Neural Mechanisms Underlying Selective Attention to Threat

SONIA J. BISHOP

Behavioural and Clinical Neuroscience Institute, University of Cambridge, Cambridge, United Kingdom, and Medical Research Council Cognition and Brain Sciences Unit, Cambridge, United Kingdom

Biased competition models of selective attention suggest that attentional competition is influenced both by bottom-up sensory mechanisms sensitive to stimulus salience and top-down control mechanisms that support the processing of task-relevant stimuli. This provides a framework for investigating the neural mechanisms underlying selective attention to threat. Both subcortical regions implicated in threat detection—specifically the amygdala—and prefrontal cortical regions implicated in top-down attentional control are activated in response to task-irrelevant threat stimuli. A number of questions including the automaticity of the amygdala response to threat distractors, the modulation by anxiety of the amygdala and prefrontal response to these stimuli, and the impact of genetic and environmental factors upon this circuitry are addressed. The empirical literature is considered in the context of theoretical accounts of the neural substrate of selective attention and conscious awareness. It is suggested that the neural activity provoked by a given visual stimulus is influenced by factors impacting upon the strength of the bottom-up trace (e.g., presentation time, backward masking), stimulus salience (including threat relatedness), competition with other visual stimuli for perceptual processing resources, and the augmentation of the stimulus trace by allocation of top-down attentional resources. Individual differences in trait and state anxiety, and in genetic makeup, are thought to modulate the influence of stimulus valence and top-down attention through their impact upon amygdala and prefrontal function.

Key words: **attention; threat; fMRI; emotion; amygdala; prefrontal cortex; awareness; genetics; COMT; 5HTT**

Overview

When we experience anxiety, our attention is drawn to cues linked to the objects or events that are the focus of our concerns. This attentional capture by threat-related stimuli is particularly characteristic of patients with anxiety disorders and has been the subject of much investigation within the clinical–cognitive literature.[1–3] Recently, the advent of neuroimaging has enabled investigation of the neural mechanisms underlying selective attention to threat. The current chapter reviews this literature and addresses the relationship between findings arising from manipulations of spatial attention and those derived from manipulations of conscious awareness through subliminal presentation of threat stimuli. In particular, centrality is given to the question of the automaticity of the amygdala response to threat stimuli, the role of "top-down" inputs from prefrontal control mechanisms, and the modulatory influence of individual differences in anxiety. In addition, genetic and environmental influences upon these neural mechanisms are discussed. Both genetic and environmental factors contribute to the etiology of anxiety disorders.[4,5] Furthermore, evidence suggests that threat-related attentional biases are not only symptomatic of anxiety but may be causally involved in the development and maintenance of anxiety disorders.[6,7] Given this, examination of genetic and environmental influences upon the neural mechanisms underlying selective attention to threat may potentially advance our understanding of the route by which such influences modulate vulnerability to anxiety.

Cognitive Processes Involved in Selective Attention to Threat

In order to make our way through everyday life, we need to be able to balance the extent to which our behavior is driven by ongoing goals versus impacted by changes in our environment. Attentional mechanisms

Address for correspondence: Sonia J. Bishop, Behavioural and Clinical Neuroscience Institute, University of Cambridge, Downing Street, Cambridge, CB2 3EB, UK; Medical Research Council Cognition and Brain Sciences Unit, 15 Chaucer Road, Cambridge, CB2 2EF, UK.
sb445@cam.ac.uk

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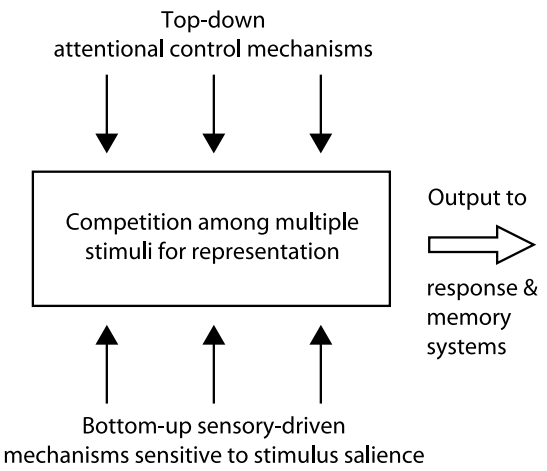

FIGURE 1. A schematic illustration of the biased competition model of selective attention,[8–10] adapted with permission.[10] According to this model, the outcome of attentional competition between visual stimuli is influenced both by bottom-up mechanisms sensitive to stimulus salience and top-down control mechanisms recruited to support the processing of task-relevant stimuli.

allow us to filter input from the outside world and select certain stimuli to which to respond. According to biased competition models of selective attention[8–10] (see FIG. 1), whether we attend to task-relevant stimuli or have our attention captured by task-irrelevant distractors that enter our visual environment depends on an interplay between "bottom-up" sensory mechanisms and "top-down" control processes. Specifically, attentional competition is thought to be influenced both by stimulus salience and by top-down prioritization of the processing of task-related stimuli. In other words, while attention is often captured by colorful, moving, or novel stimuli, this can, to some extent, be overridden by attempts to stay on-task and allocate attentional resources to a particular object or feature or to stimuli that appear in a particular location. It has been argued that this may be achieved by using prefrontal or frontoparietal cortical mechanisms to "prime" or strengthen the representations of particular stimuli, stimulus categories, or dimensions (e.g., color), or representations of stimuli that occur in given locations, increasing the likelihood that corresponding task-relevant stimuli will win attentional competition.[8–10]

An important dimension of stimulus salience is "valence," the extent to which a given stimulus is threat or reward related. There has been much interest in the extent to which threat-related stimuli may have a special status in their ability to capture attention or to be processed independently of the locus of attention. Research into this topic suggests that there is much variability across individuals. In particular, clinically anxious and high-trait anxious volunteers show an increased attentional bias toward threat-related stimuli, as indicated by slower or more error-laden processing of neutrally valenced target stimuli in the presence of threat-related distractors.[1–3] This has been observed across a number of paradigms including both the Emotional Stroop and the Probe-Detection tasks. In the former, a variant of the standard color stroop task, participants are asked to name the ink color in which a word is presented while ignoring the meaning of the word (see FIG. 2A). Anxious individuals show slower color naming for threat-related than for emotionally neutral words.[11] In the latter, participants are presented simultaneously with two visual stimuli (typically words or faces) followed by a "dot probe" in the position previously occupied by one of the two stimuli (see FIG. 2B). Here, when the stimulus pair comprises one threat-related and one neutral item, anxious individuals are faster to detect the probe or to indicate its orientation (in the case of dot-pair probes) when it replaces the threat-related stimulus.[2] Interestingly, conscious awareness of threat-related distractors does not appear to be necessary for attentional capture. Volunteers with heightened anxiety levels have been reported to show threat-related attentional biases in emotional stroop and probe-detection tasks when stimuli are briefly presented and backward-masked and participants are unable to identify or even detect the stimuli presented.[2]

