Heterogeneity of the Anxiety-Related Attention Bias: A Review and Working Model for Future Research

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Abstract

The anxiety-related attention bias (AB) has been studied for several decades as a clinically-relevant output of the dynamic and complex threat detection-response system. Despite research enthusiasm for the construct of AB, current theories and measurement approaches cannot adequately account for the growing body of mixed, contradictory, and null findings. Drawing on clinical, neuroscience, and animal models, we argue that the apparent complexity and contradictions in the empirical literature can be attributed to the field's failure to clearly conceptualize AB heterogeneity and the dearth of studies in AB that consider additional cognitive mechanisms in anxiety, particularly disruptions in threat-safety discrimination and cognitive control. We review existing research and propose a working model of AB heterogeneity positing that AB may be best conceptualized as multiple subtypes of dysregulated processing of and attention to threat anchored in individual differences in threat-safety discrimination and cognitive control. We review evidence for this working model and discuss how it can be used to advance knowledge of AB mechanisms and inform personalized prevention and intervention approaches.

Keywords: Anxiety, attention bias, individual differences

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The ability to quickly detect threat and take appropriate, responsive actions holds powerful survival value. This human threat detection-response system comprises a broad array of biological, cognitive, motivational, social-emotional, and behavioral processes and functions, which must work in close coordination. At the same time, this system must show significant flexibility, allowing it to adapt to changing environments and circumstances (Bishop, 2009; Blair et al., 2012; Roy, Dennis, & Warner, 2015) When the balance and calibration of the threat detection-response system is disrupted such that it is not able to respond to a changing environment, or when the environment overwhelms the individual's ability to adapt, psychological and physical illness can be triggered. The key to this system is therefore dynamic adaptation and flexibility (Blair & Dennis, 2010; Bonanno, Papa, Lalande, Westphal, & Coifman, 2004).

The anxiety-related attention bias (AB) has been studied for several decades as a clinically-relevant output of this dynamic and complex system. AB, or selective and exaggerated attention towards threatening information and stimuli, is thought to play a significant role in the etiology and maintenance of anxious pathology in children, adolescents and adults (Bar-Haim, Lamy, Pergamin, Bakermans-Kranenburg, & Van Ijzendoorn, 2007; Brotman et al., 2007; Fox, Russo, Bowles, & Dutton, 2001; Fox, Russo, & Dutton, 2002; Hakamata et al., 2010; Mathews & Mackintosh, 1998; Mathews & MacLeod, 1985, 2002). A strong evidence base has driven significant enthusiasm for the development of interventions that directly target the reduction of AB (Heeren, Mogoaşe, Philippot, & McNally, 2015; Kwong et al., 2018; MacLeod & Grafton, 2016; Van Bockstaele et al., 2014). For example, attention bias modification training (ABMT) is

a computerized intervention designed to reduce AB among participants evidencing symptoms across the broad spectrum of anxiety and stress-related disorders by repeatedly directing attention away from threat-relevant cues using modified dot probe and visual search paradigms (Beard, Sawyer, & Hofmann, 2012; Cristea, Kok, & Cuijpers, 2015; Cristea, Mogoaşe, David, & Cuijpers, 2015; Hakamata et al., 2010; Hallion & Ruscio, 2011; Heeren, Mogoaşe, et al., 2015; Mathews & MacLeod, 2002).

Despite research enthusiasm for the construct of AB, however, current theories and measurement approaches cannot adequately account for the growing body of mixed, contradictory, and null findings (Clarke, Notebaert, & MacLeod, 2014; Koster, Crombez, Verschuere, & De Houwer, 2006; Koster, Verschuere, Crombez, & Van Damme, 2005; Kwong et al., 2018; Roy et al., 2015; Shechner, Britton, et al., 2012). For example, research with children and adults documents significant heterogeneity in AB in clinical anxiety, including an absence of detectable bias or bias away from threat (Brown et al., 2013; Eldar et al., 2012; Monk et al., 2006; Salum et al., 2013), and trial-level dynamic variability in AB that varies with clinical anxiety status (e.g. Zvielli, Bernstein, & Koster, 2014a) and context (e.g. Egan & Dennis-Tiwary, 2018). Moreover, although ABMT, which involves the systematic training of attention away from threat, showed early evidence of being a powerful, cost-efficient and easily accessible treatment for anxiety, with promising levels of efficacy (Hakamata et al., 2010), subsequent clinical trials and meta analyses reveal null or mixed findings, low to moderate effect sizes, and little evidence that treatment effects are mediated by reduction in AB (Cristea, Kok, et al., 2015; Heeren, Mogoaşe, et al., 2015).

