Published in final edited form as:
Nat Rev Neurosci. 2013 July ; 14(7): 488–501. doi:10.1038/nrn3524.

Uncertainty and Anticipation in Anxiety:

An integrated neurobiological and psychological perspective

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Abstract

Uncertainty about a possible future threat disrupts our ability to avoid it or to mitigate its negative impact, and thus results in anxiety. Here, we focus the broad literature on the neurobiology of anxiety through the lens of uncertainty. We identify five processes essential for adaptive anticipatory responses to future threat uncertainty, and propose that alterations to the neural instantiation of these processes results in maladaptive responses to uncertainty in pathological anxiety. This framework has the potential to advance the classification, diagnosis, and treatment of clinical anxiety.

The human brain, it has been written, is an “anticipation machine, and ‘making future’ is the most important thing it does”[1]. The ability to use past experiences and information about our current state and environment to predict the future allows us to increase the odds of desired outcomes, while avoiding or bracing ourselves for future adversity. This ability is directly related to our level of certainty regarding future events – how likely they are, when they will occur, and what they will be like. Uncertainty diminishes how efficiently and effectively we can prepare for the future, and thus contributes to anxiety.

Although this relationship between uncertainty about future negative events and anxiety makes intuitive sense, there has been a disconnect between this conceptualization of anxiety and most neuroimaging investigations of clinical anxiety disorders. The predominant focus of this research has been on heightened emotional reactivity to aversive events; however, the tasks commonly used in this research might not fully engage the psychological processes that are at the heart of anxious pathology – that is, the anticipatory cognitive, affective, and behavioral processes executed to avoid or reduce the impact of a potential threat. These anticipatory processes serve an adaptive function when executed at a level commensurate with the likelihood and severity of threat, but can be maladaptive when conducted excessively[2]. Comprehensive information about the probability, timing, and nature of a future negative event promotes more efficient allocation of these resources, but such information is rarely available owing to the inherent uncertainty of the future.

Here, we argue that a common feature across anxiety disorders is aberrant and excessive anticipatory responding under conditions of threat uncertainty. This perspective has historical roots in animal research on stress responding and fear learning, as well as previous influential models of anxious pathology. We integrate and expand upon this research in our

new Uncertainty and Anticipation Model of Anxiety (UAMA), which emphasizes five processes involved in responding to threat uncertainty that function maladaptively in anxiety. We illustrate neural mechanisms associated with each of these five processes, and review evidence linking anxious pathology to disturbances in a distributed set of brain regions, including the amygdala, bed nucleus of the stria terminalis (BNST), ventromedial prefrontal cortex (vmPFC), orbitofrontal cortex (OFC), anterior mid-cingulate cortex (aMCC), and anterior insula.

Anxiety and uncertainty

What is anxiety?

The word "anxiety" can refer to a range of related phenomena: a class of psychiatric disorders, particular patterns of behavior in animal models, and trait-like negative affect (Box 1). Another perspective on anxiety specifies a future-oriented *emotional state* experienced by all humans to varying degrees:

> It is quite likely that the summed frequency and intensity of the fear responses of any given individual to clear and imminent physical or psychological threat … would lag far behind the summed amount of fear in response to the anticipation of such events and the myriad anxious "What if …" mental representations of possible future events that are common in daily life[3].

This quote underscores two critical aspects of anxiety. First, heightened anxiety in *anticipation* of aversive events might be more important than exaggerated responses to those events for understanding the neurobiological and psychological basis of anxiety disorders. Second, anxiety is related to anticipatory representations of possible (that is, *uncertain*) future events.

Fear and anxiety can be distinguished according to how much certainty one has regarding the likelihood, timing, or nature of future threat[2,4–8]. Decades of research in rodent models have provided tremendous insight into hierarchically organized defense systems, the underlying neurobiology, and the circumstances under which different defensive responses are recruited[6,9,10]. Environmental cues indicating the unambiguous presence of immediate threat give rise to intense "fearful" defensive behaviors (that is, "fight or flight"), whereas more diffuse, distal, or unpredictable threat cues produce "anxious" risk assessment behavior[11] that is likely to persist until such uncertainty is resolved. Gray's influential theory of anxiety[6], which was grounded in the specific effects of anxiolytics on anxious but not fearful behavior[12], posited a central role for a behavioral inhibition system in responding to uncertainty or conflict by increasing the negative valence of stimuli and promoting avoidance behavior. More recent translational research using fear-potentiated startle in rats and humans has provided persuasive evidence for neuropharmacological and neuroanatomical differences between short-lived, "fearful" responses to discrete threat and sustained, "anxious" responses to unpredictable threats[4,13]. Motivated by this previous work, we define anxiety here as anticipatory affective, cognitive, and behavioral changes in response to uncertainty about potential future threat.

This view of anxiety is more circumscribed than that reflected in the literature on trait anxiety (Box 1), but is highly relevant to each of the six major anxiety disorders specified in the DSM-IV[14] (generalized anxiety disorder (GAD), panic disorder (PD), social anxiety disorder (SAD), posttraumatic stress disorder (PTSD), specific phobias, and obsessive-compulsive disorder (OCD)). Despite controversy about the classification of anxiety pathology (Box 1), the experience of anxiety as defined here is central to the distress of all these disorders. Accordingly, an increased focus on neural and psychological mechanisms associated with maladaptive anticipatory responses under conditions of threat uncertainty is essential if we are to better understand clinical anxiety.

Uncertainty, unpredictability, and uncontrollability

Unpredictability and uncertainty are highly similar and are often used interchangeably, but have slightly different connotations. Unpredictability is often used in a sense that is more quantitative and amenable to experimental manipulation to describe aspects of the environment or features of a particular stimulus, such as its probability of occurring, when or where it may occur, or how intense it will be. A rich body of research in rodent models has shown that organisms consistently prefer predictable shocks and associated contexts[15–17], and that predictability ameliorates the negative effects of stress[18]. Uncertainty is a broader and more diverse construct; in the domain of decision-making (Box 2), for example, uncertainty can be decomposed into distinct levels including sensory uncertainty, state uncertainty, rule uncertainty, and outcome uncertainty[19]. Uncertainty better captures subjective aspects of one's internal state, and thus appears more frequently in the literature on human anxiety disorders, whereas unpredictability is used more frequently in laboratory studies with controlled conditions. While we discuss both constructs, our primary focus is on uncertainty, which is inextricably linked to the phenomenological experience of anxiety arising from unpredictable future events.

Uncertainty makes it difficult to prepare properly for future events: one must strike a balance between preparatory actions that are more efficient (but potentially inadequate) and those that are more effective (but potentially unnecessary). As posited below for UAMA, clinical anxiety disorders are associated with disruptions to a number of processes that bias one toward overly conservative (that is, effective but not efficient) preparatory behavior in the face of unpredictable threat.

Also relevant to uncertainty is uncontrollability (Box 1). According to one definition, uncontrollability is present when the probability or nature of a given event remains unchanged irrespective of any actions an individual may take[11,18]. Controllability over future events generally implies certainty about their occurrence, whereas the opposite need not be true. Control can also be thought of as "the belief that one has at one's disposal a response that can influence the aversiveness of an event"[20]. Thus, increased certainty about future events is an antecedent to control, not necessarily of the occurrence of events, but of adaptive anticipatory responses that can mitigate these events' negative impact. Uncertainty, on the other hand, precludes one from exercising this form of control, and leads to preparations that are "diffuse, psychologically expensive, and of questionable effectiveness"[21].

