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 that are essential for adaptive anticipatory responses to future threat uncertainty and propose that alterations in the neural instantiation of these processes result in maladaptive responses to uncertainty in pathological anxiety. This framework has the potential to advance the classification, diagnosis and treatment of clinical anxiety.

Anxiety
The suite of anticipatory affective, cognitive and behavioural changes in response to uncertainty about a potential future threat.

Ventromedial prefrontal cortex
(vmPFC). It encompasses the medial orbitofrontal cortex, posterior frontopolar cortex, subgenual anterior cingulate cortex (ACC) and inferior pregenual ACC, including Brodmann areas 11, 14 and 25, and portions of 10, 24 and 32.

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The human brain, it has been written, is an "anticipation machine, and 'making future' is the most important thing it does" (REF. 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 of the 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 behavioural processes executed to avoid or reduce the impact of a potential threat. These anticipatory processes serve an adaptive function when executed at a level that is 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 on 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, including a class of psychiatric disorders, particular patterns of behaviour in animal models and trait-like negative affect (BOX 1). Another perspective suggests that anxiety is a future-oriented emotional state that is 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." (REF. 3)

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Box 1 | **Trait anxiety, 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], STAI is used in most studies that investigate anxious characteristics in non-clinical samples. Despite its lack of specificity, the relevance of research using 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 post-traumatic stress disorder within a broad diagnostic class labelled 'anxiety disorders' has also been challenged[208]. Alternatives to the *Diagnostic and Statistical Manual of Mental Disorders* (fourth edition)[14] classification of anxiety and depression have been proposed[209,210], but controversy remains about the optimal nosology.

The striking comorbidity between anxiety disorders and depression, 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].

This quote underscores two crucial 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 a future threat[2,4–8]. Decades of research in rodent models has provided tremendous insight into hierarchically organized defence systems, the underlying neurobiology of these systems and the circumstances under which different defensive responses are recruited[6,9,10]. Environmental cues indicating the unambiguous presence of an immediate threat give rise to intense 'fearful' defensive behaviours (that is, 'fight or flight'), whereas more diffuse, distal or unpredictable threat cues produce 'anxious' risk assessment behaviour[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 behaviour[12], posited a central role for a behavioural inhibition system in responding to uncertainty or conflict by increasing the negative valence of stimuli and promoting avoidance behaviour. 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 threats and sustained, 'anxious' responses to unpredictable threats[4,13]. Motivated by this previous work, we define anxiety here as anticipatory affective, cognitive and behavioural changes in response to uncertainty about a 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 fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders*[14] (generalized anxiety disorder (GAD), panic disorder, social anxiety disorder (SAD), post-traumatic 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 experienced in all of these disorders. Accordingly, an increased focus on the neural and psychological mechanisms associated with maladaptive anticipatory responses under conditions of threat uncertainty is essential if we are to understand clinical anxiety better.

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, and it is often used 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 their 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. Although 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 the UAMA, clinical anxiety disorders are associated with the disruption of a number of processes that bias one towards overly conservative (that is, effective but not efficient) preparatory behaviour in the face of an 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

Orbitofrontal cortex
(OFC). Medial and lateral aspects of the orbital surface of the prefrontal cortex, including Brodmann areas 11, 13 and 14, and ventral portions of 10 and 47/12.

Fear-potentiated startle
The enhanced response to a startling stimulus observed in negative arousing states, such as fear or anxiety.

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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 behavioural 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 focus on 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 responses to 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].

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" (REF. 20). Thus, even when one is unable to prevent negative events from occurring, increased certainty about the future provides one with control over adaptive anticipatory responses that can mitigate these events' negative impact. Uncertainty, conversely, precludes one from exercising this form of control and leads to preparations that are "diffuse, psychologically expensive, and of questionable effectiveness" (REF. 21).