In the present paper, drawing on clinical, neuroscience, and animal models of anxiety, we argue that the apparent complexity and contradictions in the empirical AB? literature can be

attributed to the field's failure to clearly conceptualize heterogeneity in AB and the dearth of studies that consider additional cognitive mechanisms in anxiety, including disrupted threat-safety discrimination (e.g. Lissek et al., 2005), and disruptions in cognitive control (e.g. Eysenck, Derakshan, Santos, & Calvo, 2007). We review existing research and propose a working model of AB heterogeneity positing that: (a) AB is influenced by, and possibly an influence on, additional processes underlying dysregulation of attention to threat, namely threat-safety discrimination (TD) and cognitive control (CC); (b) by considering individual differences in TD and CC, we can predict empirically-documented phenotypic variability in anxiety-related AB and clinical symptom manifestation; and (c) because the weight of evidence points to multiple subtypes of dysregulation of processing of, and attention to, threat, including dynamic variability in AB, AB should no longer be conceptualized as only a bias toward threat. We review evidence for this working model and discuss how the model can be used to advance knowledge of mechanisms underlying AB and inform personalized prevention and intervention approaches.

The Anxiety-Related Attention Bias

Anxiety and stress-related disorders are highly prevalent, affecting 29% of individuals during their lifetime (Kessler, Berglund, et al., 2005; Kessler, Chiu, Demler, & Walters, 2005; Kessler, Petukhova, Sampson, Zaslavsky, & Wittchen, 2012), with an estimated societal cost of about $46.6 billion (Rosenblatt, 2010). Yet, these disorders remain difficult to treat (Pine, Cohen, Gurley, Brook, & Ma, 1998), with 30- 50% of children and adults remaining symptomatic after receiving 12-weeks of high-quality cognitive-behavioral and pharmacological treatment (Costello, Mustillo, Erkanli, Keeler, & Angold, 2003). Further, comorbidity of anxiety and stress-related disorders with other disorders is more often the rule than the exception (Kessler et al., 2012; Stirling, Eley, & Clark, 2006) suggesting a clear need to move away from current

diagnostic nosology, and towards characterization based on biobehavioral markers and cross-diagnostic mechanisms.

AB is one such putative mechanism. Defined as selective and exaggerated attention towards threat (Mathews & MacLeod, 2005), research has documented AB at multiple stages of attention, including initial attention capture, sustained dwelling, and difficulty disengaging from threat-related stimuli (Gamble & Rapee, 2009; Heeren, Mogoaşe, McNally, Schmitz, & Philippot, 2015; O'Toole & Dennis, 2012). This multi-faceted dysregulation of attention has been examined in the etiology and maintenance of anxious pathology in children, adolescents and adults (Bar-Haim et al., 2007; Brotman et al., 2007; Fox et al., 2001; Fox et al., 2002; Hakamata et al., 2010; Kessler et al., 2012; Mathews & Mackintosh, 1998; Mathews & MacLeod, 1985, 2002; Stirling et al., 2006), and is detectable across a range of anxiety disorder diagnoses (Koster, Crombez, Verschuere, & De Houwer, 2006; Mogg, Bradley, De Bono, & Painter, 1997; Monk et al., 2006; Roy et al., 2008; Waters, Mogg, Bradley, & Pine, 2008) and in those with sub-clinical high trait anxiety (Bar-Haim et al., 2007; Waters, Mogg, & Bradley, 2012).

From an etiological and developmental standpoint, AB is of growing interest to researchers because of its potential to impact a number of other processes (Roy et al., 2015). For example, AB can be likened to an information filter that increases preferential processing of aversive and threatening information. This in turn is thought to drive a cascade of cognitive, affective and behavioral changes in which behavior becomes more inhibited and avoidant, or reactivity increases, thus perpetuating the cycle of anxiety. Over time, these patterns may become rigid. Thus, attention may act as a tether (Pérez-Edgar, Kujawa, Nelson, Cole, & Zapp, 2013) tying early risk to later anxious pathology. However, this filter model cannot adequately account for the presence of significant AB heterogeneity and clinically-relevant dynamic variability in AB.