Responses to uncertainty in anxiety

To understand why uncertainty about future threat is so disruptive in anxiety, we propose five processes involved in maladaptive responses to such conditions: inflated estimates of threat cost and probability, increased threat attention and hypervigilance, deficient safety learning, behavioral and cognitive avoidance, and heightened reactivity to threat uncertainty. Each process can serve an adaptive role in responding to and reducing uncertainty about threat (Box 3). A central tenet of UAMA is that disruptions to the neural circuitry that promote these adaptive responses underlie maladaptive responses to uncertainty in pathological anxiety[2]. It is unclear whether these neural disruptions cause anxiety disorders. There is much evidence that anxiety disorders are multiply determined and involve genetic and early environmental factors that predispose individuals to pathological anxiety later in life. In addition, practicing anxious thought and behavioral patterns further strengthens associated neural connections. A patient with an anxiety disorder probably builds up neural pathways of anxiety just as a concert pianist strengthens neural pathways of musicianship, through hours of daily practice. Considered in this light, the successful treatment of so many of these patients is a testament to the amazing neuroplasticity of the human brain.

The framework proposed here is not an attempt to reject or replace other models of anxious pathology, but rather incorporates ideas from diverse perspectives and disciplines[2,4,5,7,11,15,22–30]. In fact, each of the five processes showcased here, their neurobiological correlates, and their relation to anxious pathology have been previously discussed to varying degrees. The UAMA diverges from other models in placing the five processes on equal footing, rather than focusing on a single, primary process. Similarly, a wide network of brain areas are featured rather than singling out one that is especially prominent in anxiety. The primary focus of this review is on research from the past decade that has used increasingly sophisticated imaging methods and experimental paradigms for examining anxiety in the human brain. Nonetheless, the UAMA is heavily informed by decades of research in animal models and humans emphasizing the disruptive and stressful impact of uncontrollable and unpredictable aversive events[2,4,15,16,18,31].

It is important to note that there are processes beyond the five proposed here that have received attention in prior work, most notably disrupted fear learning. Fear conditioning has been a cornerstone of translational research that has contributed monumentally to our understanding of fear and anxiety and their neurobiology. Influential learning models propose that environmental or interoceptive cues are more readily associated with threat in anxious individuals[22,30,32,33], or that impaired discriminative fear learning results in a state of internal uncertainty even when the environment is objectively predictable, thus resulting in anxiety[7,34,35]. Aberrant learning is a critical factor in anxious pathology that contributes to or interacts with several UAMA processes.

Ultimately, the theoretical advance of this paper is not in the definition of new processes that are critical for anxious pathology, but rather in the consolidation and integration of multiple perspectives and areas of research typically considered in relative isolation from one another. By focusing this body of work through the common lens of uncertainty, we provide

a unifying theme around which an integrated neurobiological and psychological model of anxious pathology can be constructed.

Inflated estimates of threat cost and probability

Adaptive responses to uncertainty about potential future threats rely on accurate estimates of the probability and cost of such events. Highly anxious individuals show neural alterations that contribute to biased assessments of the probability or cost of uncertain negative events, resulting in overly pessimistic expectations. When presented with hypothetical scenarios about negative events, whether common or rare, highly anxious individuals frequently show "judgment bias" – that is, elevated estimates of the cost or probability of such events. Such biases are seen in high trait anxiety[36–38] (Box 1) and in individuals with GAD[39,40], SAD[41,42], and elevated PTSD symptoms[43]. There is evidence that elevated cost estimates contribute more to anxious pathology than do elevated probability estimates[38,41]. Combined with the universal tendency to overestimate very small probabilities[44], this judgment bias could result in substantial anticipatory distress when anxious individuals face even the slightest possibility of a negative outcome[45] (Box 4).

Judgment biases in anxious individuals suggest abnormalities in the neural circuitry associated with expected value calculation (Figure 1a). Dorsomedial prefrontal regions (including Brodmann areas 8 and 10 and the aMCC) contribute to probability assessment[46–48], whereas activity in the orbitofrontal cortex (OFC) reflects the anticipated cost of future events[49,50]. In addition to showing activation for primary appetitive and aversive reinforcers[51], the OFC also represents the integrated value of higher-level, complex outcomes[52] or the expected value of future states[53]. Although it has weak projections to primary motor areas, the OFC influences decision-making processes by relaying information about the expected value of competing alternatives to regions involved in action selection and execution, such as the striatum, lateral PFC, and cingulate cortex[54].

The calculation of expected value is a dynamic process, and heightened threat expectancies in anxious individuals could also reflect disruptions to reinforcement learning processes that are used to update threat expectancies. Prediction error signals generated by midbrain dopaminergic neurons[55] reflect a mismatch between predicted and actual outcomes, and result in increasingly accurate future predictions for both rewarding and aversive stimuli[56]. Reinforcement learning models have been applied to functional magnetic resonance imaging (fMRI) studies of fear conditioning, revealing activity consistent with aversive prediction errors in the ventral striatum, anterior insula, and rostral cingulate cortex[57–59]. Disrupted aversive prediction error signaling in anxiety disorders results in a failure to appropriately adjust expectancies when predicted negative events do not occur[28,60].

Increased threat attention and hypervigilance

Anxiety also involves alterations to attentional processes that facilitate threat detection[61], which result in heightened perceptions of harm: "The range of stimuli that can evoke anxiety in generalized anxiety disorder may increase until almost any stimulus is perceived as a danger"[62]. This tendency to view ambiguous stimuli as threatening, called "interpretation bias," has been observed when patients with GAD are presented with ambiguously described

scenarios or spoken words with multiple meanings[40,63,64]. Disorder-specific interpretation biases have been reported for ambiguous social scenarios and facial expressions in SAD[65,66]; ambiguous interoceptive cues in PD[67]; and sentence stems that could be completed to form combat-related words in veterans with PTSD[68]. Given these interpretation biases, along with increased attention for objectively threatening stimuli ("attentional bias")[61], elevated estimates of threat under conditions of uncertainty might reflect adaptive anticipatory responses to a world that appears more dangerous to anxious individuals.

Biased threat attention and observations of hypervigilance across anxiety disorders implicate amygdala hyperactivity[2] (Figure 1B). Heightened resting metabolic activity and blood flow in the amygdala have been observed in participants with PD[69], PTSD[70,71] (but see[72,73]), and SAD[74]. In non-human primates, resting amygdala metabolism is correlated with a combined behavioral and hormonal assay of anxious temperament[75,76]. In addition to these alterations at rest, a meta-analysis of functional imaging studies in PD, PTSD, and SAD showed elevated task-induced amygdala activity across diagnoses and paradigms[77]. In GAD, studies of emotional anticipation[78] and implicit emotion regulation[79] reported amygdala hyperactivity across experimental conditions, suggesting indiscriminately elevated amygdala activation. Of particular relevance for our emphasis on uncertainty and anticipation, heightened amygdala activity has been reported in socially anxious individuals about to deliver a public speech[80] and in clinically anxious children anticipating unknown peer feedback[81].