Responses to uncertainty in anxiety

To understand why uncertainty about a future threat is so disruptive in anxiety, we propose five processes that are involved in maladaptive responses to such conditions: inflated estimates of threat cost and probability, hypervigilance, deficient safety learning, behavioural 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 the UAMA is that disruptions of 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. Substantial evidence indicates that anxiety disorders are multiply determined and involve genetic and early environmental factors that predispose individuals to pathological anxiety later in life. In addition, practising anxious thought and behavioural 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; instead, it incorporates ideas from diverse perspectives and disciplines[2,4,5,7,11,15,22–30]. In fact, all of the five processes showcased here, their neurobiological correlates and their relation to anxious pathology have previously been 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 that emphasizes 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 and 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] and 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 crucial 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 in the consolidation and integration of multiple perspectives and areas of research that are 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 'judgement bias' — that is, inflated 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 increased PTSD symptoms[43]. There is evidence that higher cost estimates contribute more to anxious pathology than do higher probability estimates[38,41]. Combined with the universal tendency to overestimate very small probabilities[44], this judgement bias could result in substantial anticipatory distress when anxious individuals face even the slightest possibility of a negative outcome[45] (BOX 4).

Hypervigilance
A state of increased attention to a perceived threat in one's environment.

Fear conditioning
The 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 the CS+ alone.

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Box 3 | **Adaptive and maladaptive responses to threat uncertainty**

To illustrate adaptive and maladaptive manifestations of processes highlighted in the uncertainty and anticipation model of anxiety (UAMA), consider the following vignette, in which each of the five UAMA processes are indicated.

Pete, home alone one night, hears rustling in the bushes and loud banging sounds outside his house. Pete immediately feels uncertain about 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 (first process). Few burglaries occur in this neighbourhood, and similar noises have never turned out to be dangerous before. Pete turns down the television to give more attention to what may be outside, but this heightened vigilance (second process) is balanced by attention to cues that indicate safety (third process). 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 (fourth process). 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 (fifth process) and fall asleep knowing that all signs point towards safety.

Next door lives Paul, a chronic worrier diagnosed with generalized anxiety disorder, who hears the same noises and experiences similar feelings of uncertainty. Instead of objectively weighing the likelihood of alternative outcomes, Paul immediately imagines burglars entering his home (first process). 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 (second process). Owing to Paul's exclusive attention towards potential threat, he does not notice that his security system is silent (third process). Concerned for his safety, Paul locks his bedroom door instead of investigating (fourth process). 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 (fifth process). 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.

Judgement biases in anxious individuals suggest that there are abnormalities in the neural circuitry associated with expected value calculation (FIG. 1a). Dorsomedial prefrontal regions (including Brodmann areas 8 and 10 and the aMCC) contribute to probability assessment[46–48], whereas activity in the OFC reflects the anticipated cost of future events[49,50]. In addition to showing activation in response to primary appetitive and aversive reinforcers[51], the OFC 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].

Expected value calculation is a dynamic process, and heightened threat expectancies in anxious individuals could also reflect disruptions of 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 MRI (fMRI) studies of fear conditioning, revealing aversive prediction error signals in the ventral striatum, anterior insula and rostral cingulate cortex[57–59]. Disrupted aversive prediction error signalling 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." (REF. 62) This tendency to view ambiguous stimuli as threatening, which is 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 panic disorder[67]; and sentence stems that could be completed to form combat-related words in veterans with PTSD[68]. Given these interpretation biases and increased attention for objectively threatening stimuli ('attentional bias')[61], increased 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] (FIG. 1b). Heightened resting metabolic activity and blood flow in the amygdala have been observed in participants with panic disorder[69], PTSD[70,71] (but see REFS 72,73) and SAD[74]. In non-human primates, resting amygdala metabolism is correlated with a combined behavioural and hormonal assay of anxious temperament[75,76]. In addition to these alterations at rest, a meta-analysis of functional imaging studies in panic disorder, PTSD and SAD showed increased 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 that there is indiscriminately increased activation of the amygdala. 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. Perspectives on anxiety that focus on fear conditioning[22,23,33] emphasize exaggerated associative learning for environmental cues and aversive outcomes[35], a process that critically involves the basolateral amygdala[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

Prediction error
The difference between predicted and actual outcomes, which results in a neural signal that leads to increasingly accurate future predictions.

