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Attention biases, anxiety, and development: Toward or away from threats or rewards?

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Abstract

Research on attention provides a promising framework for studying anxiety pathophysiology and treatment. The study of attention biases appears particularly pertinent to developmental research, as attention affects learning and has down-stream effects on behavior. This review summarizes recent findings about attention orienting in anxiety, drawing on findings in recent developmental psychopathology and affective neuroscience research. These findings generate specific insights about both development and therapeutics. The review goes beyond a traditional focus on biased processing of threats and considers biased processing of rewards. Building on this work, we then turn to treatment of pediatric anxiety, where manipulation of attention to threat and/or reward may serve a therapeutic role as a component of Attention Bias Modification Therapy.

INTRODUCTION

Anxiety disorders represent a family of conditions that share symptoms and evolve in a developmental context. Both normal and abnormal variations in childhood anxiety predict risk for diverse types of adult anxiety [1-2]. Developmental relationships between normal and pathological anxiety may be explained by perturbations in neurocognitive factors such as attention. Recent animal models and human brain imaging research charts neurocognitive factors that undergird these developmental relationships. Therefore, a focus on neuro-cognition using cross-species approaches informs understandings of pathophysiology of anxiety disorders.

In particular, research on attention provides a promising avenue for understanding cognition in the anxiety disorders. “Attention” refers to a suite of cognitive functions that allows the brain to prioritize particular stimuli for dedicated processing. The need for such prioritizing arises because cognitive resources are limited in capacity. Since a rapid response to threats facilitates survival, threats are prioritized stimuli for various mammals, including rodents, monkeys, and humans [3]. As a result, threat-attention interactions in animal models and in humans can be studied using parallel approaches. The term “orienting” refers to one particular aspect of attention, whereupon stimuli in the environment show strong capacities for garnering the brain’s limited cognitive resources. The observation of biased attention orienting to threats represents one of the best-replicated findings in research on anxiety

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disorders [4-5]. Because similar attention biases occur in different anxiety disorders, research on attention biases provides insights into the neurocognitive factors shared across these conditions. Accordingly, this review summarizes attention-orienting findings generally occurring in anxiety, but it does not discuss disorder-specificity or findings in specific anxiety states. The review adopts a particular narrow perspective, focusing specifically on orienting and one particular task used to assess it. Such a narrow focus has the advantage of facilitating deep levels of inquiry, across humans and animals of various developmental stages. However, such a narrow focus carries disadvantages, in that it does not consider research on other aspects of attention and orienting.

The study of attention biases is particularly relevant for developmental research. From a narrow perspective, attention gates the engagement of many other cognitive processes, particularly memory and other forms of learning. For example, mammals tend to learn most about those aspects of the environment to which they attend. For immature, and naive organisms, consistent pattern of input, biased by attention, may have particularly large effects on current and future behavior. From a broader perspective, attention casts a long shadow on behavioral trajectories. Learning vitally shapes development, and children show unusual capacities to learn, as reflected in the unique plasticity of the immature brain. By recurrently gating learning over time, attention shapes development. Conversely, learning also influences attention during development, as the child's experiences influence the things to which they attend. Since learning is particularly important for children, attention can be expected to exert strong effects on development, guiding the ontogeny of normative and pathological development.

The current review summarizes recent findings on the relationship between attention and anxiety. As noted above, this paper extends previous reviews by focusing relatively deeply and narrowly on attention orienting in anxiety disorders. This review unfolds in three stages. The first section summarizes findings on biased orienting to threat, an area with considerable data. As a result, this first section provides the most in-depth coverage, focusing on developmental perspectives. Next, the second section summarizes comparable findings on biased reward processing. Since less research examines reward- than threat-related attention biases, the second section provides a briefer review. In particular, the section places research on attention within the broader context of work linking anxiety to perturbed reward processing. The final section focuses on novel interventions that arise from work on attention orienting to threats and rewards. This involves studies of attention retraining, where minimal research exists. Accordingly, the final section provides a brief summary, illustrating how research on both threat and reward-related biases in attention orienting generate insights for therapeutics.

BIASES TO THREAT

Early in the 20th Century, psychologists recognized threats' unique capacity to capture attention. Beginning in the 1980's, LeDoux and colleagues were among the first to describe the neural circuitry mediating this effect, initially focusing on orienting to auditory threats in rodents. More recently, other investigators, examining the non-human primate, extended this work to the visual system [6-7]. Taken together, studies in rodents and non-human primates have identified three core components of threat orienting. The first involves a rapidly-evolving response that encodes relatively crude details concerning the nature of a threat. This early response primarily involves the amygdala, which rapidly engages other cognitive processes that contribute to the second component of orienting. This second set of processes, which evolve more slowly and codify more detailed aspects of a threat, are mediated by cortical regions engaged by the relevant sensory modality. Finally, while these first two components mediate feature representation for threats, the final component mediates the

behavioral response. This final component involves engagement of motor schemas and emotional response patterns in the prefrontal cortex (PFC). When threats signal the need to re-orient attention, these schemes draw heavily on processes regulated by a ventral-lateral expanse of the PFC [2].

This research in animal models carries two sets of implications for research in humans. First, the work illustrates the complex chronometry of threat-attention interactions. The mammalian response to threats evolves in a finely-tuned, orchestrated fashion. Thus, relatively subtle changes in the timing of threat exposures are expected to impact the nature of threat-attention interactions. Parenthetically, the finely-tuned nature of this response emphasizes the importance of focusing relatively narrowly and deeply on a few specific aspects of orienting, as might be probed by one particular set of cognitive tasks. Second, orienting behavior, per se, as opposed to the neural processes that support it, only indexes the end-stage output of a highly complex neural cascade. As a result, it should be possible to use brain imaging to dissociate anxiety-related associations with behavior, which is the culmination of multiple neural processes, from anxiety-related associations with the individual stages of neural responding, which ultimately coalesce to produce this behavior.