Attention Bias Heterogeneity

AB towards and away from threat. The measurement of AB over the past two decades has primarily relied upon the use of a reaction-time based task, the dot probe (MacLeod, Mathews, & Tata, 1986; Mathews & MacLeod, 2005), although a range of other tasks have also been used, including the emotional spatial cueing paradigm (Fox et al., 2002; Posner & Petersen, 1990; Yiend & Mathews, 2001), multi-stimulus arrays (e.g. Koster, De Lissnyder, Derakshan, & De Raedt, 2011; Öhman, Flykt, & Esteves, 2001; Wieser, Hambach, & Weymar, 2018), and the emotional Stroop (Mathews & MacLeod, 1985; Watts, McKenna, Sharrock, & Trezise, 1986; Williams, Mathews, & MacLeod, 1996). In the dot probe task, two stimuli, one threat-related and one non-threat-related, are presented simultaneously. After their offset, participants are asked to respond quickly but accurately to a target probe that appears with equal probability in the location of one of the stimuli. Faster responses to probes appearing in the location of the threatening stimulus suggest that attention was "captured" by threat. When individuals respond relatively faster to probes replacing threat versus non-threat stimuli, they are thought to have a larger AB, and indeed, AB is calculated as the averaged difference between reaction times to each cue type. Using the dot probe and related behavioral assays, a meta-analysis including 2,263 anxious and 1,768 non-anxious participants (Bar-Haim et al., 2007) showed that AB was reliably demonstrated across experimental conditions and anxiety subtypes with a small to moderate effect size ($d = 0.45$), and that AB was not observed in non-anxious people, despite the adaptive value of threat detection. They concluded that this finding "cannot be reduced to insignificance in the next 11,339 studies, even if those studies yielded only null results'' (Bar-Haim et al., 2007, p.15). Similar patterns and effect sizes were reported in subsequent meta-analyses (e.g. Van Bockstaele et al., 2014).

Along with this empirical support for the existence of preferential, biased attention to threat in anxiety, however, inconsistencies in the literature and measurement challenges highlight the importance of examining both heterogeneity and underlying mechanisms of AB (Clarke, MacLeod, & Guastella, 2013; Roy et al., 2015). For example, a growing body of research documents that many anxious individuals demonstrate no detectable bias or exhibit AB *away from* threat (Koster, Crombez, Verschuere, & De Houwer, 2006; Koster et al., 2005; Monk et al., 2006; Salum et al., 2013; Stirling et al., 2006), the latter suggesting a pattern of attentional avoidance of threat. Attentional avoidance is highly consistent with the clinical literature, which emphasizes the function of behavioral avoidance in the development and maintenance of anxiety disorders. That is, avoidance promotes anxiety by reducing opportunities to disconfirm anxiety-related beliefs and to utilize adaptive coping strategies (Foa & Kozak, 1986; Thwaites & Freeston, 2005; Wells et al., 1995). In a large-scale twin study examining behavioral and familial risk for anxiety, children diagnosed with an anxiety disorder evidenced greater attentional avoidance of threat-related stimuli than non-anxious children (Brown et al., 2013), and the magnitude of avoidance predicted the incidence of anxiety disorders independently from risk associated with familial factors.

Several studies have shown that AB towards and away from threat predict distinct symptom profiles in anxious youth, highlighting the potential clinical relevance of identifying these subtypes (Stirling et al., 2006; Taghavi, Dalgleish, Moradi, Neshat-Doost, & Yule, 2003; Waters, Bradley, & Mogg, 2014; Waters et al., 2012; Waters et al., 2008). Specifically, a greater bias towards threat is associated with distress-related disorders such as generalized anxiety disorder (GAD) whereas a greater bias away from threat is associated with fear-related pathology (e.g., phobias and panic disorder). In a large study of 5- 13 year olds ($N = 435$), Waters et al. (2014)

found that, compared to healthy controls, children with a principal distress disorder (GAD) showed AB towards threat measured via a visual probe task, whereas those with a principal fear disorder showed AB away from threat. Further, the direction of AB predicts treatment outcomes, such that children exhibiting a pre-treatment AB towards threat show greater reductions in anxiety following cognitive-behavioral therapy compared to those with AB away (Waters et al., 2012). This research highlights that advancing our understanding of multiple AB phenotypes has the potential to inform the development of more targeted and personalized treatment approaches.

Methodological factors may play a role in the detection of AB towards and away from threat. In anxious adults, several studies have documented that the classic congruency effect in the dot probe (i.e., that reactions times are shorter on congruent versus incongruent trials) is detectable at short stimulus durations around 500 ms, but at longer stimulus durations around 1250 ms, the congruency effect is reversed and high trait anxious individuals show attentional avoidance of threat cues (Koster et al., 2005). Attentional avoidance at long but not short cue durations has been replicated (e.g. Mogg et al., 1997), and documented using direct measurement of eye movements, and tasks other than the dot probe such as exogeneous cueing tasks (Koster et al., 2005) and visual search tasks (Pflugshaupt et al., 2005).