Rostral cingulate cortex
Encompasses the anterior cingulate cortex and anterior mid-cingulate cortex, including Brodmann areas 24, 25, 32 and 33.

Associability
The propensity of a stimulus to form associations with other stimuli in the environment; associability increases following surprising or unpredicted outcomes.

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Box 4 | **Threat assessment: 'cold cognition' versus '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 increased subjective predictions or feelings about threat. For example, judgement 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 generalized anxiety disorder 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 behaviours 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 orbitofrontal cortex and anterior insula are involved in assessing the subjective value of potential events and relaying this information to other regions to influence subsequent choices and actions[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.

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 through their ascending cholinergic projections to cortical regions after surprising events[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 towards 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, which is facilitated by the amygdala, is likely to affect the value assigned to future events, and differences in valuation, which are 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 towards 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 an unconditioned stimulus (US), these paradigms include another cue (CS–) that is presented in the absence of the US and is therefore associated with safety. Failure to show discriminative physiological responses to a CS+ and a CS–, reflecting increased fearful responding to the CS–, has been reported in panic disorder[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 responses 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 (FIG. 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 that were visually similar to a reinforced CS+, reflecting a generalization of learned fear to safe cues[105]. Indiscriminately increased amygdala activation during the anticipation of neutral and aversive pictures in GAD[78] further suggests a failure of patients to downregulate amygdala activity in response to safe neutral cues. Notably, patients with heightened anticipatory responses in the pregenual anterior cingulate cortex (ACC), which is just superior to the vmPFC, showed the largest decrease in symptoms following venlafaxine treatment[78], which is consistent with other studies of pretreatment predictors of treatment response in anxiety[106] and depression[107,108]. Thus, some preservation of regulatory function in the ACC and vmPFC has prognostic benefits in anxiety and mood disorders. Complementing this fMRI research, diffusion tensor imaging has revealed microstructural alterations in the uncinate fasciculus in individuals with GAD[109], SAD[110] and high 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

Conditional discrimination tasks
A 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 conditioned stimulus (CS+) is repeatedly presented in the absence of a contingent unconditioned stimulus (US), leading to a new association between the CS+ and safety that competes with the original association between the CS+ and US.

Diffusion tensor imaging
An MRI technique that assays the diffusion properties of water molecules, providing insight into the microstructural properties of white matter.

Uncinate fasciculus
The primary white matter tract connecting ventral portions of the prefrontal cortex and anterior cingulate cortex with medial temporal lobe structures, including the amygdala.

