB, Monk CS, Nelson EE, et al. Common and distinct amygdala-function perturbations in depressed vs anxious adolescents. Arch Gen Psychiatry. 2009;66(3):275–85. doi:10.1001/archgenpsychiatry.2008.545.
48. Monk CS, Telzer EH, Mogg K, Bradley BP, Mai X, Louro HMC, et al. Amygdala and ventrolateral prefrontal cortex activation to masked angry faces in children and adolescents with generalized anxiety disorder. Arch Gen Psychiatry. 2008;65(5):568–76. doi:10.1001/archpsyc.65.5.568.
49. Tottenham N, Hare TA, Casey BJ. A developmental perspective on human amygdala function. In: Whalen PJ, Phelps EA, editors. The human amygdala. New York: Guilford Press; 2009. p. 107–17.
50.• Casey BJ, Ruberry EJ, Libby V, Glatt CE, Hare T, Soliman F, et al. Transitional and translational studies of risk for anxiety. Depress Anxiety. 2011;28(1):18–28. doi:10.1002/da.20783. **Examines early markers that can serve as risk factors for anxiety and highlights the importance of brain region and network development**.
51. Stein M, Simmons A, Feinstein J, Paulus M. Increased amygdala and insula activation during emotion processing in anxiety-prone subjects. Am J Psychiatr. 2007;164(2):318–27. doi:10.1176/appi.ajp.164.2.318.
52. Etkin A, Klemenhagen KC, Dudman JT, Rogan MT, Hen R, Kandel ER, et al. Individual differences in trait anxiety predict the response of the basolateral amygdala to unconsciously processed fearful faces. Neuron. 2004;44(6):1043–55.
53. Bishop SJ, Duncan J, Lawrence AD. State anxiety modulation of the amygdala response to unattended threat-related stimuli. J Neurosci. 2004;24(46):10364–8.
54. Ghashghaei HT, Hilgetag CC, Barbas H. Sequence of information processing for emotions based on the anatomic dialogue between prefrontal cortex and amygdala. Neuroimage. 2007;34(3):905–23.
55. Pitman RK. Post-traumatic stress disorder, conditioning, and network theory. Psychiatr Ann. 1988;18:182–9.
56. Orr SP, Metzger LJ, Lasko NB, Macklin ML, Peri T, Pitman RK. De novo conditioning in trauma-exposed individuals with and without posttraumatic stress disorder. J Abnorm Psychol. 2000;109(2):290.
57. Milad MR, Pitman RK, Ellis CB, Gold AL, Shin LM, Lasko NB, et al. Neurobiological basis of failure to recall extinction memory in posttraumatic stress disorder. Biol Psychiatry. 2009. doi:10.1016/j.biopsych.2009.06.026.
58. Shin LM, McNally RJ, Kosslyn SM, Thompson WL, Rauch SL, Alpert NM, et al. Regional cerebral blood flow during script-driven imagery in childhood sexual abuse-related PTSD: a PET investigation. Am J Psychiatr. 1999;156(4):575–84.
59. Shin LM, Orr SP, Carson MA, Rauch SL, Macklin ML, Lasko NB, et al. Regional cerebral blood flow in the amygdala and medial prefrontal cortex during traumatic imagery in male and female Vietnam veterans with PTSD. Arch Gen Psychiatry. 2004;61(2):168–76. doi:10.1001/archpsyc.61.2.168.
60. Shin LM, Wright CI, Cannistraro PA, Wedig MM, McMullin K, Martis B, et al. A functional magnetic resonance imaging study of amygdala and medial prefrontal cortex responses to overtly presented fearful faces in posttraumatic stress disorder. Arch Gen Psychiatry. 2005;62(3):273–81. doi:10.1001/archpsyc.62.3.273.
61. Milad MR, Rauch SL, Pitman RK, Quirk GJ. Fear extinction in rats: implications for human brain imaging and anxiety disorders. Biol Psychol. 2006. doi:10.1016/j.biopsycho.2006.01.008.
62. Myers-Schulz B, Koenigs M. Functional anatomy of ventromedial prefrontal cortex: implications for mood and anxiety disorders. Mol Psychiatry. 2012;17(2):132–41. doi:10.1038/mp.2011.88.