Neurophysiological evidence for AB towards and away from threat. Consistent with these findings, the vigilance-avoidance hypothesis (e.g. Mogg et al., 1997) suggests temporally-sensitive stages of attention, in which anxious individuals first demonstrate facilitated attention to threat, followed by avoidance. Neuroscience findings provide converging evidence that anxiety-related vigilance selectively emerges at early stages of threat detection and processing. For example, anxious versus healthy individuals exhibit facilitated early threat detection measured by amygdala hyper-responsivity (Armstrong, Olatunji, Sarawgi, & Simmons, 2010;

Brown et al., 2014a; Brown, Goodman, & Inzlicht, 2012; Brown & Ryan, 2003; McClure et al., 2007; Monk et al., 2008), and show enhanced electrocortical responses associated specifically with early visual attention allocation (e.g., P1, N1; Eldar & Bar-Haim, 2010; Mueller et al., 2009) and early attention selection of threat (Judah, Grant, & Carlisle, 2016).

We, and others, have used discrete event-related potential (ERP) responses to identify heterogeneity in AB because they provide a temporally- and functionally-sensitive measure of neural processes related to AB (Dennis-Tiwary, Egan, Babkirk, & Denefrio, 2016; Eldar & Bar-Haim, 2010; Kappenman, Farrens, Luck, & Proudfit, 2014; Kappenman, MacNamara, & Proudfit, 2014; O'Toole & Dennis, 2012). ERPs further allow for the dual-process distinction between relatively rapid and automatic attention allocation to threat versus later-emerging and controlled or deliberative stages of attention to and cognitive control of threat (Codispoti, Ferrari, & Bradley, 2007; Dien, Beal, & Berg, 2005). In research using the N170 ERP, for example, which indexes attention discrimination of salient and familiar stimuli such as faces (Bentin, Allison, Puce, Perez, & McCarthy, 1996; Eimer, 2000; Rousselet, Husk, Bennett, & Sekuler, 2008), larger magnitude N170s to angry relative to neutral faces predicts anxiety symptoms in children over a two-year period (O'Toole, DeCicco, Berthod, & Dennis, 2013) and has been used to identify difficulties in threat-safety discrimination in adults diagnosed with GAD relative to healthy controls (Denefrio, Myruski, Mennin, & Dennis-Tiwary, 2018). Another ERP index of AB is the N2pc, which measures visual selective attention (e.g. Eimer & Kiss, 2007; Holmes, Bradley, Kragh Nielsen, & Mogg, 2009; Kappenman, Farrens, et al., 2014; Kappenman, MacNamara, et al., 2014). In studies of anxiety-related AB, greater selective attention towards threat has been shown to be reliably and consistently signaled by increased amplitude of the

N2pc in non-anxious (Kappenman, MacNamara, et al., 2014) and anxious adults (Fox, Derakshan, & Shoker, 2008; Judah et al., 2016).

Other research using ERPs suggests that AB heterogeneity is associated with individual differences in the recruitment of prefrontal cortical resources. The N2 and P3 ERPs provide sensitive measures of the recruitment of neural resources during tasks that require cognitive control (Folstein & Van Petten, 2008; Nieuwenhuis, Yeung, Van Den Wildenberg, & Ridderinkhof, 2003; Polich, 2007; Van Veen & Carter, 2002). In a study using the emotional Stroop, patients with panic disorder evidenced exaggerated P3 amplitudes during threat versus neutral word color naming, suggesting over-regulation (Thomas, Gonsalvez, & Johnstone, 2013). Although AB away from threat has been studied relatively rarely, additional evidence can be gleaned from studies training participants to avoid threat. For example, AB away from threat has been associated with both greater-magnitude N2 and P3 responses (Dennis-Tiwary et al., 2016; O'Toole & Dennis, 2012). Taken together, these studies suggest that as AB away from threat is increased, N2 and P3 signals are enhanced, reflecting increased recruitment of strategic attentional control required to avoid the threatening stimulus (Eldar, Yankelevitch, Lamy, & Bar-Haim, 2010).

Other research uses ERPS to track the full time-course of early vigilance and later avoidance, the latter emerging during more deliberative stages of threat processing (e.g., Denefrio et al., 2018). For example, Weinberg & Hajcak (2011) examined extended visual processing of affective versus neutral stimuli in adults diagnosed with GAD. Those diagnosed with GAD, versus healthy controls, showed increased neural responses to threat-themed relative to neutral images at early stages of attention allocation (the P1 ERP), but greater avoidance of threat-themed images at later elaborative stages of processing (the late positive potential or LPP).