Heightened amygdala activity in anxiety has implications for distinct aspects of fear learning mediated by different amygdala subregions. Influential fear conditioning perspectives[22,23,33] emphasize exaggerated associative learning for environmental cues and aversive outcomes[35], a process that critically involves the basolateral amygdala (BLA)[82]. The central nucleus of the amygdala (CeA) has a complementary role in attentional gating that moderates such learning[83,84]. According to the Pearce-Hall learning model[85], environmental cues that have previously been paired with surprising (that is, unpredicted) outcomes demand greater attentional resources, increasing the likelihood for new associations to be formed with these cues (which are thus said to have high associability). In rodents, activity in the CeA reflects a cue's associability[83,84]. A study of reversal learning in humans similarly found greater amygdala responses to cues that had been paired with surprising outcomes on recent trials[59]. The CeA projects heavily to cholinergic basal forebrain structures, which can selectively modulate sensory processing and therefore enhance learning after surprising events through their ascending cholinergic projections to cortical regions[86].

In highly anxious individuals, tonic and indiscriminate activation of the amygdala[2,69–71,74,75,77–81] results in decreased sensitivity to the associability of cues, inefficient deployment of attentional resources toward the most relevant features of the environment, and impaired learning of stimulus-outcome associations. As a result, the anxious individual is biased to interpret conditions of uncertainty as threatening; moreover, impaired discriminative learning can lead to an internal state of uncertainty about threat despite objectively predictable conditions[34]. The amygdala has rich, bidirectional

connections with the ventral striatum and OFC[87,88], which assign subjective value to potential future events. Together, these regions form a network in which increased attention to threat as facilitated by the amygdala is likely to affect the value assigned to future events, and differences in valuation as facilitated by the striatum and OFC are likely to influence attentional deployment. While the amygdala is highlighted in nearly all neurobiological accounts of anxious pathology, emphasis is often placed on its role in the expression of *fear*[2,22]. It might be more useful to consider increased amygdala activity as reflecting increased vigilance[29] under conditions of uncertainty.

Deficient safety learning

Environmental safety signals are reliable indicators that threat will not occur, and thus relieve individuals from a state of anticipatory anxiety[18,27]. Under conditions of uncertainty, weak or non-existent contingencies between cues and negative outcomes make it difficult to identify safety signals, particularly for highly anxious individuals[89] whose biased attention toward threat impedes fine-grained discriminative analysis of environmental cues. Heightened reactivity to objectively safe conditions has been observed across anxiety disorders using discriminative fear conditioning paradigms[35]. In addition to contingent presentations of a conditioned stimulus (CS+) and unconditioned stimulus (US), these paradigms include another cue (CS−) that is presented in the absence of the US and therefore associated with safety. Failure to show discriminative physiological responses to a CS+ and CS−, reflecting increased fearful responding to the CS−, has been reported in PD[90,91], PTSD[92,93], and mixed childhood anxiety disorders[94]. The application of conditional discrimination tasks[95] in anxiety disorders may clarify whether these results reflect impaired *learning* about safety or a failure to inhibit fearful responding following successful safety learning.

Investigations in rodents and humans have identified a ventral PFC–amygdala circuit involved in learning about and responding to safety in potentially threatening contexts (Figure 1C). In rats, electrical stimulation of the infralimbic cortex reduces the expression of amygdala-mediated conditioned fear responses[96], and inactivation of this region impairs the acquisition and recall of fear extinction[97]. Neuroimaging studies in humans have revealed a comparable role for the vmPFC in responding to cues that predict safety[58,98–100]. In clinical anxiety disorders, altered function and connectivity of the vmPFC and amygdala have been linked to deficient fear extinction, one of the dominant models of PTSD[101]. Impaired recall of extinction in PTSD was associated with decreased vmPFC activation[102], which has also been reported in patients with PTSD exposed to traumatic or aversive stimuli[77,103,104]. Relative to controls, individuals with GAD showed less discriminant vmPFC activity for cues visually similar to a reinforced CS+, reflecting generalization of learned fear to safe cues[105]. Indiscriminately elevated amygdala activation during the anticipation of neutral and aversive pictures in GAD[78] further suggests a failure of patients to down-regulate amygdala activity in response to safe neutral cues. Notably, patients with heightened anticipatory responses in the pregenual ACC (just superior to the vmPFC) showed the largest decrease in symptoms following venlafaxine treatment[78], consistent with other studies of pre-treatment predictors of treatment response in anxiety[106] and depression[107,108]. Thus, some preservation of regulatory function in the ACC/vmPFC has prognostic benefits in anxiety

and mood disorders. Complementing this fMRI research, diffusion tensor imaging (DTI) has revealed microstructural alterations to the uncinate fasciculus in individuals with GAD[109], SAD[110], and elevated trait anxiety[111].

Additional findings and anatomical considerations challenge a simple model in which the vmPFC inhibits the amygdala and reduces stress-related responses[112]. In Vietnam veterans, vmPFC lesions were found to protect against PTSD[113]. Several studies have reported increased activation of the vmPFC and pregenual ACC in PTSD[114,115]. In addition, lesions to the macaque OFC (extending laterally from the vmPFC) can reduce anxious behavior, perhaps by altering BNST activity[116]. Future research is needed to clarify the role of the vmPFC in anxiety, and to investigate whether alterations to specific sectors of the vmPFC or their connectivity with the amygdala explain these disparate findings[112].

Behavioral and cognitive avoidance

Avoidant behavior and thoughts, including worry, prevent anxious individuals from being exposed to evidence that might contradict negative predictions about the future[25,26,117]. According to classic two-process theory[23,30], exaggerated fear conditioning to environmental threat cues leads to operant learning of avoidance behavior to reduce fear. Whereas these processes are assumed to operate implicitly in animal models, the extension of this thinking to human anxiety disorders suggests that avoidance may further heighten threat expectancies under conditions of uncertainty. Because events that are avoided or worried about typically fail to occur, behavioral and cognitive avoidance tendencies are negatively reinforced and anxious individuals develop false beliefs that they prevented these negative outcomes[39].

According to tenets of emotional processing theory and exposure therapy[26], effective psychological interventions for fear and anxiety disorders require activation of an individual's "fear structure," which opens the door for new information about safety to compete with existing beliefs or memories of fear. In this way, exposure-based therapy is functionally and neurally similar to laboratory extinction training, and directly targets avoidant behavior. SAD, PTSD, and OCD are marked by behavioral avoidance of situations associated with potential threat or harm. Patients with PD develop beliefs that they can engage in safety-seeking thoughts or actions that prevent panic attacks, while in actuality such activities protect the CS+ from being extinguished[30,118], consistent with animal models of avoidance learning[119]. By engaging in worry, individuals with GAD and other anxiety disorders avoid intense negative emotions about potential feared outcomes, but also miss out on the opportunity to correct inaccurate beliefs about the likelihood and consequences of such events. Pushing patients to overcome their avoidant tendencies – whether that entails challenging thoughts about threat in cognitive behavioral therapy[24] (CBT) or exposure to feared scenarios in exposure therapy[26] – is a crucial first step in reducing elevated expectancies of threat in the face of uncertainty.