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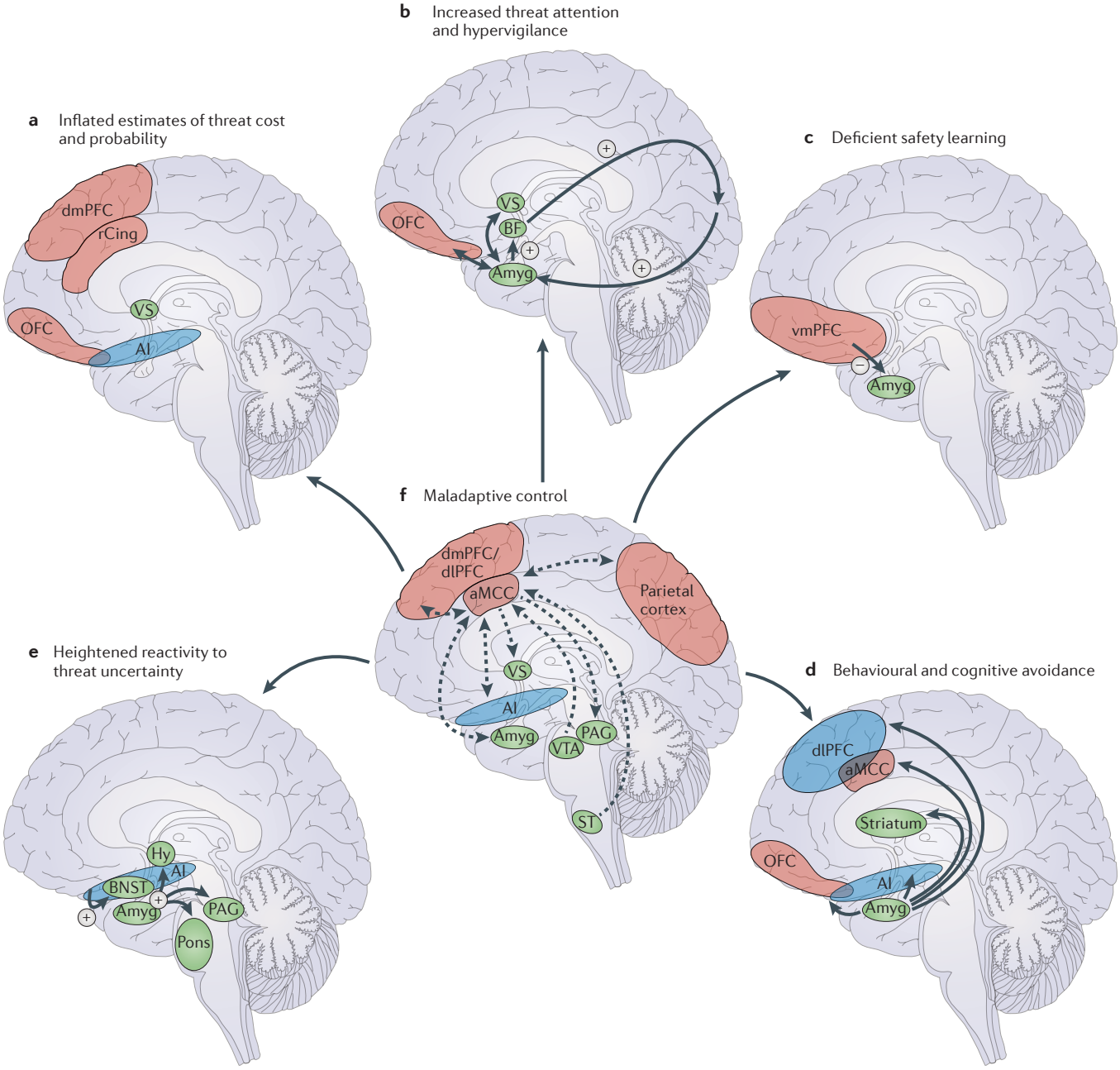

Figure 1 | **Neural regions and circuitry implicated in the UAMA.** **a** | Inflated estimates of threat cost and probability reflect disruptions to the dorsomedial prefrontal cortex (dmPFC), rostral cingulate (rCing), orbitofrontal cortex (OFC), ventral striatum (VS) and anterior insula (AI). **b** | Increased amygdala (Amyg) activity leads to increased basal forebrain (BF) modulation of visual and other sensory input and heightened attention to threat. 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** | Behavioural 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 AI. **e** | Hyperactivity of the bed nucleus of the stria terminalis (BNST) and amygdala in response to sustained, unpredictable threat modulates defensive responding as mediated by the hypothalamus (Hy), pons, periaqueductal grey (PAG) and other midbrain and brainstem structures. AI dysfunction is associated with increased 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 pink, and subcortical regions in green. Arrows in **a**–**e** depict functional pathways (plus signs indicate excitatory pathways and minus signs indicate inhibitory pathways). Dashed arrows in part **f** depict known structural connections (directionality indicated by arrowheads). ST, spinothalamic tract; VTA, ventral tegmental area.

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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 behaviour, perhaps by altering BNST activity[116]. Future research is needed to clarify the role of the vmPFC in anxiety and to investigate whether alterations in specific sectors of the vmPFC or their connectivity with the amygdala explain these disparate findings[112].

