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Neurocognitive mechanisms of anxiety: an integrative account

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Anxiety can be hugely disruptive to everyday life. Anxious individuals show increased attentional capture by potential signs of danger, and interpret expressions, comments and events in a negative manner. These cognitive biases have been widely explored in human anxiety research. By contrast, animal models have focused upon the mechanisms underlying acquisition and extinction of conditioned fear, guiding exposure-based therapies for anxiety disorders. Recent neuroimaging studies of conditioned fear, attention to threat and interpretation of emotionally ambiguous stimuli indicate common amygdala–prefrontal circuitry underlying these processes, and suggest that the balance of activity within this circuitry is altered in anxiety, creating a bias towards threat-related responses. This provides a focus for future translational research, and targeted pharmacological and cognitive interventions.

Introduction

It has been argued that fear mechanisms evolved to enable us to shift our focus from the task at hand at the first suggestion of potential danger; for example, interrupting foraging at the glimpse of a potential predator behind a tree. However, in a short evolutionary timescale our world has changed dramatically. The mass media brings news of natural disasters, potential pandemics, terrorist atrocities and violent crime straight into our homes. Perhaps it is not surprising that nearly one in four of us will experience a clinical level of anxiety within our lifetimes [1]. Previously, it might have been adaptive to attend to any potential source of danger and to interpret each ambiguous event as threat-related, but this is no longer the case. Arguably, a more interesting question is why only some individuals experience the excessive fear, worry and disruption to everyday function that characterizes clinical anxiety. This article focuses on the neurocognitive mechanisms implicated in anxiety; the literature on the genetics and neurochemistry of anxiety having been reviewed elsewhere [2,3].

Fear is viewed as a biologically adaptive physiological and behavioral response to the actual or anticipated occurrence of an explicit threatening stimulus. Anxiety crucially involves uncertainty as to the expectancy of threat [4], is triggered by less explicit or more generalized cues [5], and is characterized by a more diffuse state of distress, with symptoms of hyperarousal and worry. The human

Glossary

Backward masking: brief presentation of a given stimulus is followed by a visual mask that limits processing of the stimulus and can prevent volunteers from being able to identify it or even detect its presence.
Dot probe: a task in which participants are briefly presented with two words or two faces on either side of the screen. These stimuli are replaced by a probe (e.g. a pair of dots), which is presented in the spatial location previously occupied by one of the faces or words. Participants are asked to either simply detect the occurrence of the probe or to make a decision about its shape or orientation. On key trials, one of the two faces or words is threat-related and the other is neutral in valence. Anxious individuals are faster to respond to probes that occur in the position previously occupied by the threat-related stimulus than to probes that occur in the position previously occupied by the neutral stimulus. This difference in response times is held to provide an index of attentional capture by threat.
Emotional Stroop: a variant of the standard Stroop task in which participants are asked to name the ink color of words, which themselves are the names of colors. In this variant, the key variable is the emotional valence of the words presented, with anxious participants being slower to indicate the color of threat-related words.
Genetic polymorphism: a genetic variation that is seen in at least 1% of a given population. Each polymorphism produces two or more different alleles or versions of the DNA sequence at the locus of the polymorphism. Some genetic polymorphisms lead to changes in gene expression. These are described as functional genetic polymorphisms.
Genomic imaging: a term coined to refer to studies that use neuroimaging techniques to examine the impact of functional genetic polymorphisms upon neural activity during cognitive or emotional processing.
Pavlovian fear conditioning: repeated pairing of a neutrally valenced **conditioned stimulus (CS)**, such as a tone or a light, with an **unconditioned** aversively valenced **stimulus (US)**, such as a footshock, results in the CS alone eliciting **conditioned fear responses (CRs)**, such as freezing, increased startle reflexes and behavioral response suppression. Subsequent repeated presentation of the CS alone, in the absence of the US, leads to extinction of conditioned fear responses. **Extinction recall** refers to the retention of extinction after a period of time and is thought to depend upon presentation of the CS in the context in which extinction took place. **Reinstatement** of the conditioned fear response can occur following re-exposure to the US. **Renewal** of the conditioned fear response can occur if the CS is presented in a different context to that used for extinction, especially if this is the context in which CS–US pairings were initially established.
Perceptual load: the demand or load placed upon perceptual processing is held to become higher when the number of different-identity items that need to be perceived is increased and/or, for the same number of items, when perceptual identification is made more demanding on attention [59].
State and trait anxiety: state anxiety refers to current levels of anxiety and trait anxiety refers to the disposition to experience anxiety across multiple time points. In the human literature these are measured by means of self-report questionnaires that primarily assess symptoms of hyperarousal and worry.