Active avoidance learning paradigms in animal models have demonstrated the importance of circuitry involving the striatum and basal amygdala in acquiring learned avoidance behavior[120–122], and have shown that inhibition of the CeA by infralimbic cortex is required to inhibit freezing responses to a CS+ and allow adaptive avoidance of the US[123]. Initial

human imaging studies indicate a key role in active avoidance for the amygdala and interconnected regions involved in decision-making and subsequent action, including the OFC and lateral PFC, ventral and dorsal striatum, and aMCC[124–126] (Figure 1D). Additionally, heightened expectancies about the emotional impact of potential feared outcomes resulting from anterior insula dysfunction lead to avoidance of situations involving threat uncertainty[28,125]. Successful treatment of avoidance behavior in spider phobics led to reductions in activity in the anterior insula and aMCC[127,128] and to increased dorsolateral PFC activity[128]. As research on active avoidance in anxiety disorders evolves, the simultaneous investigation of deficient fear extinction will be highly informative for understanding interactions between avoidance and impaired safety learning.

Heightened reactivity to threat uncertainty

Because anticipating the future almost always involves some uncertainty, neural processes that influence reactivity and attitudes toward uncertainty are crucial for determining adaptive responses to this state. Across species, physiological responding to threat is enhanced when there is uncertainty about its nature, probability, or timing[15,16,129–134]. Humans show larger startle responses for cues that can precede either low or high intensity shocks than for cues that always precede high intensity shocks[129], for cues preceding shock on 20% or 60% of trials than for cues that predict shock with 100% certainty[130], and under conditions of temporal unpredictability[131]. Furthermore, aversive events that are not fully predictable have a greater negative impact on mood, state anxiety, and physiological indices of reactivity than those that are fully predictable[132–134]. Exposure to unpredictably timed, neutral tones also elicits more amygdala activity and anxious behavior in both mice and humans than predictably timed tones[135], underscoring the notion that uncertainty itself – without aversive outcomes – can increase anxiety.

Relative to healthy controls, individuals with PD[90] and PTSD[92] showed elevated startle responses during a temporally unpredictable interstimulus interval (ISI), but not for a predictable threat condition. Distinct extended amygdala regions mediate behavioral, autonomic, and endocrine responses to predictable and unpredictable threat through descending projections to hypothalamic, midbrain, and brainstem regions[6,10,13]. Whereas the medial CeA coordinates rapid, phasic fear responses to stressors that are imminent and relatively certain, the BNST is activated by conditions of sustained, unpredictable threat[4,13]. This functional dissociation is mirrored by differential responses to benzodiazepines, which reduce behavioral expressions of fear for sustained but not phasic threat in rodents[4], due at least in part to decreased BNST activity[136]. In humans, benzodiazepines also reduced fear-potentiated startle to unpredictable[137] but not predictable threats[138]. Spider phobics showed greater BNST activity than controls during temporally unpredictable anticipation of spider pictures[139]. BNST activation has also been reported in healthy populations during sustained, temporally unpredictable threat[140–142], with particularly elevated activity in individuals with high trait anxiety[143].

Individual differences in reactivity to threat uncertainty are also reflected in subjective reports. Intolerance of uncertainty (IU) is defined as the inability to accept the possibility that a negative event may occur in the future, irrespective of the probability of its

occurrence[144]. For individuals high in self-reported IU, uncertainty results in depleted attentional resources and disruptions to cognitive, behavioral, and emotional functioning[144]. IU scores are elevated in GAD[144,145], SAD[146], OCD[146], and depression[146].

Many imaging studies have shown the importance of the anterior insula (Figure 1E) in responding to uncertainty[48,133,147,148]. For example, anterior insula activity tracked levels of risk and risk prediction errors during decision-making tasks[48] and was associated with less risky decisions under uncertain conditions[147]. Patients with anterior insula lesions were insensitive to the favorability of betting odds[149], suggesting that this region biases decision-making by signaling the consequences of unfavorable bets. Increased anterior insula activation was seen during the anticipation of negative events in the absence of decision-making[133,142,150], with some studies reporting particularly heightened anticipatory insula responses under conditions of threat uncertainty[141,151]. Integrating data on anticipation and uncertainty with this region's established role in interoception and subjective emotional awareness[152,153] (Box 5), we posit that the anterior insula generates anticipatory emotional responses for hypothetical future events[154] that answer the question "How is it going to feel?". This process contributes to subjective predictions about the probability and cost of future threat[45] (Box 4). This role becomes particularly important when future events are less predictable, as anticipated feeling states contribute to adaptive decision-making and preparatory cognitive or behavioral actions under such conditions[148].

Elevated activity and altered connectivity of the anterior insula help account for the negative emotional states associated with uncertainty in highly anxious individuals, as well as heightened subjective estimates or feelings about potential future threat. This region showed hyperactivity in anticipation of negative pictures in individuals with PTSD[155], GAD and SAD[156], and high trait anxiety[157]. Spider phobics showed elevated anterior insula activity while anticipating spider pictures that appeared in a temporally unpredictable manner[139]. In addition, elevated IU was associated with increased anterior and mid-insula responses to affectively ambiguous faces[158].

In summary, exaggerated physiological and subjective emotional responses to uncertainty in anxiety are proposed to reflect alterations to the BNST and anterior insula. Anterior insula dysfunction leads to negatively biased predictions about the emotional consequences of uncertain future events and a failure to learn from errors in these predictions[28], resulting in a dissociation between heightened subjective feelings of threat and objectively accurate "cognitive" threat calculations[39] (Box 4). These biased threat expectancies contribute to persistently elevated BNST activity under conditions of uncertainty, resulting in behavioral and physiological manifestations of anxiety. The resulting negative anticipatory emotions make uncertainty particularly "intolerable" for anxious individuals[144].

Translating uncertainty into action

Unlike conditions of relative certainty, in which automatic or habitual processes allow navigation of the environment and goal attainment, uncertainty introduces potential conflict between competing options or motivating factors. Gray proposed that the septo-hippocampal system responds to such conflict by increasing vigilance and inhibiting motor function to allow for risk assessment, which in turn results in behavioral avoidance[6]. Another candidate

region for mitigating the conflict introduced by uncertainty is the aMCC. The recently proposed "adaptive control hypothesis"[126] posits that the aMCC integrates motivational, affective, and interoceptive information to provide an instructive signal that influences subsequent action under conditions of uncertainty. The aMCC is anatomically well-positioned to serve such a role, with widespread efferent and afferent connections to the regions featured for the five UAMA processes (Figure 1F).

Supporting this central role for the aMCC in responding to uncertainty are reciprocal connections with the anterior insula[159,160] that allow information regarding interoceptive and subjective emotional states to be re-represented in the aMCC[153]. Projections from the spinothalamic column, basal nucleus of the amygdala, and midbrain dopaminergic regions provide the aMCC with information about pain and other negative reinforcers[126]. Through its projections to motor centers, the amygdala, and midbrain nuclei including the periaqueductal gray, the aMCC modulates autonomic activity[161,162] and directs appropriate defensive responses[163]. Afferent projections from multiple medial and lateral prefrontal regions converge on the aMCC, which could act as a relay between those regions and the amygdala[164]. Finally, projections to dorsolateral PFC and parietal regions facilitate response selection or signal the need for increased attentional resources[126]. Taken together, disturbed function of the aMCC or its connections would have deleterious consequences for optimal responding in situations involving uncertainty: exaggerated autonomic responses and behavioral reactivity, compromised associative learning about fear and safety, heightened avoidance, altered allocation of attentional resources, and hypervigilance.