These findings have been incorporated into cognitive models of anxiety that extend biased competition models of selective attention. These models propose that attentional capture by threat is determined by competition between task-relevant stimuli and threat-related distractors, with input from both a preattentive threat detection/evaluation mechanism and top-down control mechanisms influencing the outcome of this competition.[3,12] Anxiety is held to increase the output from the threat detection mechanism, priming threat-related representations, and biasing attentional competition in a threat-related direction, even when conscious awareness of threat-related stimuli is absent. Low or nonanxious individuals are held to either not show threat-related attentional biases or to have a higher threshold or threat level that a stimulus must reach before the output from the threat detection mechanism is sufficient for the threat-related stimulus to capture attention. In the following two sections, evidence pertaining to the neural substrate of these processes will be discussed. In addition, the need to consider the possible multiple stages at which attentional

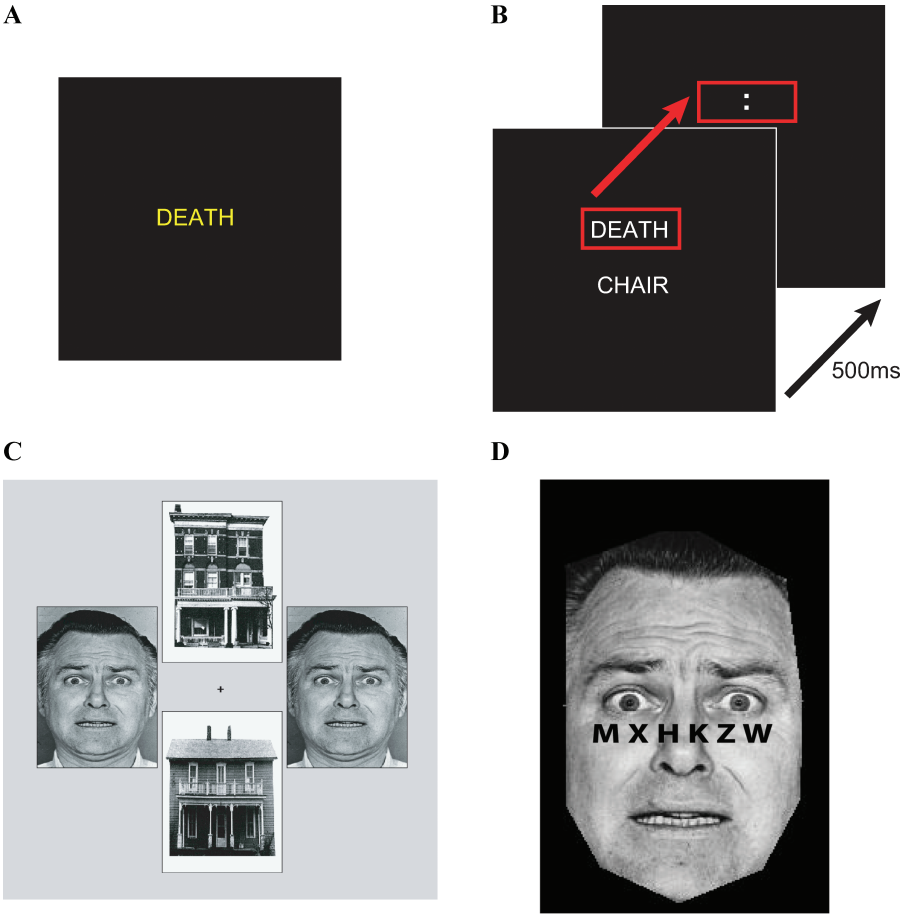

FIGURE 2. Examples of stimuli from attentional paradigms used to investigate the neural correlates and behavioral effects of task performance in the presence of threat-related versus neutral distractors. (**A**) The emotional stroop. Here participants are asked to name the color of the ink in which words are presented and to ignore the word meaning, which can be either threat-related or neutral in valence. (**B**) The probe detection task. Here participants are presented with pairs of words followed by a dot probe in the position previously occupied by one of the two words. On key trials, one word is threat related and the other neutral, the time taken to respond to probes occurring in the position previously occupied by the threat-related word is contrasted with that taken to respond to probes occurring in the position previously occupied by the neutral word. (**C**) The face/house matching task.[15,19,38] Participants are asked to match pairs of houses or faces. On key trials, participants match houses, the unattended stimuli being faces that are both either fearful or neutral in valence. (**D**) The perceptual load-face paradigm.[22] Here participants are asked to determine if either an X or N is present in a string of letters superimposed on a face. Critically, perceptual load is manipulated across blocks of trials by using letter strings comprising all Xs and all Ns (low load) or letter strings comprising different constants only one of which is an X or an N (high load). Distractor face valence (fearful or neutral) is varied from trial to trial.

competition may occur, and the relationship between this, automaticity of processing, and conscious awareness of threat stimuli, will be highlighted.

Neural Mechanisms Underlying Selective Attention to Threat

Within the neuroimaging literature on selective attention to threat, there has been an ongoing debate as to whether the amygdala shows an obligatory response to threat-related stimuli that is independent of the allocation of attentional resources. Building on findings from the basic neuroscience literature,[13,14] it has been suggested that a direct subcortical thalamoamygdala pathway may facilitate the "automatic" preattentive processing of threat-related stimuli.[15,16] In line with this position, a number of neuroimaging studies have reported that the amygdala response to

threat-related stimuli such as fearful faces is not modulated by the focus of spatial attention.[15,17] Extrapolating these findings into the clinical domain, it has been proposed that the amygdala might provide the neural substrate for the preattentive threat detection mechanism held to enable threat value to influence attentional competition in cognitive models of anxiety.[3,18] Initial findings pertaining to the modulation by anxiety of the amygdala response to unattended threat stimuli were seemingly consistent with this, high anxious individuals showing a stronger selective amygdala response to threat-related distractors.[19,20] However, opponents of strong automaticity models of the amygdala response to threat have argued that in the paradigms used in the studies referenced above, attentional resources may not have been fully occupied by the primary task, with spare attentional capacity potentially facilitating the processing of threat-related distractors.[21] Indeed, recent studies have demonstrated that when the perceptual demands or "load" of the main task is increased, a differential amygdala response to threat-related versus neutral distractors is no longer observed.[21,22]

These recent findings are in line with a model of selective attention under load put forward by Lavie.[23,24] According to this model, there are two stages of attentional competition. First, there is a stage of early perceptual competition. The processing of distractors is held to terminate at this stage when the perceptual load of the primary task is high. Second, under conditions of low perceptual load, competition is held to occur for further processing resources, including the initiation of behavioral responses, with active recruitment of control mechanisms being required to inhibit the processing of salient distractors and support task-related processing. This model has primarily been used to account for findings showing that increasing perceptual load reduces or eliminates the processing of affectively-neutral salient distractors, such as moving dot patterns, lexical stimuli that promote competing responses to that required by the current target, and colorful or novel scenes.[23–26] It can, however, be extended to the case of emotionally salient stimuli. Specifically, it is suggested that while the amygdala supports the processing of threat-related stimuli, its level of activation potentially influencing their competitive success through a priming mechanism analogous to that held to underlie the facilitation of the processing of targets by top-down attentional control, this may occur at a point in the processing steam subsequent to an initial stage of perceptual competition.