Behavioural and cognitive avoidance. Avoidant behaviour 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 the classic two-process theory[23,30], exaggerated fear conditioning to environmental threat cues leads to operant learning of avoidance behaviour 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, behavioural 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 behaviour. SAD, PTSD and OCD are marked by behavioural avoidance of potentially threatening or harmful situations. Patients with panic disorder develop beliefs that they can engage in safety-seeking thoughts or actions that prevent panic attacks; however, in reality, such activities protect the CS+ from being extinguished[30,118], as has been demonstrated in 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 their thoughts about threat in cognitive behavioural therapy (CBT)[24] or exposing them to feared scenarios in exposure therapy[26] — is a crucial first step in reducing increased 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 behaviour[120–122] and have shown that inhibition of the CeA by the 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] (FIG. 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 behaviour 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 the 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 towards 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 behaviour 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 panic disorder[90] and PTSD[92] had an increased startle magnitude during a temporally unpredictable interstimulus interval (ISI) but not under a predictable threat condition. Distinct extended amygdala regions mediate behavioural, autonomic and endocrine responses to predictable and unpredictable threats 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 under conditions of a sustained, unpredictable threat[4,13]. This functional dissociation is mirrored by differential responses to benzodiazepines, which reduce behavioural expressions of fear for sustained but not phasic threat in rodents[4], owing at least in part to decreased BNST activity[136]. In humans, benzodiazepines also reduced fear-potentiated startle in response 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 threats[140–142], with particularly increased activity in individuals with high trait anxiety[143].

Exposure therapy
A therapeutic technique in which individuals are presented with feared objects, situations or memories in a safe setting, thus causing a reduction of fearful associations.

Cognitive behavioural therapy
A diverse collection of therapies in which there is an emphasis on the correction or restructuring of inaccurate beliefs and maladaptive behaviours.

Benzodiazepines
A widely used class of GABA receptor agonists for the treatment of anxiety disorders.

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Interoception
The perception of sensory events occurring within one's body.

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 with high self-reported IU, uncertainty results in depleted attentional resources and disruptions of cognitive, behavioural and emotional functioning[144]. IU scores are higher in patients with GAD[144,145], SAD[146], OCD[146] and depression[146].

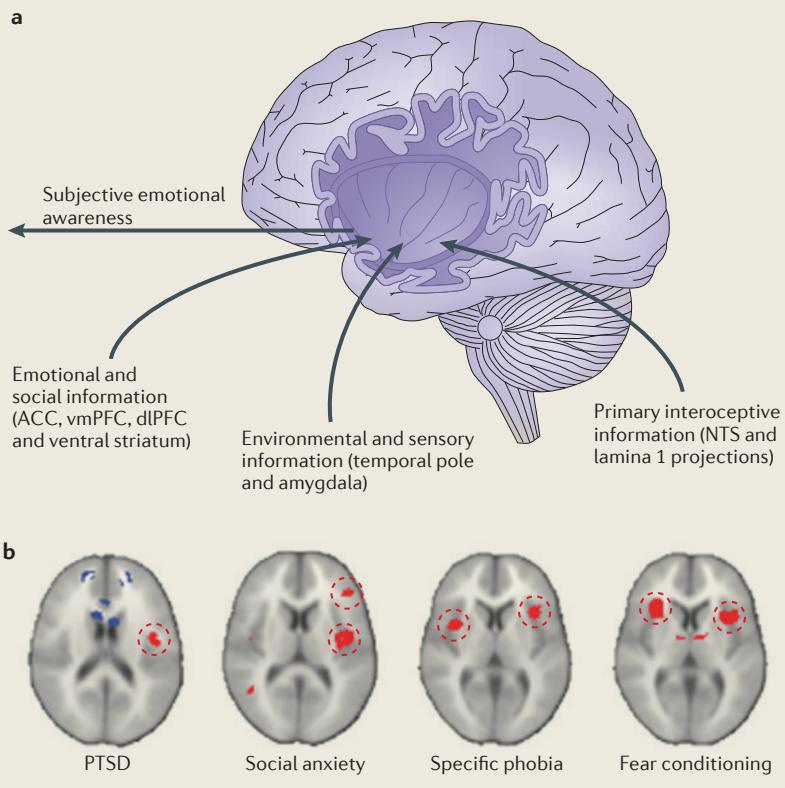
Many imaging studies have shown the importance of the anterior insula (FIG. 1e) in responding to uncertainty[48,133,147,148]. For example, anterior insula activity tracked levels of risk and risk prediction errors during decision-making tasks[48] and was associated with less risky decisions under uncertain conditions[147]. Patients with anterior insula lesions were insensitive to the favourability of betting odds[149], suggesting that this region biases decision-making by signalling the consequences of unfavourable 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]. In light of data on anticipation and uncertainty, as well as 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 threats[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 behavioural actions under such conditions[148].