Importantly, in considering findings from such brain imaging research on orienting, one might expect discordance between findings for behavioral measures and those of brain function. This might reflect differential sensitivity of behavioral and imaging techniques to between-group differences. Such differential sensitivity results from the fact that behavioral output on an orienting task only indexes the end-stage result of many, interacting complex neural events. Brain-function measures from imaging, by utilizing particular experimental design or techniques, in contrast, might index each of these many processes, as they are engaged throughout the entire series that ultimately manifests as orienting behavior. This raises questions on concordance and discordance in behavioral and brain-imaging measures of orienting, as discussed below.

Cross Sectional Associations

Considerable research links individual differences in anxiety to excessive vigilance toward minor threats. Excessive vigilance manifests as an enhanced attention-orienting response towards threats in standard attention-capture paradigms. As reviewed by Bar-Haim et al., (2007), research on threat-related attention orienting in anxiety generates relatively strong and consistent findings in various forms of anxiety [4]. In recent years, work in this area uses an experimental approach. By showing that experimentally-induced changes in attention orienting lead to changes in anxiety, such work implicates abnormal attention orienting in the etiology and maintenance of anxiety [4; 5{MacLeod, 2002 #1189; 8]}. A consensus view has emerged from this work: the attention system of anxious people, from an early age onward, is distinctively sensitive to threats. Of note, while this work generally finds anxiety-related attention bias toward threats [4; 8], in some scenarios, enhanced threat sensitivity can manifest as bias away from threats [9-10]. Such findings complicate attempts to develop novel treatments that target biased attention orienting.

While aspects of attention in anxiety disorders have been assessed with many paradigms, the emotional Stroop and the dot-probe task are the two most commonly employed paradigms for assessing threat-related attentional biases in childhood anxiety [11]. The few studies utilizing both measures generally find no correlation between estimates of threat bias that emerge from the two tasks, suggesting that they index different aspects of attention [12]. Performance on the emotional Stroop task is thought to reflect not only attentional orienting but also attempts to simultaneously suppress aspects of threat processing [13], whereas the dot-probe does not engage such additional processes. As a result, the dot-probe task is seen as a more direct indicator of orienting. In addition, most of the recent treatment studies

focusing on the re-training of attention rely on the dot-probe paradigm. Given that the current review focuses, in part, on treatment, it will focus exclusively on attentional biases measured with the dot-probe task.

In each trial of the dot-probe task [14], one threat and one neutral cue appear simultaneously in opposite hemi-fields (see Figure 1). Their disappearance is followed by a probe that appears in the location previously occupied by one of the cues. Participants are required to respond as quickly as possible to the probe without compromising accuracy. A faster reaction time to probes appearing in the location previously occupied by threat-related stimuli than probes appearing behind neutral stimuli indicates an attentional bias *toward* threat. A faster response to probes appearing in the location previously occupied by the neutral stimulus compared to probes appearing behind the threat-related stimuli indicates an attentional bias *away* from threat. Thus, a consistent difference in reaction time to probes in the two locations reflects the down-stream effects of biased orienting of attention.

Various evocative stimuli have been used as attention-orienting cues in the dot-probe task. Age-related differences in reading and verbal skill could impact the capacity of word-based orienting cues to capture attention. Accordingly, recent studies in children rely more on pictures than words as negative-valence cues. The most extensively-used design employs evocative faces as high-valence cues, capitalizing on the intrinsic capacity for faces to convey emotion. The use of high-negative (e.g. angry) and low valence (e.g. neutral) faces of the same actor also provides two stimuli matched on multiple perceptual features that differ only on emotional valence. Most studies reviewed in this section employ the dot-probe task with angry faces as threat cues, contrasted with low-valence neutral-face cues.

Many studies involving thousands of subjects use this and other varieties of dot-probe paradigm to quantify attention biases. While the observation of anxiety-related biases is consistent, manifesting with a medium effect size (Cohen's $d = 0.45$), some subtle variation exists in the nature of these associations across situations and across iterations of the dot-probe task [4]. When threat/neutral-stimulus pairs, in the dot-probe task, are presented for 500ms, anxious adults show a bias toward threat with some consistency, whereas healthy adults show no bias either towards or away from threat. However, when the duration of stimulus-cue exposures differ from 500ms, varying from 100 to 1500ms, findings are less consistent. Some data suggest that anxious adults may only show a bias toward threat when stimuli are presented for 500ms or less, and that this bias may disappear when the duration is greater than 1000ms [15]. This variation might be expected, given the above-noted work in neuroscience examining the chronometry of neural responding in animal models during threat-attention interactions. Specifically, based on the finely-timed nature of neural responding in research with animals, the anxiety-attention association would be expected to also vary with relatively subtle variations in the timing of threat exposures.

Variation in attention-biases results across studies using different threat-exposure durations has motivated researchers to generate alternative conceptual models of the anxiety-attention bias associations. These models consider numerous factors that might influence both the direction and intensity of threat bias. One such notable example is a two-stage model characterizing attention bias in anxiety as involving vigilance-avoidance patterns of attention allocation [16]. According to this model, anxious people will be fast in orienting their attention to a threat and soon after will shift their attention away from it. This model suggests that the direction of the attention bias will change during information processing from threat vigilance to threat avoidance. Thus, longer durations of stimuli presentation may capture both these processes; while shorter duration may limit the assessment to vigilance.

Findings in children and adolescents replicate those in adults. At 500ms threat-exposure duration, data in anxious children resemble those in anxious adults. In addition, unlike anxious individuals, healthy children and adolescents, much like healthy adults, typically do not show a bias toward or away from threat when stimuli are presented for 500ms. Across at least six studies, children and adolescents with anxiety disorders show a larger bias toward threat than do healthy children and adolescents [17-22].

Finally, not all studies find heightened vigilance towards threat in anxious children. For example, much as in anxious adults, some data find signs of threat avoidance in pediatric anxiety. That is, anxious children and adolescents, unlike healthy children and adolescents, can show biases away from threat in some scenarios. Specifically, three studies report greater tendencies to avoid threats in anxious than healthy children and adolescents [23-25]. A fourth study found that children with severe social phobia exhibit a bias towards threat, whereas children with mild social phobia exhibit a bias away from threat, while healthy children showed no bias [26]. Similarly, other cross-sectional data suggest that anxiety-related attention biases evolve during development. Specifically, Kindt et al. (2003) suggest that an attention bias towards threat represents a general characteristic of children, whether or not they are anxious. Healthy children might develop to overcome this bias as they age. From this perspective, findings in anxious adolescents and adults would reflect their failure to overcome their childhood tendency to attend to threat [27].