Lavie's model of selective attention under load[23–25] has also been used to account for findings that groups characterized by weakened attentional control—specifically the elderly and children—show particularly large response competition effects under low perceptual load.[27,28] It is argued that this reflects failure to actively recruit cognitive control mechanisms to prevent salient distractors from receiving further processing. In an interesting parallel to this, perceptual load has been demonstrated to modulate the extent to which high anxious individuals show a selective neural response to threat-related versus neural distractors that differs from that shown by low anxious individuals.[22] Specifically, under low but not high perceptual load, elevated trait anxiety is associated with diminished activation of prefrontal control mechanisms in response to threat distractors, while high-state anxiety is associated with augmentation of the amygdala response to these distractors (see FIG. 3).

These findings raise the possibility that anxiety may not only modulate output from an amygdala-based threat detection mechanism but may also be associated with impoverished recruitment of prefrontal control mechanisms to support the further processing of task-relevant stimuli and/or to inhibit the further processing of threat-related distractors. In line with this proposal, anxiety has been associated with lower levels of self-reported attentional control,[22,29] impaired executive function,[30] disrupted inhibition of threat-related stimuli,[31] and reduced activation of prefrontal mechanisms in response to the presentation of threat-related stimuli.[32,33] Both the nature and the origin of the disruption to prefrontal control mechanisms in anxiety remains a topic of ongoing investigation. Regarding the latter, genetic and environmental influences that impact the function of these mechanisms are discussed in the fourth section. In regard to the former, it has been suggested that specific subregions of the prefrontal cortex may play differing roles in top-down attentional control, with the anterior cingulate cortex (ACC) being involved in detecting the presence of competition for processing resources and the lateral prefrontal cortex (LPFC) in responding to increased expectation of processing competition by augmenting top-down control to support the processing of task-relevant stimuli.[34,35] Evidence for this account has primarily come from studies using response-conflict paradigms with affectively neutral stimuli,[35–37] including ones which manipulate the frequency, and hence the expectancy, of high conflict trials.[36] Given this, we used a mixed-model design to investigate whether ACC and LPFC regions also respond differentially to unexpected (infrequent) and expected (frequent) *threat-related* distractors.[38] Our findings confirmed this, suggesting that the ACC and LPFC play

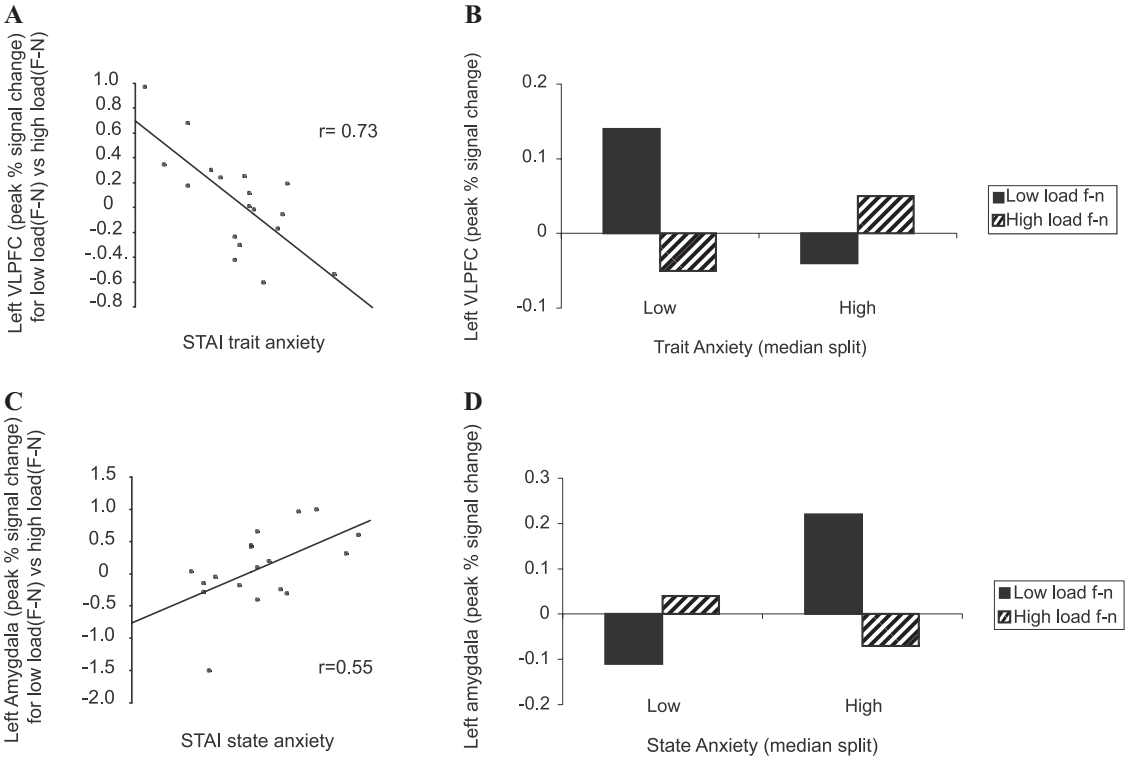

FIGURE 3. Modulatory effects of anxiety upon the neural response to threat distractors under low versus high perceptual load. (**A** and **B**) Effects of trait anxiety on the ventrolateral prefrontal cortical (VLPFC) response to fearful (F)–neutral (N) distractor faces under low versus high perceptual load. Note, similar effects were observed in dorsolaterol prefrontal and anterior cingulate cortex regions of interest. (**C** and **D**) Effects of state anxiety upon the amygdala response to fearful – neutral distractor faces under low versus high perceptual load. (Reproduced by permission From Bishop *et al.*[22])

similar respective roles in detecting and resolving processing competition arising from the threat-relatedness of task-irrelevant stimuli to those suggested in the response conflict literature, with heightened anxiety being associated with impoverished recruitment of both these mechanisms. FIGURE 4 shows a neurocognitive model of selective attention to threat that can account for these findings together with the others reviewed in this section. This extends the biased competition model of selective attention[8–10] into the emotional domain, incorporating the idea of early (perceptual) and later (selection for response and maintenance in working memory) stages of attentional competition as outlined by Lavie and colleagues[24] as well as the distinction between control mechanisms involved in detecting versus resolving the presence of competition.[34,35]

Interestingly, a recent study actually suggested a reverse role for ACC and LPFC mechanisms in threat-related conflict detection and resolution.[39] These findings are, however, difficult to interpret as, in the paradigm used, attentional competition driven by distractor valence cannot be dissociated from competition resulting from response conflict. It is also of note that, in our investigation of the prefrontal cortical response to expected and unexpected threat distractors,[38] the correlational results reported were for state anxiety. Parallel results were obtained for trait anxiety but not reported, levels of state and trait anxiety being too highly correlated to allow for separate investigation of their distinct effects. Given subsequent evidence that trait and state anxiety might have dissociable effects upon prefrontal control mechanisms and amygdala-based threat-detection mechanisms,[22] as discussed earlier, further investigation of the impact of anxiety upon ACC and LPFC control mechanisms is clearly warranted, ideally using experimental manipulation of state anxiety to dissociate trait and state effects.