Despite this growing body of research, attentional avoidance and AB heterogeneity in general has received relatively little empirical attention from a neurophysiological perspective.

Dynamic variability. Recent research suggests that AB heterogeneity also emerges in a temporally-dynamic fashion, which is obscured by typical methods of calculating AB as an aggregate score across the entirety of a behavioral assay. This traditional measurement approach assumes that AB will emerge consistently in the same way throughout an assessment and that an individual will show a bias in only one direction: either towards or away from threat. These assumptions have not been supported by the extant body of literature on AB, and fail to allow for the same individual to show a bias *both* towards and away within a single task, a pattern which may have significant clinical relevance.

Trial-level bias scores address this limitation by allowing for the creation of AB scores reflecting dynamic changes from trial-to-trial and over the course of an assessment paradigm (Zvielli, Bernstein, & Koster, 2014c). Whereas traditional, static bias scores are computed from average reaction times, the trial-level variability score is calculated as the absolute value of the sum of the mathematical differences between successive temporally contiguous pairs of trials. Thus, the variability score can capture phasic bursts in AB, while also tracking the magnitude and directionality of AB towards and *away* from threat both between and within participants. Figure 1 shows an example of high and low levels of variability (Egan & Dennis-Tiwary, 2018).

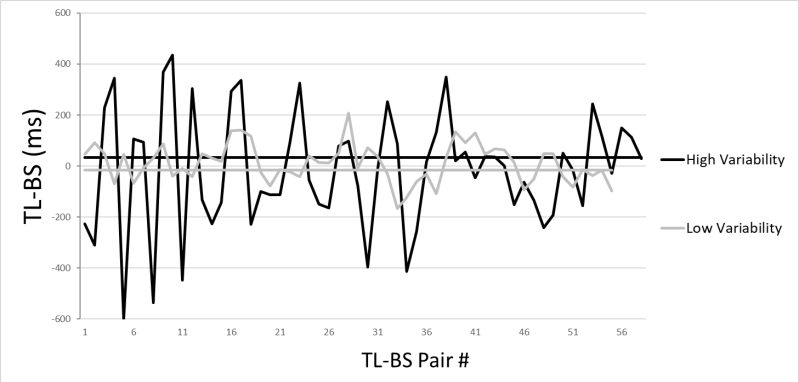

Figure 1. Example of high and low attention bias variability (from Egan & Dennis-Tiwary, 2018)

Trial-level bias scores have been shown to predict, above and beyond the static bias measure, clinical diagnoses of specific phobia (Zvielli et al., 2014a), posttraumatic stress symptoms in soldiers (Badura-Brack et al., 2015; Iacoviello et al., 2014; Naim et al., 2015), stress reactivity and neurocognitive responses to threat (Egan & Dennis-Tiwary, 2018). Further, they are directly reduced by cognitive behavioral therapy in individuals with social anxiety disorder (Davis et al., 2016). Another related approach is to measure AB variability between contexts over time. Heeren, Philippot, and Koster (2015) assessed AB stability between two distinct time points. Participants completed the dot probe task at an initial lab visit, then two weeks later prior to completing attention bias modification training (ABMT). Greater stability (test-retest reliability) in AB towards threat over the two-week period predicted poorer treatment response to ABMT. Overall, findings suggest that continued research is warranted to explore the clinical relevance of trial-level changes in AB and AB stability as forms of AB heterogeneity. In addition, trial-level approaches to measuring AB complement traditional measures that calculate an average "snapshot" of AB over many trials, losing information about dynamic change in AB over time.

The Role of Threat-Safety Discrimination and Cognitive Control in AB

Taken together, evidence reviewed above suggests that AB, as a behavioral expression of disruptions in the threat detection-response system, shows phenotypic heterogeneity - anxious individuals sometimes show a bias towards threat, away from threat, or no discernable bias at all. Evidence also suggests that AB heterogeneity can be tracked using temporally-sensitive physiological measures such as ERPs, and may be expressed dynamically over the course of assessment, such that greater anxiety severity might be associated with greater trial-level variability in bias towards and away from threat. Therefore, to move the study of AB forward, it will be crucial to examine other threat-related processes in anxiety that might influence the heterogeneity and temporal characteristics of AB. Here we review evidence for two candidate processes, threat-safety discrimination and cognitive control, and discuss the possibility that they might in turn be "tuned" through a reciprocal feedback-feedforward loop with AB.