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cognitive anxiety literature has provided compelling evidence that anxious individuals show increased attentional capture by cues signaling danger and are more likely to interpret emotionally ambiguous stimuli in a threat-related manner. It has been suggested that these cognitive biases are implicated in the maintenance, and possibly even the etiology, of anxiety [6,7]. The neural substrate of these processes, however, is not easily amenable to investigation with animal models. This contrasts with associative fear mechanisms, where basic neuroscience studies of Pavlovian fear conditioning (see Glossary) have extensively investigated the neural mechanisms mediating the acquisition and extinction of learned or conditioned fear. Although research into factors influencing extinction has been influential in informing exposure therapy for anxiety disorders, there has been little integration of this work with the literature on attentional and interpretative biases in anxiety.

Several recent findings have highlighted the possible interaction of associative and attentional processes in determining the response to threat-related stimuli, while also suggesting conceptual links between associative and interpretative processes [8–10]. Crucially, the advent of neuroimaging has provided a route for examining the neural substrate of these processes in humans. Thus, we can investigate whether the neurocognitive mechanisms underlying attention to, and interpretation of, potentially threat-related stimuli are related to those identified by the animal literature as underlying conditioned fear. The emergence of affective cognitive neuroscience has seen a surge in neuroimaging studies in this area. Findings from these studies support the contention that amydala-prefrontal circuitry is centrally involved in enabling both representations of stimulus emotional salience and top-down control mechanisms to influence associative, attentional and interpretative processes. Initial evidence suggests disruption of this circuitry in anxiety, with deficient recruitment of prefrontal control mechanisms and amygdaloid hyper-responsivity to threat potentially leading to alterations in associative, attentional and interpretative processes that sustain a threat-related processing bias in anxious individuals.

Mechanisms involved in the processing of threat and their disruption in anxiety

Selective attention to threat

Patients suffering from anxiety disorders have been reported to show a bias in selective attention towards threat-related stimuli [11,12]. Similar findings have been observed for individuals with high levels of trait anxiety. Here, however, the results are less robust, and it has been suggested that a combination of high trait and high state anxiety might be required for threat-related attentional biases to be observed in non-clinical populations [13].

Several paradigms, including the emotional Stroop and dot probe tasks, have been used to establish the presence of anxiety-related biases in selective attention. Anxiety is associated with slower reaction times and increased error rates in conditions requiring a response to an emotionally neutral stimulus or stimulus attribute (e.g. word color) presented simultaneously with task-irrelevant threat-related information. Conscious awareness of threat-related distractors is not necessary for attentional capture, anxious individuals orienting to the position previously occupied by briefly presented backward-masked threat-related stimuli despite being unable to identify these stimuli or even to detect their occurrence [13].

Drawing on these findings, cognitive models of anxiety have extended biased competition models of attention [14] to argue that selective attention to threat is determined by the relative signal strength from a pre-attentive threat evaluation mechanism versus that from top-down control mechanisms [12]. Anxiety is held to increase the output from the threat evaluation mechanism, biasing attentional competition in a threat-related direction, even when conscious awareness of the threat-related stimulus is absent.

Interpretation of emotionally ambiguous stimuli

Anxious individuals also judge future negative life events to be more likely to occur and are more prone to choose negative (or less positive) interpretations of emotionally ambiguous stimuli than non-anxious volunteers [12]. Negative interpretative biases of emotionally ambiguous stimuli have been reported across studies using verbal stimuli (e.g. threat-neutral homophones such as die-dye) [11], facial expressions [15] and complex social vignettes [16]. Both clinically anxious populations and high trait anxious individuals have been found to show threat-related interpretative biases, although, in the latter case, manipulations are often used to elevate state anxiety prior to task performance, leaving open the possibility that a combination of high trait and high state anxiety might increase the likelihood of interpretative biases [17,18]. It has been argued that these interpretative biases can be accounted for by the same mechanisms as those held to explain threat-related attentional biases. Specifically, competition is held to occur between alternate interpretations of emotionally ambiguous stimuli (e.g die versus dye), the outcome of this competition being influenced by threat evaluation and top-down mechanisms, with anxiety strengthening the activation of threat-related representations by augmenting the output from the proposed threat-evaluation mechanism and so making the selection of threat-related interpretations more likely [12].

Fear conditioning

Processes involved Stimuli with acquired or conditioned threat value can capture attention, and provoke physiological and behavioral fear responses, in a similar manner to intrinsically threat-related stimuli [8,9]. In patients with anxiety disorders, stimuli that for many of us are neutral or only mildly aversive (the sight of a spider, a car back-firing, or the perception of one's heart beating while giving a talk) can give rise to extreme hyperarousal, vigilance, emotional distress and attempts to escape from or avoid the anxiety-provoking object or situation. How do these disproportionate fear responses develop? Consideration of this issue has led Pavlovian fear conditioning to become widely used as a theoretical framework for the pathogenesis and treatment of anxiety disorders [19]. In conditioned fear, a conditioned stimulus (CS) generates a conditioned fear response (CR) as a result of its association with an intrinsically aversive unconditioned stimulus (US). Repeated presentation of