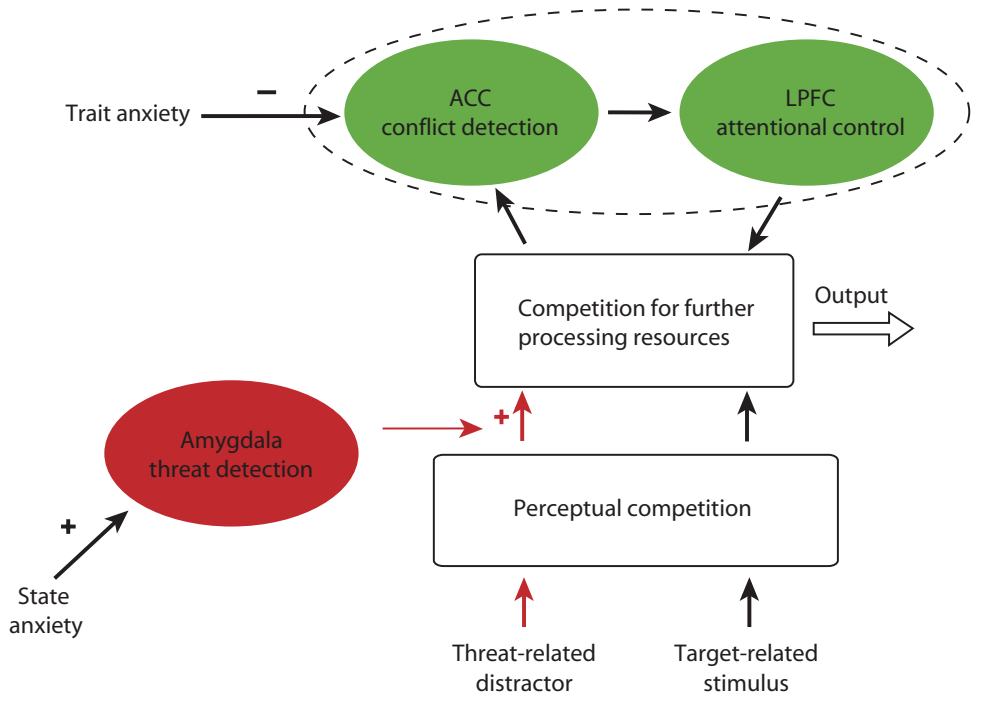

FIGURE 4. Neurocognitive model of selective attention to threat. Attentional competition involves both early competition for perceptual resources and later competition for further processing resources. This later competition is influenced both by the strength of a threat-detection signal from the amygdala and the strength of a top-down control signal supporting task-related processing. The latter is thought to emanate from the lateral prefrontal cortex (LPFC), with a rostral anterior cingulate cortical (ACC) region signaling the presence of attentional competition from threat distractors.[38] Anxiety is held to modulate processing subsequent to the initial stage of perceptual competition, elevated anxiety being associated with amygdala hyperresponsivity and prefrontal hyporesponsivity. Recent findings suggesting that the amygdala response is primarily modulated by state anxiety while prefrontal recruitment is primarily influenced by individual differences in trait anxiety[22] are incorporated into the model. (Reproduced by permission from Bishop.[76])

Neural Activity to "Unseen" Threat Stimuli: Effects of Subliminal Presentation May Differ from Those of Inattention

Studies examining the amygdala response to briefly presented backward-masked threat-related stimuli have also been cited as supporting the automaticity of the amygdala response to threat and as providing evidence for the proposed thalamo-amygdala "fast route" for threat processing. The current section considers the empirical evidence for whether a selective amygdala response is observed to threat-related stimuli that cannot be consciously reported. In addition, it tackles the question of what conclusions can be drawn from these findings as to the automaticity of the amygdala response to threat and the existence of the proposed thalamoamygdala route for the rapid processing of threat-related stimuli. Finally, an attempt is made to integrate these findings with those reviewed in the previous section.

With regard to the empirical data, the extent to which the amygdala responds to threat-related visual stimuli in the absence of conscious awareness is still hotly under debate. Early data pertaining to this issue comes from seminal neuroimaging studies conducted in the 1990s. These reported amygdala activity to briefly presented threat-related (fearful or aversively conditioned) faces masked by the immediate subsequent presentation of a second face, which was always neutral in valence.[40,41] It has since been argued that the target-mask presentation parameters used in these studies might not necessarily have prevented all individuals from having conscious access to the target faces. Indeed, using similar presentation parameters (target face presented for 33 ms, immediately followed by a neutral face mask for 100 ms), Pessoa and colleagues reported reliable detection of masked fearful faces in 60% of volunteers.[42] In addition, they subsequently

reported that a selective amygdala response to fearful versus neutral masked faces was only observed in those volunteers able to discriminate the emotionality of target faces.[43]

The findings by Pessoa and colleagues appear to suggest that a selective amygdala response to briefly presented backward-masked threat-related stimuli is only observed when individuals are, to some extent, aware of the emotional valence of the target faces. However, a number of other findings question this conclusion. Several recent neuroimaging studies investigating the amygdala response to backward-masked fearful versus neutral faces or face components (eyes), have used extremely brief target durations (17–20 ms) combined with objective assessment of target detection and/or discrimination.[44–46] These studies have provided evidence for a selective amygdala response to masked threat-related versus neutral facial stimuli, even when chance performance at discriminating target valence is determined at an individual rather than a group level.[44]

How do we interpret these findings? One possibility is that the discrepancies in results arise as a result of individual variability in the amygdala response to subliminally presented threat stimuli. In line with this, Etkin and colleagues have reported that trait anxiety is positively correlated with the strength of the amygdala response to backward-masked fearful faces.[47] In addition, the presentation time required to prevent conscious access to target face valence is so brief that the activation trace for these stimuli is inevitably weak. Consequently, the power to detect amygdala activation associated with these stimuli is likely to be low, potentially contributing to variability in findings across studies.