Despite some variability in cross-sectional research, the weight of the evidence actually suggests that both anxious children and adults, unlike their healthy peers, exhibit a bias toward threat [28-31]. Only occasionally do studies find evidence supporting a bias away from threat in anxious people or a bias towards threat in healthy people. Most studies finding such biases away have been performed in unique circumstances, such as life threatening contexts [9], military-training scenarios [10], or stressful experimental contexts [23]. Moreover, the similarities are greater than the differences when comparing findings in cross-sectional studies on anxiety-related orienting biases to threats in children, adolescents, and adults.

Development

Clearly, cross-sectional studies provide limited evidence of age specificity in the attention-anxiety relationship. However, some evidence of age-specificity emerges from longitudinal work. Longitudinal work on threat orienting parallels two broad trends in developmental research on cognition [32]. First, if attention gates the child's ability to learn, one might expect longitudinal work to show that attention shapes the trajectory of anxious behavior. Second, recent research demonstrates marked plasticity in attention; therefore, anxious behavior in early development might show different relationships with attention, measured concurrently, as opposed to later in development.

Research on temperament provides a unique window on development. Children at risk for later anxiety can be identified early in life, providing the opportunity to chart development in the anxiety-attention relationship and, in some individuals, the emergence of an anxiety disorder (for review see [33]). Some infants react with distress when confronting novelty and then, as toddlers, show excessive fear in novel social situations. Thus, anxiety can show a changing ontogeny, first manifesting as distress to general novelty before becoming specific mainly towards social novelty. Children showing this pattern are labeled as having a behaviorally-inhibited temperament. This temperament is moderately stable and predicts a two-to-four fold increased risk for anxiety disorders in adolescents, with particularly strong associations with social phobia [34-35]. As demonstrated by the studies reviewed below, individual differences in orienting, particularly to threat, might moderate the link between early temperament and later anxiety.

Development complicates work on the anxiety-attention interface. Age-related changes necessitate the use of different attention-orienting measures at different stages of development. Paradigms must be adapted to assess orienting in infants incapable of performing the dot-probe task. For example, Perez-Edgar et al., (2010) tested orienting in nine-month-old infants using a simple, high-contrast schematic figure as a novel distracter. This distracter appeared suddenly in the periphery, while the infant's attention was engaged centrally by an enjoyable video, projected directly within the focus of attention. Eye movements away from the video, and thereby towards the distracters, were used to index orienting. Both in this task and in the dot-probe task, the child's attention is engaged centrally by a non-frightening scenario. In infants, attention is engaged by an enticing video. In the dot-probe task, attention is engaged by a simple motor task. Similarly, both in the infant task and the dot-probe task, attention orienting to a cue is quantified. In infants, orienting to schematic figures is monitored, whereas in the dot-probe task, orienting to emotional faces is monitored. Nevertheless, in both paradigms, capture of attention is analogously assessed, based on the tendency for these peripherally-appearing schematic or emotional-face cues to interfere with video-viewing for the infant and motor responding for the child. As such, both tasks can be used with children of different ages to test the hypothesis that individual differences in attention orienting moderate the stability of anxiety.

Three studies examine longitudinal associations between perturbations in orienting and anxious behavior. The first assesses attention orienting in infants and then charts the stability of anxious behavior into adolescence. Infants who orient towards distracters manifest more stable, socially-anxious behavior through childhood than infants who ignore the distracters [36]. The second study assesses attention orienting in pre-schoolers using the dot-probe task, again charting the stability of anxious behavior over time. Here, much like infants who orient towards distracters, behaviorally inhibited preschoolers who orient towards threats on the dot-probe task show more stable forms of social withdrawal than behaviorally inhibited preschoolers who do not orient towards threats [37]. The third study extends data on early anxiety and the dot-probe task to adolescents. This study again finds that early-childhood behavioral inhibition predicts stable socially withdrawn behavior only when coupled with threat orienting on the dot-probe task [28]. Thus, across three studies, attention orienting differentiates forms of early-childhood behavioral inhibition that most strongly predict social withdrawal, which is associated with social anxiety.

Consistent with developmental perspectives on the attention-anxiety interaction, other data suggest that the relationship between temperament and attention changes as children mature. Before school age, behavioral inhibition and orienting do not correlate. As noted above, two studies assess attention orienting using a novelty-orienting task with infants and a the dot-probe task with pre-schoolers While both find that orienting modulates the association between behavioral inhibition and anxiety, neither finds direct relationships between behavioral inhibition and attention. On the other hand, early inhibition does predict threat orienting in adolescence [28]. Thus, age-specificity may manifest in anxiety-attention associations.

In summary, cross-sectional data provide minimal evidence of developmental variation in the anxiety-attention relationship. Nevertheless, the only available longitudinal studies in this area find evidence of two developmental trends: a) attention orienting shapes the trajectory of anxious behavior; b) anxious behavior in childhood shows different relationships with attention orienting in childhood as opposed to in adolescence. Since experimental work directly links changes in attention to changes in anxiety [8], future developmentally-focused experimental work might extend these longitudinal observations on the attention-anxiety relationships through other experimental-therapeutic research attempting to attenuate risk for an anxiety disorder.

Brain and Behavior

Brain imaging can probe neural mechanisms that contribute to orienting behavior. Activation of some brain regions reflects engagement of processes that support attention biases, resulting in positive correlations with levels of anxiety symptoms. Activation in other regions, in contrast, reflects engagement of compensatory processes, resulting in negative correlations with anxiety symptoms. Hence, attention orienting behavior is merely the late-stage, down-stream, behavioral output of a multifaceted, precisely-orchestrated interaction among neural components of a circuit.

Considering the circuit that supports orienting, preliminary findings in functional magnetic resonance imaging (fMRI) and other imaging studies extend research in rodents and non-human primates on the chronometry of circuitry engagement during threat orienting. Across species, research implicates the amygdala and the ventral lateral prefrontal cortex (vlPFC) in threat-orienting. Moreover, brain-imaging data suggest that the chronometry of circuitry function in humans resembles that in rodents and non-human primates.