There is extensive evidence that the structure, function, and connectivity of the aMCC are altered in clinical anxiety. Individuals with PTSD showed reduced aMCC volume[165] as well as increased aMCC activity to an extinguished CS+[102], to a context in which electric shocks had previously been administered[166], and during cognitive interference tasks[167]. Elevated baseline aMCC metabolism in veterans with PTSD and their monozygotic twins[73] suggests that aMCC hyperactivity represents a genetically influenced risk factor for developing PTSD. Individuals with SAD showed reductions in functional connectivity between the aMCC and anterior insula while viewing fearful faces[168], and specific phobics exposed to conditions of sustained, temporally unpredictable threat showed aMCC hyperactivity[139]. Structural imaging showed reductions in aMCC volume in PD[169], and two cases of aMCC surgical resection were associated with subsequent panic symptoms[170]. Cingulotomies (targeting the aMCC) resulted in significant symptom reduction in patients with OCD[171], and the aMCC showed the most consistent reductions in gray matter volume in a meta-analysis of structural MRI studies of OCD[172]. Trait anxiety has been associated with abnormal functional coupling of the aMCC and amygdala[163,173]. Finally, anxious adolescents with elevated IU scores had increased aMCC activation during decision-making under conditions of uncertainty[174].

Despite extensive evidence for aMCC abnormalities in clinical anxiety, additional research is needed to test the hypothesis that maladaptive behavioral, cognitive, or emotional control is directly linked to aMCC dysfunction. Investigation of functional activation, functional connectivity, and structural connectivity in the same subjects will help to clarify the precise

role of the aMCC and its many connections in maladaptive anticipatory responses to threat uncertainty in anxiety.

Uncertainty and Anticipation Model of Anxiety (UAMA)

The evidence reviewed here provides strong support for the central and disruptive role of uncertainty about potential threat in subclinical and clinical anxiety. An interconnected set of neurobiological and psychological processes are involved in adaptive anticipatory responding under conditions of uncertainty, and deficits in one or more of these processes underlie maladaptive responses to future uncertainty in anxious individuals.

As depicted in Figure 2, at the core of UAMA are elevated expectancies of threat under conditions of uncertainty, which can take the form of either disrupted “cognitive” estimates of probability and cost, or heightened subjective feelings about negative future events. These elevated threat expectancies reflect alterations to the ventral striatum and OFC, which are involved in expected value calculations and reinforcement learning. Heightened subjective feelings about threat under conditions of uncertainty suggest dysfunction of the anterior insula and vmPFC. Amygdala hyperactivity results in increased vigilance, biased attention toward threat, and deficient associative learning, all of which contribute to heightened threat expectancies. These biased expectancies result in a feedback loop in which anxious individuals are increasingly vigilant and ever more attentive toward perceived threat. Also contributing to elevated threat expectancies are impaired safety learning and an inability to inhibit fearful responding under conditions of safety, the result of deficient inhibitory vmPFC-amygdala communication.

Elevated threat expectancies naturally lead to avoidance of situations involving uncertainty about threat. By avoiding situations in which negative outcomes are expected, however, the anxious individual cannot accumulate disconfirmatory evidence or learn about safety cues, and therefore consolidates biased expectancies. Greater threat expectancies exacerbate BNST-dependent physiological and behavioral reactivity under conditions of uncertainty, whereas anterior insula dysfunction contributes to heightened anticipatory emotional responses and subjective feelings of negative events’ probability and cost. Finally, looming over all of these disrupted processes outlined in UAMA are abnormal function and connectivity of the aMCC (Figure 1F), which prevents the anxious individual from identifying and executing adaptive anticipatory responses in the face of uncertainty.

Directions for future research

The UAMA is based primarily on three lines of evidence: neural responses to uncertainty in healthy individuals; behavioral, self-reported, or peripheral physiological responses to uncertainty in anxiety disorders; and neurobiological disruptions not directly related to uncertainty in anxiety disorders. There is little data on the convergence of these three areas. Functional imaging research in anxiety has largely assessed neural *responses* to symptom provocation stimuli or negative emotional stimuli, which we argue fail to engage those processes most central to clinical anxiety. Anxiety is a future-oriented emotion, and *anticipating* or “pre-viewing” the future induces anxiety largely because the future is intrinsically uncertain. Studies in healthy individuals have used paradigms that elicit

anticipatory anxiety through exposure to sustained, unpredictable threat[100,140–143]. These paradigms engage brain regions implicated in pathological responses to uncertainty, including the amygdala, anterior insula, BNST, rostral cingulate, and vmPFC. We propose that these and other paradigms be extended to specifically target hypothesized disruptions to the five processes highlighted above, as framed in several questions below.

Does heightened anxiety in response to sustained, unpredictable threat reflect abnormally elevated BNST activation[4]? A combination of high-resolution imaging, differential temporal response profiles[141,142], probabilistic fiber tracking techniques[175], and pharmacological fMRI would allow for improved localization of extended amygdala subdivisions.

Are biased threat expectancies in anxiety directly related to increased amygdala activity and resulting hypervigilance? For a paradigm with different cue/outcome contingencies, anxious individuals would be expected to show biased threat expectancies in proportion to elevated amygdala responses for unpredictable contexts[135]. Functional connectivity analyses could be used to address whether elevated amygdala responses under conditions of uncertainty are related to deficient vmPFC inhibition, altered communication with the aMCC[163] or both.

Do anxious individuals show deficits in reinforcement learning? If so, are such deficits specific to aversive outcomes? Disrupted negative prediction error signaling (i.e., the non-occurrence of expected aversive events) would result in a prolonged state of uncertainty despite the absence of predicted aversive events. Reversal learning paradigms could identify abnormalities in brain regions involved in aversive prediction error signaling (ventral striatum, anterior insula, and rostral cingulate)[57–59].

Is there evidence in anxiety for deficits in “somatic” aversive prediction error signaling[28]? This could help explain heightened anticipatory “feelings” about threat likelihood, despite accurate “cognitive” probabilistic estimates (Box 4). Does such dysfunction result from inaccurate interoceptive feedback to the insula regarding errors in predicting somatic states, or from a failure to update predictions based on accurate interoceptive feedback?

Does heightened responding to objectively safe cues reflect impaired safety learning, or deficits in fear inhibition? Conditional discrimination tasks[95] and functional imaging could differentiate between these possibilities. Modified safety learning or fear extinction paradigms that provide the option to *avoid* the CS[117] could be used to investigate relationships among avoidance, safety learning, and fear extinction.

Speaking more generally, causality needs to be assessed using longitudinal designs in high-risk populations. Do elevated threat expectancies, deficient identification of safety, and heightened responses to uncertainty increase one’s risk of developing an anxiety disorder? Or are these disruptions consequences of living with anxiety? Is successful treatment associated with normalization of behavioral and neural responses to threat uncertainty?