The theoretical significance of these results are considered next. Specifically, how do they relate to findings from studies using attentional paradigms and what if anything can we conclude about the automaticity of the amygdala response to threat and the existence of the proposed thalamoamygdala route for the rapid processing of threat-related stimuli? One problem facing the neuroimaging literature on emotion, is that terms such as the "preattentive," "obligatory," and "unconscious" processing of threat often have been used interchangeably, findings from both backward-masking studies and paradigms manipulating attentional focus having been taken as evidence for a thalamoamygdala fast route that enables the automatic processing of threat. Recently, reviews of the growing literature on the neural correlates of consciousness have argued for the importance of distinguishing between cases where conscious awareness of visual stimuli is eliminated by (1) reduction of the strength of the stimulus trace or (2) unavailability of attentional resources. In particular, Dehaene and colleagues have drawn a useful distinction between "subliminal" and "preconscious" processing.[48,49] Together with others,[50] they have argued that conscious awareness of a visual stimulus involves reverberation of activity between occipital–temporal areas that are specifically responsive to visual stimuli and frontoparietal regions that enable coherent concepts to be maintained, manipulated, and acted upon. Subliminal processing of target stimuli is held to occur when feed-forward (bottom-up) stimulus-related activity is too weak to trigger such reverberatory activation. This is held to be the case when conscious report of target characteristics is prevented through backward masking. While the stimulus trace is held to be weak, it is not, however, thought to be curtailed at an early subcortical stage of processing. According to this position, amygdala activation in response to backward-masked threat stimuli would not necessarily prove the operation of a noncortical thalamoamygdala pathway. In line with this, research using direct intracranial recording has reported amygdala activity in response to subliminally presented emotional words that is first detected at about 800 ms after presentation of the words.[51] This would appear to be more consistent with a weak trace reaching cortical regions required for semantic processing prior to triggering a valence-dependent amygdala response than with activation of a direct rapid thalamoamygdala pathway. Here, it is it not being argued that the existence of this rapid pathway is discredited, simply that reports of amygdala activity in subliminal processing paradigms such as that achieved through backward masking may not be sufficient to prove its existence.

Subliminal processing is distinguished from preconscious processing where the ability to detect or discriminate a target stimulus is curtailed by reduced availability of attentional resources. Examples of tasks held to result in preconscious processing include the attentional blink and inattentional blindness paradigms.[49] Reportability of distractor stimuli may similarly be reduced in other paradigms using spatial manipulations of attention such as the house/face matching paradigm described earlier[15,19,38] (see FIG. 2C). It is argued that during preconscious processing there is strong feed-forward neuronal activity, but that fronto—parietal activation required to support conscious awareness is curtailed.[48] Here, the feed-forward activity would arguably be sufficient to account for amygdala responsivity to nonreported threat-related stimuli within these

paradigms. As will be returned to later, this clearly relates to the findings regarding amygdala responsivity to threat-related distractors presented in the previous section.

The Dehaene model suggests that both bottom-up and top-down influences can impact upon the accessibility of visual stimuli to conscious report. In line with this, there is evidence that both stimulus valence and attentional focus can interact with presentation parameters (duration of stimulus presentation, masking, etc.) to determine the strength of stimulus-related activity. In regard to valence, it has been shown through manipulating target-mask stimulus onset asynchrony that the threshold for conscious awareness is lower for threat-related words than for neutral words.[52] In addition, attentional focus has been shown to modulate the neural response to visual stimuli even when conscious awareness of these stimuli is prevented through continuous-flash suppression.[53] The latter finding suggests that attending to a given stimulus can increase the strength of associated neural activity even when this is insufficient to give rise to conscious awareness of the stimulus.

The predictions made by the Dehaene model with regard to preconscious processing, or processing under conditions of reduced attentional resources, are in line with the findings reported in the previous section regarding amygdala responsivity to threat distractors under conditions of low perceptual load. They do not, however, account for the effects of manipulating perceptual load.[21,22] This can be overcome by integrating the Dehaene account with the neurocognitive model of selective attention to threat presented in FIGURE 4. Specifically, it is suggested that the neural activation generated by a given visual stimulus may depend upon the following factors: the extent of competition for perceptual resources from other stimuli within the visual array; the bottom-up strength of the stimulus trace (impacted by presentation duration, backward masking, etc.); stimulus salience (e.g., threat-relatedness); and the recruitment of top-down attentional mechanisms to support competition for further processing resources, including both maintenance in working memory and guidance of response selection. Feed-forward neuronal activity may only be curtailed at a sufficiently early stage of processing to prevent amygdala activity to threat-related stimuli under conditions of high perceptual load. In all other cases, the strength of the amygdala response to threat stimuli may be determined by an interaction between factors impacting upon stimulus trace strength (presentation duration, level of threat-relatedness), augmentation or inhibition of the signal by top-down attentional control mechanisms according to task relevance, and modulatory influences arising from individual differences in trait and state anxiety. Feedback connections from the amygdala may in turn modulate activity in occipital–temporal visual regions. According to this account, and on the basis of the evidence reviewed earlier in the chapter, the amygdala response to threat stimuli does not reach the criteria for "strong" automaticity,[54] in that it is not independent of the availability of attentional resources. However, it is arguably "obligatory," given that neither conscious awareness not volitional allocation of attention appear to be required for an amygdala response to threat-related stimuli to be observed.[19–22,44–47]

Genetic and Environmental Influences on the Neural Mechanisms Underlying Selective Attention to Threat

The final section of this review addresses the rapidly developing literature concerning genetic and environmental influences on the mechanisms thought to underlie selective attention to threat. As has been discussed earlier in the chapter, attentional capture by threat stimuli is thought to depend on the relative activation of representations of threat-related distractor stimuli versus task-relevant stimuli, with these activation levels being influenced by input from amygdala threat detection and prefrontal control mechanisms. Amygdala and prefrontal cortical function are both modulated by monoamine neurotransmission and subject to genetic and environmental influences.[55–59] Interest in genetic influences upon these mechanisms has increased recently as a result of advances in what has come to be known as "genomic imaging." This assesses the impact of specific genetic polymorphisms upon neural activity during task performance. It has been argued that genetic influences may be observed more clearly at the neurophysiological level as measured by the blood oxygen level–dependent (BOLD) signal in fMRI than at the level of behavior, the former level being held to be closer to the neurobiological effects of specific genes and less susceptible to the sources of noise that can influence task performance.[60,61] Two particularly robust findings of relevance to the mechanisms under consideration are emerging from early studies in this field. The first is that a polymorphism in the promoter region of the serotonin transporter gene (5HTT-LPR) influences the amygdala response to threat-related stimuli,[58] with the variance accounted for being even more striking when an additional polymorphism (5HTT rs25531 A/G) is

also taken into account.[62] The second is that a polymorphism (val^{158}met) in the COMT gene, which influences dopamine metabolism in the prefrontal cortex, accounts for substantial between-subject variation in prefrontal cortical activation during tasks requiring top-down control or executive processing.[63–65] These findings alone point to how a small number of common genetic polymorphisms could potentially impact upon the mechanisms underlying selective attention to threat. Indeed, early data from our lab indicate that the COMT val^{158}met polymorphism modulates both the strength of the prefrontal cortical response to threat distractors and the accompanying level of activity in regions involved in representing task-relevant stimuli,[66] while the 5HTT-LPR polymorphism impacts upon the amygdala response to threat distractors (unpublished data). As yet, our sample size is insufficiently large to investigate the manner in which these influences interact. Clearly, other genetic variants influencing monoamine transmission are also likely to impact upon amygdala, and prefrontal function and investigations of gene by gene interactions are likely to be central to advancing our understanding of genetic influences upon these mechanisms.