Monk et al. (2008) used short-duration threats (17ms) in the dot-probe task. Such stimuli were shown to preferentially activate the amygdala in anxious compared with non-anxious youth, suggesting that group differences in orienting to threats can be detected relatively early, immediately following exposure to a threat. Interestingly, orienting behaviors assessed in this study did not differ between anxious and healthy adolescents [38]. In a different fMRI study, Monk et al. (2006) used longer-duration (500ms) threats. Since the amygdala habituates to threat, 500msec threat was expected to engage different components of threat-orienting circuitry. Consistent with this possibility, this study found no between-group differences in amygdala activity but higher vlPFC activation in anxious compared to healthy adolescents, as well as a negative correlation between vlPFC engagement and anxiety [23]. Taken together, when considering the chronometry of circuitry engagement, the two studies dissociate amygdala and vlPFC contributions to orienting. Early amygdala activation reflects engagement of processes that might support biased orienting of attention in anxiety, whereas later vlPFC activation reflects engagement of compensatory processes that regulate attention and its association with anxiety.

An additional fMRI study charts changes in threat orienting following treatment. Specifically, the study maps associations among anxiety, threat orienting, and amygdala-vlPFC circuitry function before and after treatment with cognitive behavioral therapy (CBT) and selective serotonin re-uptake inhibitor (SSRI) [39]. The study again found that neural circuitry engagement was more sensitive than behavior to between-group differences in orienting: treatment-related changes only occurred in brain function but not in behavioral measures of orienting. Moreover, the study also provided further evidence on dissociable roles of the amygdala and vlPFC in anxiety-related orienting biases. As in cross-sectional data, the vlPFC and amygdala once again exhibited unique associations with anxiety. Treatment produced greater increases in vlPFC activation among successfully treated patients than in healthy comparison children. This provides further evidence that vlPFC activation may indeed reflect engagement of compensatory processes that regulate attention and associated anxiety.

Without question, behavioral data on attention orienting demonstrate important developmental relationships. Nevertheless, work on the neuroscience of attention demonstrates discordance between brain function and behavior: the same behavioral output can arise from different forms of neural function. As noted above, measures of orienting behavior, such as reaction times or eye movements, only index the end-stage output of a complex neural cascade, whereas measures of brain function can assess the engagement of processes from the initiation through the end of an orienting event. Thus, neural engagement

earlier in this cascade, as it relates to underlying initial attention capture, can be dissociated from neural engagement later in the cascade, as it underlies the orienting response and its manifestation in behavior. As such, data on behavior provide relatively limited insights on underlying mechanisms, whereas neuroimaging data has the advantage of studying specific brain activities along the cascade of the cognitive process. This suggests that imaging data may be more sensitive to the multiple functional processes involved, relative to behavioral data.

In some contexts, both healthy and anxious children might manifest similar-appearing orienting behavior. However, such similar appearing behavior in healthy and anxious children could reflect distinct neural processes. In this context, similar-appearing behaviors could reflect either adaptive responses, associated with positive, healthy outcomes, or maladaptive responses, associated with neural dysfunction that places children at risk for poor long-term outcome. To evaluate the capacity for neural function to predict outcome, current brain imaging methods can quantify neural-system engagement among healthy and anxious children, in the service of similar appearing orienting behaviors. Of note, the presence of similar behavior among healthy and anxious children in the context of differing neural response patterns should not be construed to indicate that behavior is irrelevant for research on brain function. This is because disorder-related perturbations in brain function are charted in the particular context of threat orienting, a context where other research does link orienting behavior to anxiety.

Rapid advances in brain imaging technology have affected dramatically perspectives on psychological research. For example, whether reliable and informative neural differences can be detected or interpreted, independent of behavioral differences, is now a question. Clearly, basic science work discussed above on the discordance between orienting behavior and its underlying circuitry in rodents and non-human primates demonstrates that behavior and brain function readily can be dissociated. However, questions arise concerning the sensitivity of brain imaging measures to such discordance as it relates to individual differences. Thus, with the current state of imaging technology, debate surrounds the question about the sensitivity as well as the interpretation of brain-based relative to behavioral markers of individual differences, such as those related to anxiety disorders. Based on this debate, different investigators see advantages and disadvantages to imaging paradigms that do or do not elicit between-group differences in behavior, in the context of between-group differences in brain function.

On the one hand, ultimately, many functional imaging studies hope to identify the underlying neural architecture of behaviors that vary between anxious and healthy populations. Thus, for studies of attention orienting, imaging studies seek the neural concomitants of enhanced threat bias in patients. From this perspective, an imaging study on anxiety disorders that fails to detect these behavioral differences in orienting is open to criticism. This is because an imaging study not detecting behavioral differences could not map the neural architecture of enhanced threat bias in a group of patients where the expected behavioral difference manifests. This perspective suggests the importance of imaging studies where both behavioral differences and their associated perturbations in the brain can be mapped (Carter et al. 2008).

On the other hand, the absence of behavioral differences in an imaging study finding between-group differences in brain function can also be seen as desirable. Such findings indicate that the observed neural differences do not reflect an artifact of behavioral differences or so-called “performance confounds”. Thus, performance differences also complicate interpretations, since they may reflect factors such as task-difficulty discrepancies between populations. For imaging studies focused specifically on orienting,

studies in rodents and non-human primates reviewed above show that behavioral performance only represents a final output of a complex neural cascade. Because this output can arise from multiple neural events, behavioral measures of orienting are insensitive to some component cognitive processes that are abnormal in patients. In contrast, neural circuitry methods permit the study of rapid, and differing cognitive systems that may reveal important differences between patients and controls and between different patient groups.

Further discussion of this complex and intriguing issue is beyond the scope of this paper. Nevertheless, the narrow focus on orienting behavior and its neural correlates provides an intriguing glimpse into the complementary nature of behavioral and brain-imaging data. Thus, the increasing use of imaging technology in attention research is expected to generate further examples of brain-behavior discrepancies, which are likely to become increasingly scientifically relevant (for further discussion see [40]).