Threat-safety discrimination (TD). To understand AB as dysregulated attention to threat, the literature on anxiety-related disruptions in TD must be considered. Lang and colleagues (Lang, Davis, & Öhman, 2000) have broadly proposed that anxiety results from the failure to inhibit fear in the presence of safety cues. For example, compared to healthy controls, anxious youth display exaggerated fear responses to safety cues when these cues are in the context of threat cues (Jovanovic et al., 2014). In anxiety, deficits in the ability to discriminate between threat and safety triggers such overgeneralized fear responses due to an increased interpretation of safety cues as ambiguous or potentially dangerous (Waters & Kershaw, 2015).

Research on TD generally utilizes fear conditioning paradigms. According to a meta-analysis of 20 fear-conditioning studies (Lissek et al., 2005), clinically anxious individuals exhibit slower acquisition of fear learning, which relies upon discrimination of fear and safety cues. Clinical anxiety is also associated with continued conditioned responding during extinction, which

suggests that anxious patients show a reduced ability to inhibit the fear response even in the presence of conditioned stimuli associated with safety cues (CS-) and absence of actual threat. Consistent with this finding, several studies comparing anxious patients and healthy controls report heightened fear-potentiated startle (Grillon & Ameli, 2001; Grillon & Morgan III, 1999), electrodermal responses (Orr et al., 2000; Peri, Ben-Shakhar, Orr, & Shalev, 2000) and subjective anticipatory anxiety (Clum, 1969; Hermann, Ziegler, Birbaumer, & Flor, 2002) in response to CS- cues. Research including animal models of anxiety mirror these findings (Likhtik & Paz, 2015).

Human neuroimaging studies provide further support, finding that state and trait anxiety are associated with reduced amygdala differentiation between threat-relevant and neutral stimuli (e.g. Somerville, Kim, Johnstone, Alexander, & Whalen, 2004). In a clinical sample, Nitschke et al. (2009) found greater bilateral dorsal amygdala activation to warning cues predicting both aversive and neutral images in a group diagnosed with GAD relative to controls, suggesting indiscriminate threat monitoring. The magnitude of these responses predicted treatment outcome. In a recent ERP study, adults diagnosed with GAD, relative to health controls, showed reduced discrimination between threat and non-threat information at both the level of rapid visual processing (the N170), as well as at the level of response monitoring of errors (the error-related positivity or Pe (Denefrio et al., 2018). Taken together, research in humans and animals suggests that disruptions in TD may be a marker for pathological anxiety (Lissek et al., 2014; Lissek, Rabin, Heller, et al., 2009; Lissek, Rabin, McDowell, et al., 2009).

In terms of behavioral reaction times and the calculation of AB metrics, reduced TD in anxiety could contribute to the expression of AB in multiple ways. For example, those with poor TD could show no bias (comparable reaction times following threat versus non-threat cues) or

show highly variable bias towards and away from threat on a trial-level basis because attention would be divided between threat and non-threat. On the other hand, some anxious individuals may show relatively intact TD, and this might be associated with the more conventional AB pattern of exaggerated attention to threat. Moreover, when interpreting the direction of bias, it must be considered whether a bias away from threat (avoidance) reflects disengagement from threat to regulate arousal, or, conversely, selective attention towards the ambiguous, poorly discriminated neutral cue in those with low TD in order to determine its threat-relevance. This may be particularly relevant when considering the threat-related context in which AB is measured (e.g. Bar-Haim et al., 2010). For example, one study (Shechner, Pelc, Pine, Fox, & Bar-Haim, 2012) showed that, following fear conditioning, non-anxious adults demonstrated greater AB away from threat when the measurement context included CS+, but not CS-. While this previous study did not examine TD per se, these findings, and others (Koster, Crombez, Van Damme, Verschuere, & De Houwer, 2004; Notebaert, Crombez, Van Damme, De Houwer, & Theeuwes, 2011; Van Damme, Crombez, & Notebaert, 2008) suggest that fear conditioning alters attentional processes that can be captured by AB assessment via the dot-probe. In sum, individual differences in TD alone cannot explain patterns of AB heterogeneity or variability. As discussed below, another individual difference, cognitive control, is proposed to interact with TD to explain heterogeneity of AB.