63. Etkin A, Prater KE, Schatzberg AF, Menon V, Greicius MD. Disrupted amygdalar subregion functional connectivity and evidence of a compensatory network in generalized anxiety disorder. Arch Gen Psychiatry. 2009;66(12):1361–72. doi:10.1001/archgenpsychiatry.2009.104.
64. Ding J, Chen H, Qiu C, Liao W, Warwick JM, Duan X, et al. Disrupted functional connectivity in social anxiety disorder: a resting-state fMRI study. Magn Reson Imaging. 2011;29(5):701–11. doi:10.1016/j.mri.2011.02.013.
65. Qiu C, Liao W, Ding J, Feng Y, Zhu C, Nie X, et al. Regional homogeneity changes in social anxiety disorder: a resting-state fMRI study. Psychiatry Res Neuroimaging. 2011;194(1):47–53. doi:10.1016/j.pscychresns.2011.01.010.
66. Martin EI, Ressler KJ, Binder E, Nemeroff CB. The neurobiology of anxiety disorders: brain imaging, genetics, and psychoneuroendocrinology. Psychiatr Clin N Am. 2009. doi:10.1016/j.psc.2009.05.004.
67. Schienle A, Ebner F, Schäfer A. Localized gray matter volume abnormalities in generalized anxiety disorder. Eur Arch Psychiatry Clin Neurosci. 2011;261(4):303–7. doi:10.1007/s00406-010-0147-5.
68. Paulesu E, Sambugaro E, Torti T, Danelli L, Ferri F, Scialfa G, et al. Neural correlates of worry in generalized anxiety disorder and in normal controls: a functional MRI study. Psychol Med. 2010. doi:10.1017/S0033291709005649.
69. Quidé Y, Witteveen AB, El-Hage W, Veltman DJ, Olff M. Differences between effects of psychological versus pharmacological treatments on functional and morphological brain alterations in anxiety disorders and major depressive disorder: a systematic review. Neurosci Biobehav Rev. 2012;36(1):626–44. doi:10.1016/j.neubiorev.2011.09.004.
70. Porto P, Oliveira L, Mari J, Volchan E, Figueira I, Ventura P. Does cognitive behavioral therapy change the brain? A systematic review of neuroimaging in anxiety disorders. J Neuropsychiatry Clin Neurosci. 2009;21:114-25.
71. Gross JJ. The emerging field of emotion regulation: an integrative review. Rev Gen Psychol. 1998;2(3):271–99. doi:10.1037/1089-2680.2.3.271.
72. Ochsner KN, Gross JJ. The cognitive control of emotion. Trends Cogn Sci. 2005. doi:10.1016/j.tics.2005.03.010.
73. Quirk GJ, Beer JS. Prefrontal involvement in the regulation of emotion: convergence of rat and human studies. Curr Opin Neurobiol. 2006. doi:10.1016/j.conb.2006.07.004.
74.• Kim MJ, Gee DG, Loucks RA, Davis FC, Whalen PJ. Anxiety dissociates dorsal and ventral medial prefrontal cortex functional connectivity with the amygdala at rest. Cereb Cortex. 2011;21(7):1667–73. doi:10.1093/cercor/bhq237. **Describes differences in resting functional connectivity between prefrontal cortex and amygdala based on individual differences in self-reported anxiety levels**.
75. Linnman C, Zeidan MA, Furtak SC, Pitman RK, Quirk GJ, Milad MR. Resting amygdala and medial prefrontal metabolism predicts functional activation of the fear extinction circuit. Am J Psychiatr. 2012;169(4):415–23.
76. Kim MJ, Whalen PJ. The structural integrity of an amygdala-prefrontal pathway predicts trait anxiety. J Neurosci. 2009;29(37):11614–8. doi:10.1523/JNEUROSCI.2335-09.2009.

77. Bishop SJ. Trait anxiety and impoverished prefrontal control of attention. Nat Neurosci. 2009;12(1):92–8. doi:10.1038/nn.2242.
78. Amir N, Klumpp H, Elias J, Bedwell JS, Yanasak N, Miller LS. Increased activation of the anterior cingulate cortex during processing of disgust faces in individuals with social phobia. Biol Psychiatry. 2005. doi:10.1016/j.biopsych.2005.01.044.