Taken together, research on behavioral and neural correlates of threat orienting extends findings in other areas of clinical neuroscience, suggesting that aberrant orienting behavior only weakly and indirectly indexes underlying neural processes that are more sensitively quantified with fMRI. This specifically mirrors data on neurological illnesses such as Parkinson and Alzheimer diseases [41-42]. While orienting behavior is expected to relate to anxiety less sensitively than measures of basal ganglia or hippocampal function relate to Parinson or Alzheimer diseases, orienting behavior still may generate markers of risk for persistent anxiety, analogous to the the way that early decrements in motor skill and memory performance more potently indiex risk for Parkinson and Alzheimer diseases. As with research on brain imaging more generally, this again does not suggest that behavior is irrelevant, only that it indirectly indexes illness. Current research on these conditions has begun to use brain imaging to identify early targets for novel treatments that might be directed at underlying neural dysfunction, before the appearance of symptoms. Research on the threat-attention interactions similarly might generate biological indicators that inform research on risk prediction and therapeutics.

Finally, the current review focuses specifically on threat-orienting in anxiety. However, anxiety disorders frequently present concurrently with other conditions, particularly major depressive disorder (MDD). The degree to which MDD and anxiety disorders represent discrete conditions with unique neurocognitive correlatesremains unclear, particularly among children and adolescents where the two groups of disorders co-occur both concurrently and over time [43]. Considerable work in children, adolescents, and adults maps the commonalities and specificities in cognitive correlates of these disorders. This includes considerable work on threat orienting. Some behavioural data find that perturbed attention orienting to threats arises specifically in anxiety disorders but not in MDD [12; 44-45]. Moreover, findings suggest that attention biases in comorbid anxiety-depression cases appear similar to those in non-comorbid depression, both of which differ from attention biases in non-comorbid anxiety (Dalgleish 2003). However, other findings suggest that biases appear similar in comorbid and non-comorbid anxiety cases (Monk et al. 2006). Imaging data yield similar inconsistencies. Some studies have demonstrated distinct neural correlates in anxious compared to depressed adolescents [43; 46-47], while other studies have shown similar brain activation among these two groups [23; 38]. This controversy is likely to still be under scrutiny in the years to come.

BIASES TO REWARD

While more neuroscience research has examined interactions of attention with threat than with reward, recent data generate interest in the latter. Rewards are positive stimuli that reinforce behaviours and motivate the organism to approach. In addition, stimulus salience

is amplified through pairing with rewards. Interest in contrasting reward-modulated and threat-modulated behaviour arises both from clinical data linking anxiety and depression as well as from basic science data on the commonalities and differences in the neural circuitry engaged by rewards and threats. Fundamentally, differences in engaged neural architecture can be expected based on the unique behaviours elicited by rewards and threats. In the case of reward, the typical behavioural response is “approach”, and in the case of threat, the response is “avoidance”. However, in both cases, the relevant cues acquire heightened salience, as reflected in attention capture, which can be measured using a dot-probe-task approach. Thus, diverse stimuli are rewarding in that they elicit approach. These stimuli include happy faces, which are commonly used to punctuate success in games and which elicit approach in social encounters. Happy faces also have been used in the dot-probe task. In this context, one might expect to see some form of bias, reflecting greater attention directed to the happy faces than the neutral faces.

Unlike amygdala-based work on threat, work on reward focuses on fronto-striatal circuitry. This circuitry is central to the processing of motivation, which is reflected in the direction and intensity of behaviour [48]. Thus, engagement of the fronto-striatal circuit regulates reward modulation of behaviour at least partially through the coding of salience [49], in the service of stimulus-response learning [50]. Indeed, when organisms attend to one set of cues and ignore others, they form stronger and more sustainable associations between the attended cues and associated reinforcements, relative to the ignored cues. Given that attention influences stimulus-response learning, this work generates interest in reward-attention interactions.

Such interest also follows from a select set of reward-imaging studies in pediatric anxiety. FMRI studies involving monetary incentive tasks find enhanced striatal responding in pediatric anxiety [51-52] and behavioral inhibition [53-54]. Specifically, anxiety is associated with striatal hyper-activation on a select set of trials in fMRI experiments. In these experiments, anxiety-related hyper-activation only occurs on the trials when reward is contingent on subjects’ performance. In contrast, the trials when rewards are delivered regardless of the subject’s behaviour are not associated with such hyper-activation in anxious participants. This suggests that behavioral characteristics, such as self-agency, constrain group differences in brain activation to incentives.

Other types of rewards, such as food [55-56], odor [57], or pleasant faces [58] have been used in fMRI studies. Tasks using happy faces have been employed in comparisons of children and adolescents classified based on various features, including the presence of an anxiety disorder [59-60], behavioral inhibition [61], measures of familial risk [62], and developmental level or gender [63]. These studies document consistent striatal engagement to happy faces in adolescents but no consistent anxiety-related group differences. Nevertheless, as with many tasks, findings markedly vary based on the particular features of the task [64].

In summary, findings of striatal responses in anxious individuals vary across fMRI paradigms. Work on the circuitry of reward-related orienting biases could extend relevant behavioral data on anxiety-related differences in orienting to rewards. Hence, before focusing on brain imagining data per se, the next section reviews available behavioral data.

Cross Sectional Associations

Relevant behavioral data concerning attention bias towards reward do exist. As with threats, the dot-probe task generates measures of reward bias. Much as angry faces can be used in the dot-probe task to index threat bias, happy faces can be used to index reward bias. In this case, each dot-probe trial is comprised of a happy face and a neutral face, followed by a

reaction-time probe. Faster response to probes in the location previously occupied by the happy face indicates bias towards reward.

Recent studies use this approach to examine orienting to positive stimuli in adults. The pattern of attention orienting to positive stimuli is different than to threats. For threats, only anxious but not healthy adults show threat bias. For positive stimuli, reward-related biases seen in healthy adults are attenuated in anxiety (for a review and meta-analysis see [15]).

Findings in children and adolescents are less consistent than in adults, as summarized in Table 1. Some studies report no bias to happy faces in either healthy or anxious children and adolescents [23-24; 26; 31; 39; 65]. Others find a bias toward happy faces in anxious but not healthy children [66], and still others find a bias towards happy faces in both anxious and non-anxious children [67]. Based on the scarcity of the data, it is difficult to understand reasons for these discrepancies. However, if the data do indeed reflect real age differences in orienting behavior, with older people exhibiting a stronger bias to positive valance stimuli than do children, the data might suggest that development involves changes in reward-attention interactions.