An assessment of which UAMA processes are intact vs. disrupted could provide insight into the nosology of affective pathology and advance biologically informed, individualized diagnosis and treatment[176]. Adaptive responses to uncertainty require flexible coordination among these different processes, and alterations to any region would have consequences for

functions of additional regions, particularly given the heavy reciprocal structural connections and functional co-activation of many of the regions described here[4,87,88,126,177,178]. Assessment of the functional and structural integrity of these networks is likely to provide a more informative picture of anxious pathology than the measurement of any one region in isolation[179–181].

Implications for treatment

The UAMA supports two avenues for treatment. First, to the extent that deleterious consequences of uncertainty result from elevated threat expectancies, patients might benefit from interventions that emphasize accurate prediction of future events and learning from inaccurate predictions. Bias modification[182] could be used to target elevated threat estimates. Individuals deficient in identifying safety signals might benefit from therapy emphasizing attention to contexts, cues, and coping strategies to reduce threat uncertainty[27]. For individuals with objectively accurate predictions but subjectively exaggerated threat expectancies[39,45], the therapist can highlight this inconsistency and bring subjective feelings about threat in line with objectively accurate predictions. Pharmacological agents designed to enhance neuroplasticity and emotional learning processes could further promote the efficacy of these therapies. For example, D-cycloserine (DCS) has been used to enhance the effects of exposure therapy in specific phobia[183,184], SAD[185], OCD[186], and PTSD[187], behavioral therapy in OCD[188], CBT in PD[189], and attentional bias modification in highly trait-anxious individuals[190].

Second, treatment efforts must also encourage individuals to become more tolerant of uncertainty[27]. Real-time fMRI, which allows participants to monitor and alter activity in specific brain regions during fMRI scanning[191], could help anxious individuals learn to down-regulate anterior insula activity in response to uncertainty, and thereby reduce negative anticipatory emotions[192]. Similarly, modulation of aMCC activity could encourage adaptive control over cognitive, affective, and behavioral responses to uncertainty.

A simpler strategy involves encouraging patients to spend less time worrying about what might come, and instead to focus on life in the present[193]. Complete absorption in the present moment obviates anxiety about the future. One path toward the reduction of anxiety might involve transitioning “from inaccurate expectations to more accurate expectations to no expectations at all”[193]. The incorporation of mindfulness traditions into CBT – namely, emphasizing awareness of moment-to-moment internal and external events, and non-judgmental acceptance (rather than avoidance) of negative emotional states – allow one to tolerate unavoidable uncertainties[194], and help those suffering from anxiety to understand that uncertainty about the future need not rule their lives.

Acknowledgments

The authors wish to thank Lyn Abramson, Richie Davidson, Ned Kalin, John Curtin, and members of the Curtin lab for feedback on previous versions of this manuscript. This work was supported by the National Science Foundation (Graduate Research Fellowship to DWG) and the National Institute of Mental Health (R01-MH74847, K02-MH082130 to JBN).

Glossary Terms

fear-potentiated startle	The enhanced response to a startling stimulus observed under negative arousing states such as fear or anxiety
anxiety	The suite of anticipatory affective, cognitive, and behavioral changes in response to uncertainty about potential future threat
orbitofrontal cortex (OFC)	Medial and lateral aspects of the orbital surface of the prefrontal cortex, including Brodmann areas 11, 13, 14, and ventral portions of 10 and 47/12
prediction error	The difference between predicted and actual outcomes, which results in a neural signal that leads to increasingly accurate future predictions
fear conditioning	Process by which a neutral conditioned stimulus (CS+) becomes associated with an aversive, unconditioned stimulus (US) through repeated contingent presentations of the CS+ and US, resulting in fear expression following presentation of CS+ alone
rostral cingulate cortex	Encompasses ACC and aMCC, including Brodmann areas 24, 25, 32, and 33
hypervigilance	State of increased attention to perceived threat in one's environment
associability	The propensity of a stimulus to form associations with other stimuli in the environment; associability increases following surprising or unpredicted outcomes
conditional discrimination task	Variant of fear conditioning paradigms that allows for the independent investigation of safety learning and the inhibition of fear responses in the presence of learned safe cues
fear extinction	An active learning process in which a CS+ is repeatedly presented in the absence of a contingent US, leading to a new association between the CS+ and safety that competes with the original association between the CS+ and US
ventromedial prefrontal cortex (vmPFC)	Encompasses medial OFC, posterior frontopolar cortex, subgenual ACC, and inferior pregenual ACC, including Brodmann areas 11, 14, 25, and portions of 10, 24, and 32
diffusion tensor imaging (DTI)	MRI technique that assays the diffusion properties of water molecules, allowing for inferences regarding microstructural properties of white matter
uncinate fasciculus	The primary white matter tract connecting ventral portions of the PFC and ACC with medial temporal lobe structures including the amygdala

exposure therapy	Therapeutic technique in which individuals are presented with feared objects, situations, or memories in a safe setting, thus allowing for the reduction of fearful associations
cognitive behavioral therapy	Diverse collection of therapies that emphasize the correction or restructuring of maladaptive behaviors and inaccurate beliefs
benzodiazepines	A widely used class of GABA agonists for the treatment of anxiety disorders
interoception	The perception of sensory events occurring within one's body
D-cycloserine (DCS)	Partial agonist of the NMDA glutamate receptor that has been shown to enhance learning

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Box 1

Trait anxiety and relationships between anxiety disorders and depression

The phrase “trait anxiety” is a bit of a misnomer, as the measure to which it most commonly refers – Spielberger’s State-Trait Anxiety Inventory (STAI)[195] – shows an equally close association with anxiety and depression[196,197]. Trait anxiety may thus be better described as negative affect (also indexed by other commonly used instruments[198,199]), and probably reflects a general risk factor for emotional disorders. Although other self-report scales can distinguish anxiety disorders from depression[200–203], the STAI is used in most studies that investigate anxious characteristics in non-clinical samples. Despite its lack of specificity, the relevance of research using the STAI is underscored by its sensitivity as a marker of risk for anxiety disorders.

The six anxiety disorders and depression have both shared and unique characteristics[204,205]. Some research has questioned whether generalized anxiety disorder aligns more closely with anxiety disorders or depression[206,207]. The positioning of obsessive-compulsive disorder and posttraumatic stress disorder within a broad diagnostic class labeled “Anxiety Disorders” has also been challenged[208]. Alternatives to the DSM-IV classification of anxiety and depression have been proposed[209,210], but controversy remains about the optimal nosology.

The striking comorbidity between depression and anxiety disorders, as well as their shared features and genetic basis[209], raises the question of how they are similar or different with regard to uncertainty and uncontrollability. Helplessness models of depression[11] have emphasized a lack of control over stressful events as a precipitating and maintaining factor in depression. It has also been suggested that uncontrollability is a shared feature of anxiety and depression, and that the two are differentiated by predictions about negative events[211]: anxiety is accompanied by uncertainty about future negative events, whereas depression is accompanied by the perception that negative events are unavoidable, leading to hopelessness[212]. Mixed anxiety and depression is characterized by uncertainty about the occurrence of negative events and feelings of helplessness regarding control over those events[213].