Increased activity and altered connectivity of the anterior insula help to account for the negative emotional states associated with uncertainty in highly anxious individuals as well as the heightened subjective estimates or feelings about a 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 increased anterior insula activity while anticipating spider pictures that appeared in a temporally unpredictable manner[139]. In addition, higher 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 in 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

Box 5 | **The anterior insula and subjective emotional awareness**

The insula is a band of cortex that is tucked within the folds of the Sylvian fissure and 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 prefrontal cortex (PFC) and orbitofrontal cortex, ventromedial PFC (vmPFC), cingulate, amygdala, bed nucleus of the stria terminalis and ventral striatum[177,178] (FIG. 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 (depicted in red in part **b** of the figure) of the anterior and mid-insula (circled) is one of the most common neuroimaging findings across different anxiety disorders and during fear conditioning[77]. Hypoactivation is depicted in blue. ACC, anterior cingulate cortex; dlPFC, dorsolateral PFC; NTS, nucleus tractus solitarius; PTSD, post-traumatic stress disorder. Part **b** is adapted, with permission, from REF. 77 © (2007) American Psychiatric Association.



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biased threat expectancies contribute to persistently increased BNST activity under conditions of uncertainty, resulting in behavioural 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[6] proposed that the septo-hippocampal system responds to such conflict by increasing vigilance and inhibiting motor function to allow risk assessment, which in turn results in behavioural avoidance. Another candidate region for mitigating the conflict introduced by uncertainty is the aMCC. The recently proposed 'adaptive control hypothesis' (REF. 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 associated with the five UAMA processes (FIG. 1f).

Supporting this central role of 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 centres, the amygdala and midbrain nuclei, including the periaqueductal grey, 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, including exaggerated autonomic responses and behavioural 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]. Increased 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 a sustained, temporally unpredictable threat showed aMCC hyperactivity[139]. Structural imaging showed reductions in aMCC volume in panic disorder[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 grey 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, there was increased aMCC activation in anxious adolescents with high IU scores 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 behavioural, 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

The evidence reviewed here provides strong support for the central and disruptive role of uncertainty about a 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 FIG. 2, at the core of the UAMA are increased 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 increased threat expectancies reflect alterations in 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 towards 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 even more attentive towards a perceived threat. Also contributing to increased threat expectancies are impaired safety learning and an inability to inhibit fearful responding under conditions of safety, which is the result of deficient inhibitory vmPFC–amygdala communication.

Increased 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

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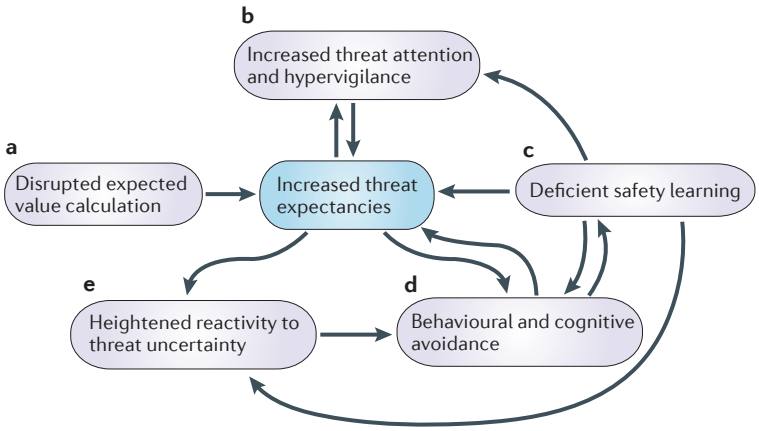