Development

As with threat bias, orienting towards rewards might moderate relations between early temperament and later anxiety. In one recent study, early inhibition does not predict orienting to happy faces in preschool-age children (Perez Edgar, et al., 2011). However, in another study [28], early behavioral inhibition predicts reduced bias towards happy faces in adolescence, consistent with the pattern found in research on adult anxiety. Of note, however, in this second study, Perez-Edgar et al. (2010) also report that threat bias but not happy bias moderates relations between early inhibition and later social-withdrawn behavior.

Since more dot-probe studies focus on psychopathology than on temperament, it is important to consider if happy bias moderates the relationship between early temperament and clinical indices of social anxiety symptoms in adolescents. Published data present associations that classify adolescents based on measures closely tied to adolescent temperament (Perez-Edgar et al. (2010). Figure 2 displays unpublished data in the same subjects described in Perez-Edgar et al. (2010). However, unlike the published data, this analysis classifies subjects as either high or low anxious based on their scores on a clinical self-report measure of social anxiety symptoms, the Social Anxiety Scale (SAS) and the presence or absence of early childhood behavioral inhibition (a 2X2 cross-classification based on early inhibited behavior and later adolescent clinical social anxiety).

The findings suggest that three groups show clear evidence of happy bias, consistent with data in healthy adults. However, only the fourth group, characterized by both high levels of childhood behavioral inhibition and high ongoing adolescent social anxiety symptoms, fails to exhibit happy bias. The data from this group are consistent with data in anxious adults and at least one study in anxious children [26].

Brain and Behavior

fMRI data on reward-related striatal hyper-sensitivity in anxiety, together with behavioral data in dot-probe studies, raise questions on associations between anxiety and striatal response on the dot-probe task. Behavioral findings in dot-probe studies appear relatively consistent in adults. This contrasts with research in children, where inconsistent findings emerge, and this in turn suggests that developmental variation exist in reward orienting. Consistent with this possibility, in one of the few studies to directly compare orienting in adolescents and adults, Lindstrom et al. (2009) find that happy faces, viewed in the context

of an fMRI-based dot-probe task, produce larger reaction-time bias in healthy adults than healthy adolescents [68]. Unlike the behavior, larger striatal responses were found in adolescents than adults. As with work on threat biases, these imaging data reveal discrepancies between behavioral and fMRI data.

Finally, preliminary data find no association between pediatric anxiety and striatal response to happy-face events in the dot-probe task. Monk et al. (2006; 2008) include happy-face events in the two previously-discussed fMRI studies on pediatric anxiety where threat-related perturbations manifest in amygdala-vlPFC circuitry. Striatal responses to happy faces do not differ between healthy and anxious adolescents in either study. Nevertheless, based on Figure 2, perturbed striatal responding might be expected only in the sub-group of anxious adolescents who had also manifested behavioral inhibition during early childhood. Prospective imaging studies are needed to evaluate critically this possibility.

ATTENTION TRAINING

If biased orienting maintains anxiety, treatments that alter attention orienting should alleviate anxiety. For example, patients can be told how to orient their attention to minimize their anxiety. Indeed, such procedures are a component of cognitive behavioral therapy (CBT), where a therapist might teach a socially-anxious patient to avoid focusing on frowning audience members while delivering a speech. However, research on the neural correlates of attention suggests that this approach has limitations. Orienting has a precise, rapidly-evolving chronometry, and imaging studies find that anxiety-related orienting biases involve dysfunction in early stages of the complex, precisely-timed orienting cascade. Because patients are unaware of this attention bias, therapists cannot easily tell them how to change it.

Research in various areas of neuroscience suggests that these biases can be alleviated by implicit training procedures. In such procedures, patients are not explicitly told how to change their behavior. Rather, they are exposed repetitively to experiences that gradually shape their behavior, even as they remain unaware of how their behavior is changing. This form of implicit learning is similar to the learning that occurs with various motor routines, such as when people learn through repetition how to automatically manipulate the steering wheel while driving home each evening.

The purpose of Attention Bias Modification Therapy (ABMT) is to implicitly shape anxiety-related biases in attention orienting. ABMT uses the dot-probe task as a therapeutic tool. During training, the target location is systematically manipulated to increase the proportion of targets appearing at the location opposite the patient's bias. For example, in a training protocol intended to reduce threat bias, targets would appear more frequently at locations of neutral than threat stimuli. Attending to such contingencies affects task performance over time, producing an implicitly learned bias away from threat (for detailed review see [69]).

Threat Attention Training

The effect of ABMT on anxiety is summarized in a recent meta-analysis of 12 studies using ABMT with the dot-probe task to train participants to focus their attention away from negative-valence stimuli [8]. The studies in the meta-analysis include three studies examining patients with anxiety disorders and nine studies examining non-patient groups, including seven in groups selected for high scores on anxiety-rating scales. The meta-analysis reports a moderate effect, $d = 0.61$, suggesting that training to orient away from threat reduces anxiety more than control training. Of note, while the meta-analysis only includes data in adults, data on temperament suggest that attention biases might powerfully influence anxiety over time in developing children. One recent study preliminarily suggests

that ABMT reduce pediatric anxiety, though the study used the Posner attention task and not the dot-probe task which is typically used in ABMT procedures [70].

One major question arising from this work concerns the nature of attention training that might maximize clinical effects in anxious children. Many individuals with anxiety do show a bias toward the threat, but others show a bias way from the threat, at least in some contexts, and still others show no bias at all. It remains unclear the degree to which groups with varying levels of threat bias all should receive similar training. Should training always teach patients to shift their attention away from threats? Such questions appear particularly important in light of data suggesting that avoidance on the dot-probe task predicts poor outcome in some groups of anxious adults [9-10; 71]. These data raise concerns about exacerbating anxiety by training patients to avoid threat, if they do not have a pre-treatment bias towards threat. Such concerns might be particularly heightened in children, considering their vulnerable state, coupled with the noted effect of attention on the development of anxiety in children with behavioral inhibition.