Turning to the question of environmental influences upon the mechanisms underlying selective attention to threat, there is also strong evidence that exposure to stress may have long-term effects resulting in both prefrontal hyporesponsivity and amygdala hyperresponsivity to threat-related stimuli. Findings in support of this come both from symptom provocation studies in patients with posttraumatic stress disorder (PTSD) and from basic neuroscience studies of exposure to stressors. In rats, exposure to chronic stress parallels the effect of prefrontal lesions in reducing inhibition of the central nucleus of the amygdala's response to aversive stimuli.[67] One potential mechanism for this involves dendritic retraction in the prefrontal cortex, dendritic changes having been shown to occur as a result of chronic stress and to be accompanied by impairments in attentional regulation.[68] In addition, early life stress impacts upon gene expression, notably increasing corticotropin-releasing factor (CRF) expression in the amygdala and altering the noradrenergic response to subsequent stressors.[69] In convergence with these findings, PTSD is reported more frequently in war veterans exposed to major stressors in childhood, and has been shown to be accompanied by increased catecholamine reactivity, frontal hyporesponsivity, and amygdala hyperresponsivity to trauma-related stimuli.[33,70] These findings suggest an effect of exposure to major stressors upon amygdala–prefrontal circuitry in humans that parallels that demonstrated in animal models. Interestingly, heritability studies suggest that genetic factors may also contribute modestly to vulnerability to PTSD following exposure to trauma.[71,72] In summary, the findings reviewed in this section suggest that the amygdala–prefrontal circuit underlying selective attention to threat may be the focus of both genetic and environmental effects that can confer heightened vulnerability to anxiety.

Remaining Issues and Future Directions

While there are many questions still to be addressed in this area of research, a few will be highlighted here. First, research into genetic influences upon the neural mechanisms underlying selective attention to threat is clearly still in its infancy. Here, there are a number of challenges. Moving beyond examining the effects of just one or two specific polymorphisms at a time will require huge increases in sample sizes and the modeling of potentially nonlinear effects. In addition, while heritability studies have examined gene by environment interactions in some detail, few genomic imaging studies have as yet integrated considerations of environmental factors into their design. This is an exciting avenue for future investigation.

Second, interest in the proposed thalamoamygdala "fast" route for threat processing has prompted investigation of the temporal dynamics of the processes underlying selective attention to threat.[73,74] The conclusions that can be drawn from this research are constrained by difficulty in localizing activity originating from the amygdala due to its deep position and electronically closed structure.[74] Here, findings from intracranial recording studies are highly exciting,[51,75] but arguably limited in the extent to which their findings can be reliably extrapolated to healthy neural function.

Third, while a relatively large number of neuroimaging studies have examined the neural mechanisms underlying selective attention to threat, there has been comparatively little work on the neural mechanisms underlying selective attention to positively valenced stimuli. Potential confounds between stimulus valence and arousal ratings make it unclear whether the failure to replicate findings of amygdala responsivity to threat distractors with positively valenced distractors is due to (1) a genuine differential responsivity of the amygdala to these stimuli or (2) difficulty in matching the arousal levels of threat distractors using positive stimuli taken from standardized sets. Further work on this is required.

Concluding Remarks

The literature reviewed here suggests that neural mechanisms underlying bottom-up sensory and top-down control processes interact to determine the extent of processing received by threat-related stimuli. Manipulations of attentional focus, primary-task perceptual load, and stimulus presentation parameters (duration, backward masking, etc.) have differing influences upon amygdala and prefrontal activation to such stimuli. Under high perceptual load, competition for perceptual resources appears to curtail the processing of threat distractors at an early stage, eliminating the amygdala response to these stimuli.[21,22] In contrast, under low perceptual load, feed-forward or bottom-up activity can be sufficient for such distractors to lead to amygdala activity. Under these conditions, it is argued that salient distractors compete for further processing resources, such as entry to working memory and guidance of response selection. In line with this, under low perceptual load, prefrontal cortical regions implicated in top-down attentional control are selectively activated in response to the occurrence of threat-related distractors.[22]

In contrast to manipulations of perceptual load, brief stimulus presentation combined with backward masking appears to weaken the strength of the bottom-up signal produced by threat stimuli rather than curtailing the stage of processing that this activation reaches. This reduction in signal strength can be sufficient to eliminate conscious awareness of the target stimulus, even in the absence of attentional competition. Under these conditions, an amygdala response to threat stimuli may be detected although the strength of this signal is often reduced.[45]

Individual differences in anxiety modulate the strength of the amygdala signal to threat stimuli, even when volunteers are not attending to or consciously aware of these stimuli.[19,22,47] The main exception appears to be under conditions of high perceptual load,[22] consistent with the possibility that, under such conditions, stimulus processing may be curtailed at a point prior to amygdala activation. Elevated anxiety is also associated with reduced recruitment of prefrontal control mechanisms in response to processing competition from threat-related distractors.[22,38] Both genetic and environmental factors impact upon this amygdala–prefrontal circuitry.[57–59] Arguably, these factors might contribute to vulnerability to anxiety by altering the relative predominance of amygdala versus prefrontal influences when threat stimuli compete to gain control of limited processing resources.

Competing Interest

The author declares no competing interest.