Figure 2 | **Altered anticipatory processes in response to threat uncertainty in anxiety.** Dynamic interactions among five key psychological processes (in grey) allow for anticipatory responses to uncertainty about future threat. The uncertainty and anticipation model of anxiety (UAMA) posits that alterations in these processes and associated core brain circuitry (FIG. 1) are responsible for maladaptive cognitive, behavioural and affective responses to uncertainty in highly anxious individuals. At the core of the UAMA are heightened expectancies about the probability and cost of future threat (in blue). These increased expectancies are the result of alterations in the calculation of expected value and aversive prediction error signalling (**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 increased cognitive and behavioural 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 behavioural reactivity under conditions of uncertainty (**e**), and this heightened reactivity to uncertainty leads to further avoidance of such conditions.

accumulate disconfirmatory evidence or learn about safety cues and therefore consolidates biased expectancies. Greater threat expectancies exacerbate BNST-dependent physiological and behavioural reactivity under conditions of uncertainty, whereas anterior insula dysfunction contributes to heightened anticipatory emotional responses and subjective feelings about the probability and cost of negative events. Finally, looming over all of these disrupted processes outlined in the UAMA are abnormal function and connectivity of the aMCC (FIG. 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; behavioural, self-reported or peripheral physiological responses to uncertainty in anxiety disorders; and neurobiological disruptions that are indirectly 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 provoking stimuli or negative emotional stimuli, which we argue fail to engage those processes that are 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 threats[100,140–143]. These paradigms engage brain regions that are implicated in pathological responses to uncertainty, including the amygdala, anterior insula, BNST, rostral cingulate and vmPFC. We propose that these and other paradigms should be extended to specifically target hypothesized disruptions of the five processes highlighted above, as framed in several questions below.

Does heightened anxiety in response to a sustained, unpredictable threat reflect abnormally increased BNST activation[4]? A combination of high-resolution imaging, differential temporal response profiles[141,142], probabilistic fibre tracking techniques[175] and pharmacological fMRI would allow 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 increased amygdala responses in unpredictable contexts[135]. Functional connectivity analyses could be used to address whether increased 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 signalling (that is, 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 signalling (ventral striatum, anterior insula and rostral cingulate)[57–59].

Is there evidence for deficits in 'somatic' aversive prediction error signalling in anxiety[28]? This could help to 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 increased threat expectancies, deficient identification of safety and heightened responses to uncertainty increase one's risk of developing an anxiety disorder? Or are these disruptions the consequences of living with anxiety? Is successful treatment associated with normalization of behavioural and neural responses to threat uncertainty?

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D-cycloserine
A partial agonist of the NMDA glutamate receptor that has been shown to enhance learning.

An assessment of which UAMA processes are intact versus those that are 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 the functioning of additional regions, particularly given the dense 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, as deleterious consequences of uncertainty result from increased 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 increased threat estimates. Individuals who are unable to identify safety signals might benefit from therapy that emphasizes 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 has been used to enhance the effects of exposure therapy in specific phobias[183,184], SAD[185], OCD[186] and PTSD[187], behavioural therapy in OCD[188], CBT in panic disorder[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 to learn to downregulate 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 behavioural 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 towards the reduction of anxiety might involve transitioning "from inaccurate expectations to more accurate expectations to no expectations at all" (REF. 193). The incorporation of mindfulness traditions into CBT — namely, emphasizing awareness of moment-to-moment internal and external events, and non-judgemental acceptance (rather than avoidance) of negative emotional states — allows one to tolerate unavoidable uncertainties[194] and helps those suffering from anxiety to understand that uncertainty about the future need not rule their lives.

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