In light of these concerns, two options for ABMT threat-based studies might seem most reasonable for research in anxious children. In the first approach all anxious children could be assessed for their pre-treatment bias, and only those with a pre-existing bias towards threat might receive ABMT training designed to train patients to avoid threat. Nevertheless, this approach limits the applicability of ABMT: only anxious children who exhibit attention biases to threats would be eligible for ABMT. A second option would be to tailor treatment based on the pre-existing nature of the child's bias, training some children to attend to threat and training others to avoid it. The problem with this approach is that heterogeneity in the response to treatment could be attributed either to pre-existing group differences in attention bias or to between-group differences in the nature of training, the two of which would be nested.

Yet a third alternative would be to consider how to combine ABMT with other, known, efficacious treatments. The therapeutic effects of exposure therapy have been confirmed by numerous studies (for review see [72]). These studies have shown that repeated exposure to fear provoking threats, in the absence of negative consequences, results in new associations that weaken the stimuli's fear-eliciting capacity. Consequently, a major therapeutic goal in CBT is decreasing patients' avoidance from such stimuli. From this stand point, it might be mistakenly argued that attention training away from fear eliciting stimuli contradicts this rudimentary principle. However, if attention gates the ability to learn, then shifting attention away from this stimuli would result in either (a) an increase in the processing of other relevant information or (b) alterations in threat perception [73]. In either instance, this could result in stronger and more resistant extinction learning. And indeed some data suggest that attention bias to threat might enhance fear learning and interrupt with extinction learning [74-75]. Since CBT also attempts to facilitate extinction learning, research relating attention retraining to changes in extinction suggests that the combination of CBT and ABMT in pediatric anxiety may augment the therapeutic response seen in CBT alone,

Reward Attention Training

As of this writing, no published ABMT study in any age group has used the dot-probe task to train subjects to monitor rewards. This is not surprising, given that findings on reward-related biases in the dot-probe task among anxious patients appear less consistent than for threat biases. Moreover, imaging data on threat bias, implicating early amygdala dysfunction in anxiety, provide a stronger rationale for threat-related ABMT than imaging data on reward bias. Nevertheless, although sparse, most studies of healthy adults and some studies of healthy children find that healthy individuals manifest a bias towards rewards on the dot-probe task, unlike anxious individuals, who tend to show an attenuation of this bias.

Accordingly, training anxious individuals to attend to happy faces on the dot-probe task could alleviate anxiety. Moreover, unlike threat-based ABMT, this would train patients to manifest a behavior where all evidence finds associations with adaptive functioning. Hence, relative to threat-related ABMT, this form of training raises fewer concerns about the potential for exacerbating anxiety.

While no ABMT study uses the dot-probe paradigm to train attention to rewards, findings do exist for procedures similar to ABM. In a series of studies, Dandeneau et al., (2007) used a visual-search attention-training method, where adults were taught to rapidly detect happy faces appearing against a background of various distracters, including frowning faces [76]. Preliminary evidence suggests that this training procedure, much like ABM with the dot-probe task, reduces anxiety [77]. Therefore, future studies might consider the therapeutic potential of reward-based dot-probe training procedures.

CONCLUSION

Research on orienting in anxiety strongly implicates biased processing of threats in the maintenance of anxiety. These biases arise from perturbations in underlying neural circuitry, some of which instantiate biased threat processing and others of which compensate for these biases. Research less strongly implicates biased orienting away from rewards in anxiety, though brain imaging studies suggest that some form of reward-attention perturbation likely occurs in anxiety. For both threats and rewards, effects on attention are likely to shape development by modulating the relationship between early temperament and later clinical anxiety. Biased orienting towards threats and rewards may be modified through training, and these training regimens may provide a novel means for alleviating anxiety and limiting its effects on development.

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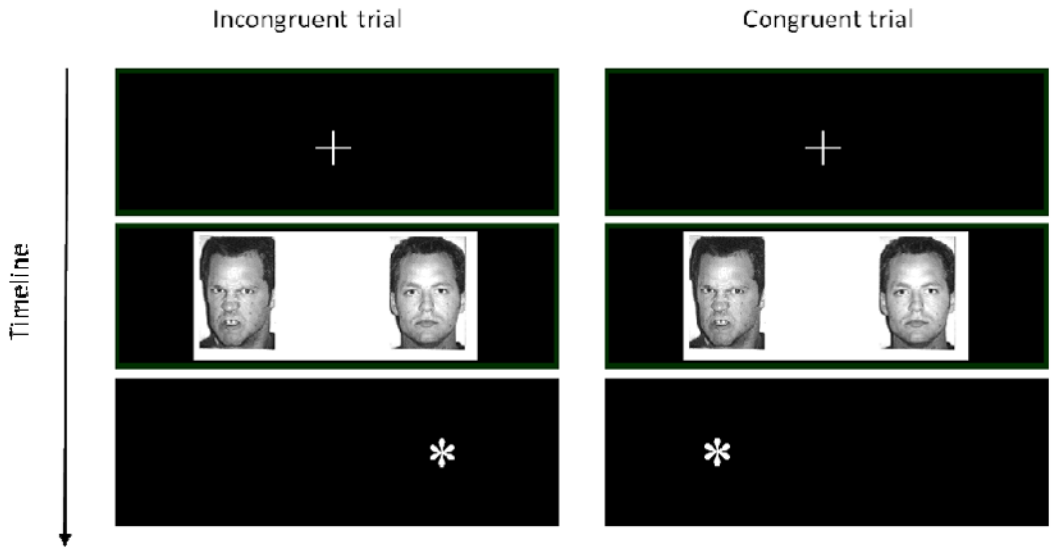