Cognitive control (CC) and anxiety: under- and over-regulation. Early evidence supports the impact of individual differences in CC on AB (e.g. Bardeen & Orcutt, 2011; Derryberry & Reed, 2002; Taylor, Cross, & Amir, 2016), with both under- and over-regulation of cognition and attention documented in anxiety research. Eysenck et al. (2007) Attention Control Theory (ACT) highlights the role of under-control. ACT emerged out of a previous theory by Eysenck and

Calvo (1992) called Processing Efficiency Theory (PET). At the core of PET is the concept of cognitive efficiency, which reflects the relation between quality of task performance (effectiveness) and the cognitive resources spent to accomplish that level of effectiveness. Efficiency decreases as more resources are invested to attain a given level of task performance. Anxiety is proposed to have a selectively greater negative impact on efficiency rather than effectiveness. It is further posited that the main cognitive effects of anxiety, via the worry component of anxious thinking, are on executive functions, such as the ability to deliberatively inhibit or shift attention away from threat.

ACT extends these concepts by focusing on how attentional processes influence the impact of anxiety on executive functions and performance efficiency (see also Luu, Tucker, Derryberry, Reed, & Poulsen, 2003; Power & Dalgleish, 1997). Anxiety results from goals being threatened. At the same time, threat to goals adaptively causes attention to be allocated to detecting the source of the threat and problem solving around how to respond. This concept is consistent with the basic notion of AB (e.g. Fox et al., 2002; Mogg et al., 1997; Mogg et al., 2000; Wilson & MacLeod, 2003).

ACT further suggests that anxiety disrupts this adaptive process by causing an imbalance between the automatic, stimulus-driven attentional system and the top-down, goal directed executive control system. The cause of this imbalance is generally described to be a decreased influence of the executive system relative to the stimulus-driven system, as well as the failure to efficiently recruit attention control as measured by reduced activity of areas of the prefrontal cortex such as the dorsal lateral prefrontal cortex (DLPFC; Bishop, Duncan, Brett, & Lawrence, 2004; Bishop, 2009). Similar to the concept of AB, this under-regulation of attentional biases towards threat – expressed as difficulty in inhibiting attention towards threat and in disengaging

attention once it is captured - is hypothesized to be a key process underlying anxiety. Consistent with this perspective, clinically anxious adults show worse performance on a range of tasks requiring executive control (e.g. antisacade task; Fox et al., 2008) and show difficulties inhibiting orienting towards neutral and emotional material (Wieser, Pauli, & Mühlberger, 2009), suggesting a deficit in attention control operating as a buffering mechanism against prolonged engagement with threat (e.g., Bardeen & Orcutt, 2011).

In contrast, other theories highlight the role of over-control and over-regulation in anxiety, particularly their contribution to avoidance symptoms. For example, anxious individuals tend to experience feelings of apprehension and anxious arousal as highly aversive, and thus regulate thoughts and behaviors to avoid these subjective experiences. The "fear of fear" model of panic disorder (Barlow, Gorman, Shear, & Woods, 2000) and the cognitive avoidance (Borkovec, Alcaine, & Behar, 2004) and contrast avoidance (Newman & Llera, 2011) theories of generalized anxiety disorder are specific examples of this. The central premise of these models is that behavior and cognition can be over-regulated in order to avoid the experience of anxiety. Thus, a range of "over-regulation strategies" may be employed to avoid both the elicitation of fear/anxiety or, if the emotion is already generated, to suppress it. Indeed, individuals with an anxiety or mood disorder report less acceptance of their emotions, less emotional clarity, and more emotion regulatory attempts compared to healthy controls (Campbell-Sills, Barlow, Brown, & Hofmann, 2006). Suppression, a masking or inhibition of emotional experience or expression, has been conceptualized as an avoidance strategy that is maladaptive, particularly if used frequently and rigidly, and may boost attentional avoidance. For example, in a study of Vietnam vets, those with PTSD, compared to those without, utilized suppression more often and more

effortfully (Roemer, Litz, Orsillo, & Wagner, 2001), and regularity of suppression use was related to severity of PTSD symptoms.

While vigilance-avoidance models of anxiety-related attention disruptions (e.g., Mogg et al., 1997) reviewed above suggest that anxious individuals evidence both a bias towards and away from threat over the full time-course of attention processing, it is unclear how attentional avoidance is facilitated by the general deficits in attention control that "under-control" theories posit. Indeed, attentional avoidance and difficulty disengaging seem to reflect distinct mechanisms, with avoidance appearing to require active CC/inhibition of threat (Koster, Crombez, Verschuere, & De Houwer, 2006). While differences in the nature of attention assays may account for this seeming contradiction (e.g. Weierich, Treat, & Hollingworth, 2008b) argue that individuals may overtly avoid threat while covertly maintaining attention towards threat) there is a lack of both empirical evidence and theoretical accounts that provide a framework for understanding this heterogeneity.