Box 2

Uncertainty in neuroeconomics and decision-making

The investigation of neural responses to uncertainty is not confined to research on anxiety. Investigations of uncertainty in behavioral economics and neuroeconomics distinguish between decision-making under conditions of risk (when one faces multiple potential outcomes of known probabilities) and ambiguity (when one faces multiple potential outcomes of unknown probabilities). These studies typically emphasize explicit, cognitive calculations related to different outcomes and their expected utilities, with a heavy emphasis on choices individuals make when faced with different kinds of uncertainty. By contrast, the mechanisms discussed here largely involve responses to uncertainty in the absence of explicit decision-making. Additionally, the neuroeconomics literature includes many studies investigating uncertainty about financial and other rewards, which recruit distinct neural mechanisms from those involved in responses to uncertainty about threat. Our perspective primarily relates to research on the anticipation of threat uncertainty in the absence of decision-making, such as reinforcement learning models of fear conditioning. Others have highlighted the potential of applying neuroeconomics frameworks to the study of anxiety disorders and other psychiatric conditions[19,60,214].

Box 3

Adaptive and maladaptive responses to threat uncertainty

To illustrate adaptive and maladaptive manifestations of processes highlighted in UAMA, consider the following vignette, in which each of the five UAMA processes has been indicated by number:

Pete, home alone one night, hears rustling in the bushes and loud banging sounds outside his house. Pete immediately feels uncertain regarding whether these noises are benign (curious raccoons) or threatening (burglars). An adaptive response to this uncertainty begins with a rational assessment of the probability of threat (**1**). This neighborhood has few burglaries, and similar noises have never turned out to be dangerous before. Pete turns down the TV to give more attention to what may be outside, but this heightened vigilance (**2**) is balanced by attention to cues that indicate safety (**3**). Because Pete's security system is silent and the windows and doors are locked, he has reliable signs that nobody has entered his house. Nevertheless, Pete explores the situation to reduce nagging questions (**4**). Heading downstairs, he sees trash strewn about the garbage cans, and surmises the likely culprit was a raccoon. Despite some unresolved uncertainty, Pete can calm his racing heart (**5**) and fall asleep knowing that all signs point toward safety.

Next door lives Paul, a chronic worrier diagnosed with GAD, who hears the same noises and experiences similar uncertainty. Instead of objectively weighing the likelihood of alternative outcomes, Paul immediately imagines burglars entering his home (**1**). Uncontrollable worries and cascading "what if …" thoughts course through his head, and he generates increasingly elaborate scenarios of what evils may befall him. He becomes increasingly attuned to every movement in the branches or creak in the floorboards of his old house (**2**). Owing to Paul's exclusive attention toward potential threat, he never notices that his security system is silent (**3**). Concerned for his safety, Paul locks his bedroom door instead of investigating (**4**). Having avoided exploring the situation, Paul is left with greater unresolved uncertainty than Pete about the source of the noises. He tries to sleep but his racing heart and sweaty palms keep him from relaxing (**5**). Not having learned that the situation was safe, Paul will be more likely to assume the worst the next time he hears a noise in the night.

Box 4

Threat assessment: “cold cognition” vs. “subjective feelings”

There is an important distinction between “cold, cognitive” estimates of probability and cost, and subjective estimates or “feelings” about potential threat[45]. Anxious individuals predominantly display elevated subjective predictions or feelings about threat. For example, whereas judgment biases in high trait anxiety are observed when subjects report probability estimates using verbal labels (that is,“not at all likely” to “very likely”), the few published studies that did not find such biases asked subjects to report probability estimates using precise numeric anchors[38,215]. Similarly, individuals with GAD reported higher subjective feelings about the likelihood of negative events than their logical, objective estimates[39]. These data are corroborated by clinical observations of patients who persistently worry about the potential occurrence of negative outcomes, despite being aware that those outcomes, objectively speaking, are highly unlikely[24].

Through the simulation of future events (or “prospection”), humans can generate embodied predictions of events’ emotional impacts before their occurrence[154]. The “risk-as-feelings” hypothesis[45] proposes that anticipatory emotions frequently lead to choices and behaviors that diverge from those considered objectively “optimal” in terms of maximizing benefits and minimizing harm. Predictions stemming from these anticipatory emotions are probably implicitly generated and may not reach conscious awareness, although they can still exert a powerful influence on one’s preparations for the future. The medial OFC and anterior insula are involved in assessing the subjective value of potential events and relaying this information to other regions to influence subsequent choice and action[152,153]. Disruptions to this circuitry may lead to more vivid or visceral simulations of potential events, and bias anxious individuals’ feelings about threat under conditions of uncertainty.

Box 5

The anterior insula and subjective emotional awareness

The insula is a band of cortex, tucked within the folds of the Sylvian fissure, that stretches from prefrontal to posterior parietotemporal regions of the brain (see the figure, part **a**). Its anatomical position allows extensive connections with cortical and subcortical regions, including the lateral PFC and OFC, vmPFC, cingulate, amygdala, BNST, and ventral striatum[177,178] (Figure 1A, D–F). Superimposed on the insula is a posterior-anterior functional gradient, in which increasingly rich and complex representations of one's bodily state arise[153]. The posterior insula is primary somatosensory cortex that receives interoceptive and exteroceptive information regarding pain, temperature, touch, itch, taste, and visceral changes[153]. As this basic sensory information is transmitted to middle and anterior regions of the insula, it is integrated with homeostatic, motivational, emotional, and cognitive information from an array of cortical and subcortical regions. At the top of this ascending hierarchy, the anterior insula is involved in the perception of subjective interoceptive states, and might be involved more broadly in supporting subjective emotional awareness or a "global feeling state" across time[153].

Hyperactivation of the anterior and mid-insula is one of the most common neuroimaging findings across different anxiety disorders and during fear conditioning[77] (see the figure, part **b**: hyperactivation is depicted in red (with anterior and mid-insula circled), and hypoactivation in blue). NTS=nucleus tractus solitarius. Part **b** is adapted, with permission, from[77].