References

1. Mathews, A. & C. MacLeod. 1994. Cognitive approaches to emotion. Annu. Rev. Psychol. **45:** 25–50.
2. Mogg, K. & B.P. Bradley. 1998. A cognitive-motivational analysis of anxiety. Behav. Res. Ther. **36:** 809–848.
3. Mathews, A. & B. Mackintosh. 1998. A cognitive model of selective processing in anxiety. Cogn. Ther. Res. **22:** 539–560.
4. Hettema, J.M., M.C. Neale & K.S. Kendler. 2001. A review and meta-analysis of the genetic epidemiology of anxiety disorders. Am. J. Psychiatry **158:** 1568–1578.
5. Hettema, J.M., C.A. Prescott, J.M. Myers, *et al.* 2005. The structure of genetic and environmental risk factors for anxiety disorders in men and women. Arch. Gen. Psychiatry **62:** 182–189.
6. MacLeod, C., E. Rutherford, L. Campbell, *et al.* 2002. Selective attention and emotional vulnerability: assessing the causal basis of their association through the experimental manipulation of attentional bias. J. Abnorm. Psychol. **111:** 107–123.
7. Mathews, A. & C. MacLeod. 2002. Induced processing biases have causal effects on anxiety. Cogn. Emot. **16:** 331–354.
8. Desimone, R. & J. Duncan. 1995. Neural mechanisms of selective attention. Annu. Rev. Neurosci. **18:** 193–222.
9. Duncan, J. 2006. EPS Mid-Career Award 2004: brain mechanisms of attention. Q. J. Exp. Psychol. **59:** 2–27.
10. Kastner, S. & L.G. Ungerleider. 2000. Mechanisms of visual attention in the human cortex. Annu. Rev. Neurosci. **23:** 315–341.
11. Williams, J.M., A. Mathews & C. MacLeod. 1996. The emotional stroop task and psychopathology. Psychol. Bull. **120:** 3–24.
12. Mathews, A., B. Mackintosh & E.P. Fulcher 1997. Cognitive biases in anxiety and attention to threat. Trends Cogn. Sci. **1:** 340–345.
13. Armony, J.L. & J.E. LeDoux. 1999. How danger is encoded: Towards a systems, cellular, and computational understanding of cognitive-emotional interactions in fear circuits. *In* The Cognitive Neurosciences. M.S. Gazzaniga, Ed.: 1067–1080. MIT Press. Cambridge, MA.
14. LeDoux, J.E. 2000. Emotion circuits in the brain. Annu. Rev. Neurosci. **23:** 155–84.
15. Vuilleumier, P., J.L. Armony, J. Driver, *et al.* 2001. Effects of attention and emotion on face processing in the human brain: an event-related fMRI study. Neuron **30:** 829–841.
16. Dolan, R.J. & P. Vuilleumier 2003. Amygdala automaticity in emotional processing. Ann. N. Y. Acad. Sci. **985:** 348–355.
17. Anderson, A.K., K. Christoff, D. Panitz, *et al.* 2003. Neural correlates of the automatic processing of threat facial signals. J. Neurosci. **23:** 5627–5633.
18. Ohman, A. & S. Wiens 2004. The concept of an evolved fear module and cognitive theories of anxiety. *In*

Feelings and Emotions: The Amsterdam Symposium. A.S.R. Manstead, N.H. Frijda & A.H. Fischer, Eds.: 58–80. Cambridge University Press. Cambridge, UK.
19. Bishop, S.J., J. Duncan & A.D. Lawrence. 2004. State anxiety modulation of the amygdala response to unattended threat-related stimuli. J. Neurosci. **24:** 10364–10368.
20. Straube, T., H.J. Mentzel & W.H. Miltner. 2006. Neural mechanisms of automatic and direct processing of phobogenic stimuli in specific phobia. Biol. Psychiatry **59:** 162–170.
21. Pessoa, L., S. Padmala & T. Morland. 2005. Fate of unattended fearful faces in the amygdala is determined by both attentional resources and cognitive modulation. Neuroimage **28:** 249–255.
22. Bishop, S.J., R. Jenkins & A.D. Lawrence. 2007. Neural processing of fearful faces: Effects of anxiety are gated by perceptual capacity limitations. Cereb Cortex **17:** 1595–1603.
23. Lavie, N. 2000. Selective attention and cognitive control: dissociating attentional functions through different types of load. *In* Control of Cognitive Processes: Attention & Performance, Vol 18. S. Monsell & J. Driver, Eds.: 175–194. MIT Press. Cambridge, MA.
24. Lavie, N. 2005. Distracted and confused? Selective attention under load. Trends Cogn. Sci. **9:** 75–82.
25. Lavie, N. 2001. The role of capacity limits in selective attention: behavioural evidence and implications for neural activity. *In* Visual Attention and Cortical Circuits. J. Braun & C. Koch, Eds.: 49–68. MIT Press. Cambridge, MA.
26. Rees, G., C.D. Frith & N. Lavie. 1997. Modulating irrelevant motion perception by varying attentional load in an unrelated task. Science **278:** 1616–1619.
27. Maylor, E. & N. Lavie. 1998. The influence of perceptual load on age differences in selective attention. Psychol. Aging **13:** 563–573.
28. Huang-Pollock, C.L., T.H. Carr & J.T. Nigg. 2002. Development of selective attention: perceptual load influences early versus late attentional selection in children and adults. Dev. Psychol. **38:** 363–375.
29. Derryberry, D. & M.A. Reed. 2002. Anxiety-related attentional biases and their regulation by attentional control. J. Abnorm. Psychol. **111:** 225–236.
30. Eysenck, M.W. & M.G. Calvo. 1992. Anxiety and performance: the processing efficiency theory. Cogn. Emot. **6:** 409–434.
31. Fox, E. 1994. Attentional bias in anxiety: a defective inhibition hypothesis. Cogn. Emot. **8:** 165–195.
32. Cannistraro, P.A. & S.L. Rauch. 2003. Neural circuitry of anxiety: evidence from structural and functional neuroimaging studies. Psychopharmacol. Bull. **37:** 8–25.
33. Shin, L.M., S.L. Rauch & R.K. Pitman. 2006. Amygdala, medial prefrontal cortex, and hippocampal function in PTSD. Ann. N. Y. Acad. Sci. **1071:** 67–79.
34. Cohen, J.D., M.M. Botvinick & C.S. Carter. 2000. Anterior cingulate and prefrontal cortex: Who's in control? Nat. Neurosci. **3:** 421–423.
35. Botvinick, M.M., J.D. Cohen & C.S. Carter. 2004. Conflict monitoring and anterior cingulate cortex: an update. Trends Cogn. Sci. **12:** 539–546.
36. Carter, C.S., A.M. Macdonald, M. Botvinick, *et al.* 2000. Parsing executive processes: strategic vs. evaluative functions of the anterior cingulate cortex. Proc. Natl. Acad. Sci. USA **97:** 1944–1948.
37. MacDonald, A.W., 3rd, J.D. Cohen, A. Stenger, *et al.* 2000. Dissociating the role of the dorsolateral prefrontal and anterior cingulate cortex in cognitive control. Science **288:** 1835–1838.
38. Bishop, S., J. Duncan, M. Brett, *et al.* 2004. Prefrontal cortical function and anxiety: controlling attention to threat-related stimuli. Nat. Neurosci. **7:** 184–188.
39. Etkin, A., T. Egner, D.M. Peraza, *et al.* 2006. Resolving emotional conflict: a role for the rostral anterior cingulate cortex in modulating activity in the amygdala. Neuron **51:** 871–882.
40. Whalen, P.J., S.L. Rauch, N.L. Etcoff, *et al.* 1998. Masked presentations of emotional facial expressions modulate amygdala activity without explicit knowledge. J. Neurosci. **18:** 411–418.
41. Morris, J.S., A. Ohman & R.J. Dolan. 1998. Conscious and unconscious emotional learning in the human amygdala. Nature **393:** 467– 470.
42. Pessoa, L., S. Japee & L.G. Ungerleider. 2005. Visual awareness and the detection of fearful faces. Emotion **5:** 243–247.
43. Pessoa, L., S. Japee, D. Sturman, *et al.* 2006. Target visibility and visual awareness modulate amygdala responses to fearful faces. Cereb. Cortex. **16:** 366–375.
44. Whalen, P.J., J. Kagan, R.G. Cook, *et al.* 2004. Human amygdala responsivity to masked fearful eye whites. Science **306:** 2061.
45. Williams, L.M., B.J. Liddell, A.H. Kemp, *et al.* 2006. Amygdala-prefrontal dissociation of subliminal and supraliminal fear. Hum. Brain Mapp. **27:** 652–661.
46. Liddell, B.J., K.J. Brown, A.H. Kemp, *et al.* 2005. A direct brainstem-amygdala-cortical 'alarm' system for subliminal signals of fear. NeuroImage **24:** 235–243.
47. Etkin, A, K.C. Klemenhagen, J.T. Dudman, *et al.* 2004. Individual differences in trait anxiety predict the response of the basolateral amygdala to unconsciously processed fearful faces. Neuron **44:** 1043–1055.
48. Dehaene, S., J.P. Changeux, L. Naccache, *et al.* 2006. Conscious, preconscious, and subliminal processing: a testable taxonomy. Trends Cogn. Sci. **10:** 204–211.
49. Kouider, S. & S. Dehaene. 2007. Levels of processing during non-conscious perception: a critical review of visual masking. Philos. Trans. R. Soc. Lond. B Biol. Sci. **362:** 857–875.
50. Lamme, V.A. 2006. Towards a true neural stance on consciousness. Trends Cogn. Sci. **10**, 494–501.
51. Naccache, L., R. Gaillard, C. Adam, *et al.* 2005. A direct intracranial record of emotions evoked by subliminal words. Proc. Natl. Acad. Sci. USA **102:** 7713–7717.
52. Gaillard, R., A. Del Cul, L. Naccache, *et al.* 2006. Nonconscious semantic processing of emotional words modulates conscious access. Proc. Natl. Acad. Sci. USA **103:** 7524–7529.
53. Bahrami, B., N. Lavie & G. Rees. 2007. Attentional load modulates responses of human primary visual cortex to invisible stimuli. Curr. Biol. **17:** 509–513.