Figure 1.
The dot-probe task to measure threat bias

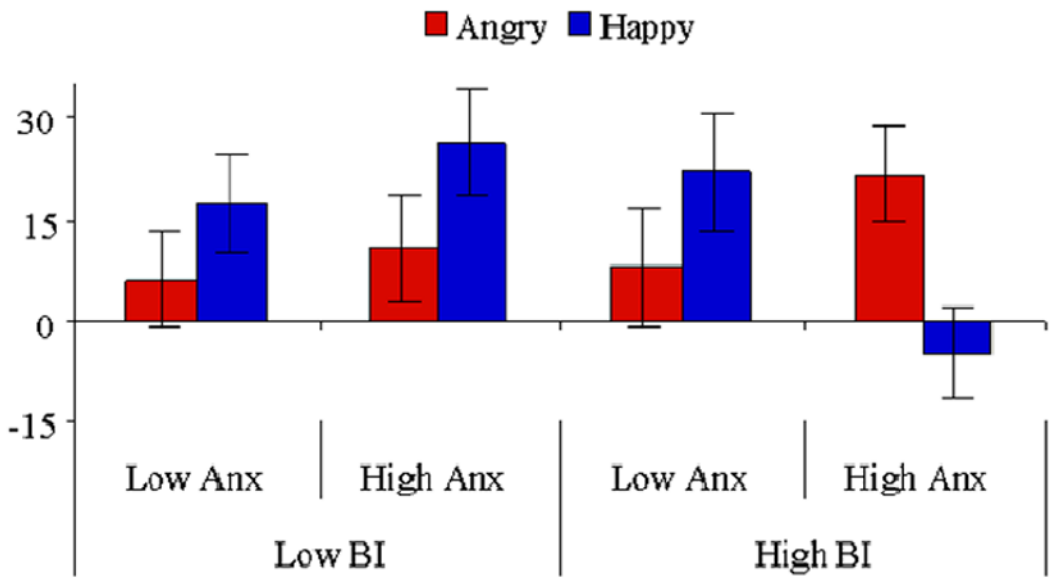

Figure 2.
Attention bias to emotional faces among high and low behaviorally inhibited (BI) children with high and low anxiety scores. Data are from the same subjects reported in Perez-Edgar et al. (2010).

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Table 1

Published data on attentional biases to happy faces in youth using a dot probe task

Authors	Participants	Age	Face Presentation Duration	Findings
No bias to happy				
Maslowsky, Mogg, Bradley, McClure-Tone, Ernst, Pine & Monk (2010)	**Clinical**: 14 anxious GAD adolescent compared to 10 healthy controls	Mean 14	500 ms	No difference between control and treatment groups in bias to happy or threat before or after treatment. No change in bias to happy or threat in neither group.
Pine, Mogg, Bradley, Montgomery, Monk, McClure, et al. (2005)	**Clinical**: 34 children with history of maltreated and 21 who had not been maltreated	Range 7 - 13	500 ms	Maltreated (PTSD) children showed a bias away from threat compared to control. No differences in bias to happy.
Roy, Vasa, Bruck, Mogg, Bradley, Sweeney, Bergman, McClure & Pine (2008)	**Clinical**: 101 anxious and 51 non-anxious children and adolescents	Range 7 - 18	500 ms	Anxious children showed a bias to threat. No group differences in bias to happy.
Waters, Kokkoris, Mogg, Bradley, Pine (2010)	**Non Clinical**: 50 school-age children	Range 9 -12	500/1250 ms	Above median levels anxiety showed a bias toward threat in 500 and 1250 ms. No bias to happy.
Swartz, Graham-bermann, Mogg, Bradely & Monk (2011)	**Clinical**: 31 Children who were exposed to intimate partner violence: 10 with PTSD and 21 with no PTSD diagnosis.	Range 4 - 7	500 ms	Children with PTSD had greater bias towards angry faces than children without PTSD. No group differences in bias to happy.
Waters, Mogg, Bradley & Pine (In press)	**Clinical**: 27 socially phobic and 27 matched controls	Range 5 – 13	500 ms	Highly anxious showed a bias to threat Low anxious showed a bias away from threat. No group differences in bias to happy. Negative correlation between bias to happy and anxiety symptoms intensity.
Perez-Edgar, Reeb-Sutherland, Mcdermott, White, Henderson, Degnan, Hane, Pine & Fox (2011)	**Behaviorally inhibited (BI)**: 187 youth assessed at 5 years. Characterized for BI in 24 & 36 months	5 years	500 ms	No differences in bias score to happy or to angry.
Bias to happy in highly anxious children				
Waters, Mogg, Bradley & Pine (2008)	**Clinical**: 23 GAD children compared to 25 controls	Range 7-12	500 ms	Only the highly anxious children showed a bias to threat and happy.

Authors	Participants	Age	Face Presentation Duration	Findings
				Low anxious kids showed a tendency away from happy.
Bias to happy in anxious and healthy children				
Reinholds-Dunne, Mogg, Esbjorn & Bradely (In press)	**Non Clinical**: 67 school-age children	Range 7 - 14	500 ms	Younger children showed a greater bias to emotional faces than older children. Younger children that were above median anxiety levels showed a bias to both angry and happy faces.
Hunt, Keogh & French (2007)	**Non clinical**: 23 high physical anxiety sensitive and 16 low physical anxiety sensitive	Range 8 - 10	1000 ms / 14 ms	High physical anxiety sensitivity showed a bias towards positive and negative emotional stimulous relative to low physical anxiety sensitive. Bias towards emotions were stronger in the masked (14 ms) than unmasked (1000 ms) condition.
Waters, Henry, Mogg, Bradley & Pine (2010)	**Clinical**: 29 anxious children divided to high and low anxious compared to 24 non-anxious	Range 8-12	500 ms	Bias towards angry only among highly anxious children and not low clinically anxious or controls. All sample showed a bias towards happy, no differences between groups
Bias to happy in children with low behavioral inhibition (BI) temperament scores				
Perez-Edgar, Bar-Haim, Mcdermott, Choronis-Tuscano, Pine & Fox (2010)	**Behaviorally inhibited (BI)**: 138 assessed in adolescence. 20% had current of life time presence of social anxiety. Characterized for BI in 14 & 24 months, 4 & 7 years	Mean 15	500/1500ms.	500 ms: no differences between groups in bias to threat. High BI showed avoidance from happy relative to low BI. Bias to threat (500ms) moderated the relation between childhood BI and adolescent social withdrawal. No difference for 1500 ms.

GAD=Generalized Anxiety Disorder, PTSD=Post-traumatic stress disorder. Age in years.