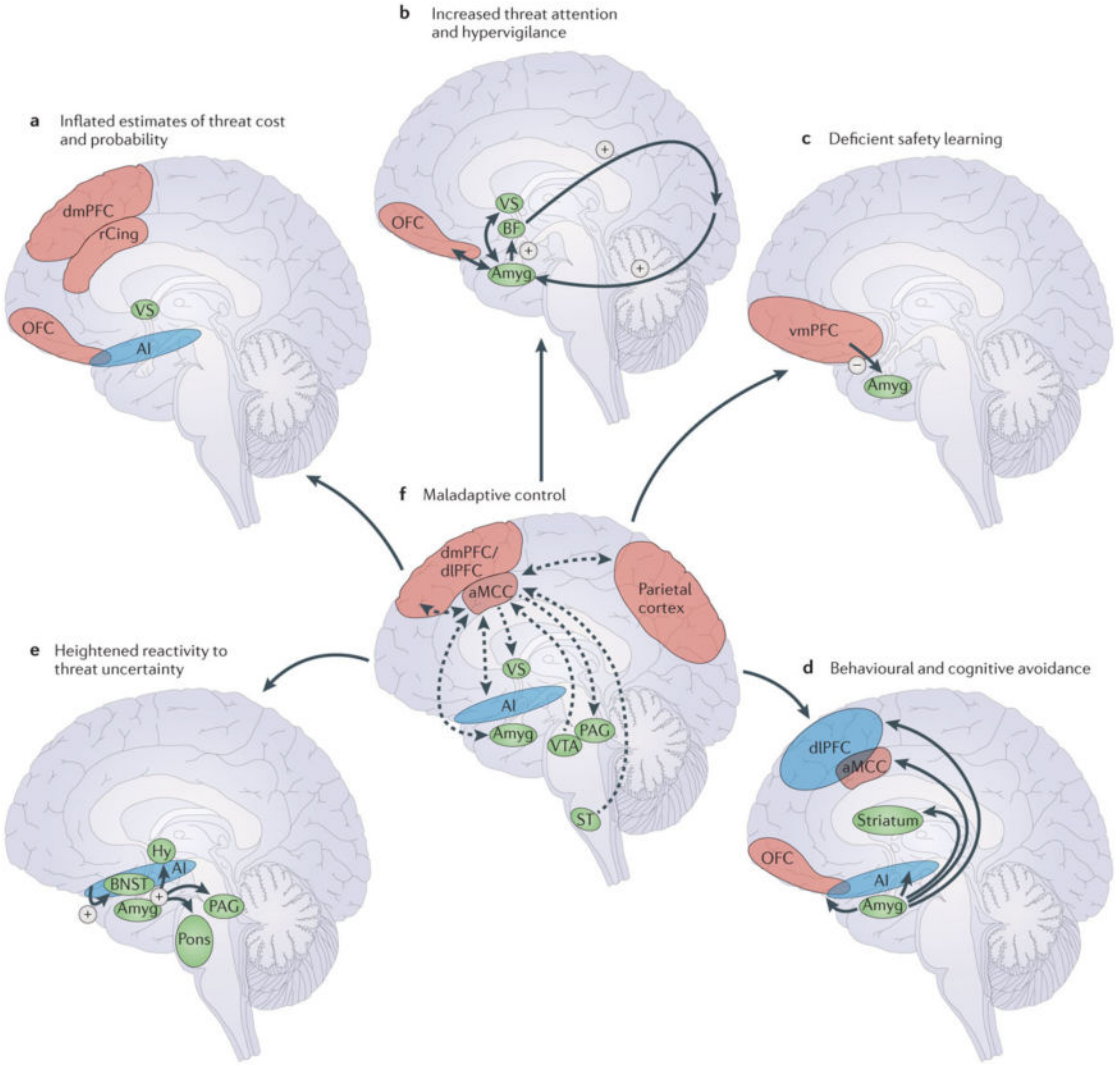

Figure 1. Neural regions and circuitry implicated in the UAMA

A. Inflated estimates of threat cost and probability reflect disruptions to the dorsomedial prefrontal cortex (dmPFC), rostral cingulate (rCing), orbitofrontal cortex (OFC), ventral striatum (VS), and anterior insula (AI). **B.** Elevated amygdala (Amyg) activity leads to increased basal forebrain (BF) modulation of visual and other sensory input **[Au: could we label the region that the arrow from BF points to 'sensory cortex'?]** and heightened threat attention. Interactions between the amygdala, OFC, and VS further increase threat expectancies and threat attention. **C.** Deficient safety learning reflects disrupted inhibitory ventromedial PFC (vmPFC)-amygdala circuitry. **D.** Behavioral and cognitive avoidance reflects interactions between the amygdala and circuitry involved in decision-making and action selection, including the OFC, dorsolateral PFC (dlPFC), striatum, anterior mid-cingulate cortex (aMCC), and anterior insula. **E.** Hyperactivity of the bed nucleus of the stria terminalis (BNST) and amygdala in response to sustained, unpredictable threat modulate defensive responding as mediated by the hypothalamus (Hy), pons, periaqueductal gray (PAG), and other midbrain/brainstem structures. Anterior insula dysfunction is associated with elevated intolerance of uncertainty and further contributes to BNST and amygdala

hyperactivity. **F.** Dysfunction of the aMCC, or disrupted structural connectivity between the aMCC and interconnected regions, prevents individuals from identifying and executing adaptive responses to uncertainty and contributes to the disruptions highlighted in A–E. Lateral cortical regions are shown in blue, medial cortical regions in green, and subcortical regions in orange. The functional pathways in A–E are indicated with red arrows (excitatory) and blue arrows (inhibitory). The known structural connections in F are indicated with purple arrows (directionality indicated by arrowheads). ST=spinothalamic tract; VTA=ventral tegmental area.

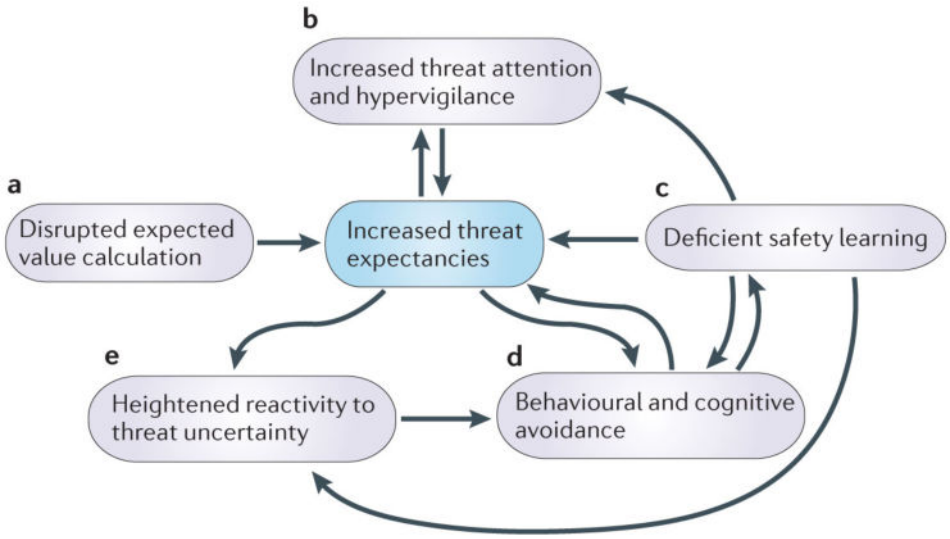

Figure 2. Altered anticipatory processes in response to threat uncertainty in anxiety

Dynamic interactions among five key psychological processes (in purple) allow for anticipatory responses to uncertainty about future threat. The UAMA posits that alterations to these processes and associated core brain circuitry (see Figure 1) are responsible for maladaptive cognitive, behavioral, and affective responses to uncertainty in highly anxious individuals. At the core of UAMA are heightened expectancies about the probability and cost of future threat (in blue). These elevated expectancies are the result of alterations in the calculation of expected value and aversive prediction error signaling (**A**), increased threat attention and hypervigilance (**B**), and deficient safety learning or an inability to inhibit anxious responding in the presence of safety (**C**). These heightened expectancies and an inability to identify safety in situations of uncertainty contribute to elevated cognitive and behavioral avoidance (**D**), which leads to further difficulties in identifying safety and reducing threat expectancies. Heightened threat expectancies and an inability to identify safety signals contribute to exaggerated physiological and behavioral reactivity under conditions of uncertainty (**E**), and this heightened reactivity to uncertainty leads to further avoidance of such conditions.