79. Bush G, Luu P, Posner MI. Cognitive and emotional influences in anterior cingulate cortex. Trends Cogn Sci. 2000. doi:10.2307/1694556?ref=no-x-route:777b52a786100de0d844c4a2e8e385f7.
80. Nitschke J, Sarinopoulos I, Oathes D, Johnstone T, Whalen P, Davidson R, et al. Anticipatory activation in the amygdala and anterior cingulate in generalized anxiety disorder and prediction of treatment response. Am J Psychiatr. 2009;166(3):302–10. doi:10.1176/appi.ajp.2008.07101682.
81. Jappe L, Klimes-Dougan B, Cullen KR. Brain imaging and the prediction of treatment outcomes in mood and anxiety disorders. In: *Functional brain mapping and the endeavor to understand the working brain*. 2013, 279-300. doi:10.5772/55446.
82. Etkin A, Egner T, Peraza DM, Kandel ER, Hirsch J. Resolving emotional conflict: a role for the rostral anterior cingulate cortex in modulating activity in the amygdala. Neuron. 2006;51(6):871–82. doi:10.1016/j.neuron.2006.07.029.
83. van Tol MJ, van Der Wee NJA, van den Heuvel OA, Nielen MMA, Demenescu LR, Aleman A, et al. Regional brain volume in depression and anxiety disorders. Arch Gen Psychiatry. 2010;67(10):1002–11. doi:10.1001/archgenpsychiatry.2010.121.
84. Zhang L, Zhang Y, Li L, Li Z, Li W, Ma N, et al. Different white matter abnormalities between the first-episode, treatment-naive patients with posttraumatic stress disorder and generalized anxiety disorder without comorbid conditions. J Affect Disord. 2011;133(1–2):294–9. doi:10.1016/j.jad.2011.03.040.
85. Etkin A, Wager T. Functional neuroimaging of anxiety: a meta-analysis of emotional processing in PTSD, social anxiety disorder, and specific phobia. Am J Psychiatry. 2007;164:1476–88.
86. Blair KS, Geraci M, Smith BW, Hollon N, DeVido J, Otero M, et al. Reduced dorsal anterior cingulate cortical activity during emotional regulation and top-down attentional control in generalized social phobia, generalized anxiety disorder, and comorbid generalized social phobia/generalized anxiety disorder. Biol Psychiatry. 2012. doi:10.1016/j.biopsych.2012.04.013.
87.• Klumpp H, Post D, Angstadt M, Fitzgerald DA, Phan KL. Anterior cingulate cortex and insula response during indirect and direct processing of emotional faces in generalized social anxiety disorder. Biol Mood Anxiety Disord. 2013;3(1):7. doi:10.1186/2045-5380-3-7. **Highlights the influence of attention and the ability to shift focus from social stimuli in the behavioral and neural manifestation of gSAD**.
88. Simmons A, Matthews SC, Paulus MP, Stein MB. Intolerance of uncertainty correlates with insula activation during affective ambiguity. Neurosci Lett. 2008;430(2):92–7. doi:10.1016/j.neulet.2007.10.030.
89. Engel K, Bandelow B, Gruber O, Wedekind D. Neuroimaging in anxiety disorders. J Neural Transm. 2009;116(6):703–16. doi:10.1007/s00702-008-0077-9.
90. Craig AD. How do you feel—now? The anterior insula and human awareness. Nat Rev Neurosci. 2009;10(1):59–70. doi:10.1038/nrn2555.
91. van Tol MJ, Demenescu LR, van der Wee N, Kortekaas R, Nielen MMA, Den Boer JA, et al. Functional magnetic resonance imaging correlates of emotional word encoding and recognition in depression and anxiety disorders. Biol Psychiatry. 2012. doi:10.1016/j.biopsych.2011.11.016.
92. Liao W, Chen H, Feng Y, Mantini D, Gentili C, Pan Z, et al. Selective aberrant functional connectivity of resting state networks in social anxiety disorder. NeuroImage. 2010;52(4):1549–58. doi:10.1016/j.neuroimage.2010.05.010.
93. Critchley HD, Mathias CJ, Dolan RJ. Fear conditioning in humans: the influence of awareness and autonomic arousal on functional neuroanatomy. Neuron. 2002;33(4):653–63. doi:10.1016/S0896-6273(02)00588-3.