54. KAHNEMAN, D. & A. TREISMAN. 1984. Changing views of attention and automaticity. *In* Varieties of Attention. R. Parasuraman & D.R. Davies, Eds.: 29–61. Academic Press. New York.
55. MILLAN, M.J. 2003. The neurobiology and control of anxious states. Prog. Neurobiol. **70:** 83–244.
56. ARNSTEN, A.F.T. 1998. Catecholamine modulation of prefrontal cortical cognitive function. Trends Cogn. Sci. **2:** 436–447.
57. WINTERER, G. & D. GOLDMAN. 2003. Genetics of human prefrontal function. Brain Res. Brain Res. Rev. **43:** 134–163.
58. HARIRI, A.R. & A. HOLMES. 2006. Genetics of emotional regulation: the role of the serotonin transporter in neural function. Trends Cogn. Sci. **10:** 182–191.
59. MCEWEN, B.S. 2007. Physiology and neurobiology of stress and adaptation: central role of the brain. Physiol. Rev. **87:** 873–904.
60. GOLDBERG, T.E. & D.R. WEINBERGER. 2004. Genes and the parsing of cognitive processes. Trends Cogn. Sci. **8:** 325–335.
61. HARIRI, A.R. & D.R. WEINBERGER. 2003. Imaging genomics. Br. Med. Bull. **65:** 259–270.
62. SMOLKA, M.N., M. BUHLER, G. SCHUMANN, *et al.* 2007. Gene-gene effects on central processing of aversive stimuli. Mol. Psychiatry **12:** 307–317.
63. EGAN, M.F., R.E. STRAUB, T.E. GOLDBERG, *et al.* 2001. Effect of COMT Val108/158 Met genotype on frontal lobe function and risk for schizophrenia. Proc. Natl. Acad. Sci. USA **98:** 6917–6922.
64. BLASI, G., V.S. MATTAY, A. BERTOLINO, *et al.* 2005. Effect of catechol-O-methyltransferase val158met genotype on attentional control. J. Neurosci. **25:** 5038–5045.
65. BERTOLINO, A., G. BLASI, V. LATORRE, *et al.* 2006. Additive effects of genetic variation in dopamine regulating genes on working memory cortical activity in human brain. J. Neurosci. **26:** 3918–3922.
66. BISHOP, S.J., J.D. COHEN, J. FOSSELLA, *et al.* 2006. COMT genotype influences prefrontal response to emotional distraction. Cogn. Affect. Behav. Neurosci. **6:** 62–70.
67. CORRELL, C.M., J.A. ROSENKRANZ & A.A. GRACE 2005. Chronic cold stress alters prefrontal cortical modulation of amygdala neuronal activity in rats. Biol. Psychiatry **58:** 382–391.
68. LISTON, C., M.M. MILLER, D.S. GOLDWATER, *et al.* 2006. Stress-induced alterations in prefrontal cortical dendritic morphology predict selective impairments in perceptual attentional set-shifting. J. Neurosci. **26:** 7870–7874.
69. FRANCIS, D.D., C. CALDJI, F. CHAMPAGNE, *et al.* 1999. The role of corticotropin-releasing factor–norepinephrine systems in mediating the effects of early experience on the development of behavioral and endocrine responses to stress. Biol. Psychiatry **46:** 1153–1166.
70. SOUTHWICK, S.M., J.D. BREMNER, A. RASMUSSON, *et al.* 1999. Role of norepinephrine in the pathophysiology and treatment of posttraumatic stress disorer. Biol. Psychiatry **46:** 1192–1204.
71. TRUE, W.R., J. RICE, S.A. EISEN, *et al.* 1993. A twin study of genetic and environmental contributions to liability for posttraumatic stress symptoms. Arch. Gen. Psychiatry **50:** 257–264.
72. STEIN, M.B., K.L. JANG, S. TAYLOR, *et al.* 2002. Genetic and environmental influences on trauma exposure and posttraumatic stress disorder symptoms: a twin study. Am. J. Psychiatry **159:** 1675–1681.
73. HOLMES, A., P. VUILLEUMIER & M. EIMER. 2003. The processing of emotional facial expression is gated by spatial attention: evidence from event-related brain potentials. Cogn. Brain Res. **16:** 174–184.
74. EIMER, M. & A. HOLMES. 2007. Event-related brain potential correlates of emotional face processing. Neuropsychologia **45:** 15–31.
75. KROLAK-SALMON, P., M.A. HENAFF, A. VIGHETTO, *et al.* 2004. Early amygdala reaction to fear spreading in occipital, temporal, and frontal cortex: a depth electrode ERP study in human. Neuron **42**, 665–676.
76. BISHOP, S.J. 2007. Neurocognitive mechanisms of anxiety: an integrative account. Trends Cogn. Sci. **11:** 307–316.