These two separable components of AB, attentional engagement and disengagement, have received significant empirical interest due to their potential contribution to selective processing of threat (Bar-Haim et al., 2007; Rudaizky, Basanovic, & MacLeod, 2014), their differential impact on anxiety in the context of ABMT (Heeren, Lievens, & Philippot, 2011; Hirsch et al., 2011) and methodological challenges in evaluating them as unique processes (Clarke et al., 2013). Disruptions in engagement and disengagement components may be differentially sensitive to CC. For example, Cisler and Koster (2010) posited a model of anxiety-related AB in which relatively automatic, valence-specific processes and strategic, CC-related processes interact to influence dysregulated attention to threat. According to the model, both difficulty disengaging from threat and attentional avoidance of threat are selectively influenced by

prefrontal-cortex-mediated deficits in attention control, whereas facilitated engagement and attention towards threat is selectively influenced by amygdala-mediated threat detection mechanisms. While we propose below that individual differences in neural circuits rather than distinct neural regions drive broad phenotypic heterogeneity in AB towards and away from threat, Cisler and Koster (2010) convincingly argue that a critical question for future research is how these mediating mechanisms, such as attention control and their neural bases, interact to influence expression of AB.

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Despite the growing interest in the potential separable contribution of engagement and disengagement to AB, current methods may not be capable of measuring them as distinctive processes (Clarke et al., 2011). In addition, because attentional engagement and disengagement are mainly posited to represent specific mechanisms in selective and exaggerated spatial attention towards threat, or as sub-components of AB (e.g., Cisler & Koster, 2010; Clarke et al., 2011), it is unclear how difficulty disengaging might contribute to AB away from threat. These issues point to the continued importance of assessing the predictive and clinical relevance of both functionally-specific biobehavioral measures of AB, and measures of AB reflecting disruptions at multiple points in the ongoing, temporal sequence of threat detection, discrimination, and control (Roy, et al., 2015; Dennis-Tiwary et al., 2016; Egan & Dennis-Tiwary, 2018).

A Working Model of AB Heterogeneity

Taken together, the research reviewed above suggests that current conceptualizations of AB fail to account for clinically-significant heterogeneity and variability in dysregulated attention to threat associated with anxiety. Moreover, theories of AB have evolved in the absence of clear integration with empirically- and theoretically-robust research on broader cognitive disruptions in anxiety.

Addressing these issues, we propose the Threat Discrimination-Control Model (TDCM) of anxiety-related AB. Drawing on behavioral and neurocognitive research with humans and animal models of anxiety, TDCM posits that anxiety-related AB is a downstream reflection of dysregulated threat responses expressed behaviorally as discrete subtypes described by the direction of bias (towards or away) and degree of stability/dynamic variability in AB over time. These AB subtypes, which have been documented in the literature, can be accounted for by individual differences in two key processes, threat-safety discrimination (TD) and cognitive control (CC), and broadly reflect either under- or over-regulation of attention to threat.

As depicted in Figure 2, low and high levels of TD and CC interact to predict four key AB subtypes. These patterns of attention to threat can be detected in extant studies with anxious adults and children, but they have not been conceptualized as reflecting meaningful and clinically-relevant subtypes of AB heterogeneity. They are: (a) labile, (b) vigilant, (c) avoidant, and (d) no bias. Lability and vigilance reflect under-regulation of attention towards threat (low CC), but differ in TD; whereas avoidance and no bias reflect intact or over-regulation of attention towards threat (high CC), but again differ in TD.

		Threat-Safety Discrimination	
		Low	High
Cognitive Control	Low	**Labile** – high variability towards & away	**Vigilant** – bias towards
	High	**No Detectable Bias**	**Avoidant** –bias away

Figure 2. The Threat Discrimination-Control Model of Attention Bias

Under-regulation: Vigilant and labile. The TDCM specifies two phenotypic expressions of under-control depending on level of discrimination between threat and non-threat. When TD is intact – i.e., threat is efficiently and accurately distinguished from non-threat – low CC is expressed on the behavioral level as attentional vigilance, or exaggerated attention to and dwell time on threat-related stimuli (Lonigan & Vasey, 2009; Susa, Pitică, Benga, & Miclea, 2012). In other words, the vigilant subtype is comprised of individuals showing reduced CC because they have fewer top-down resources to regulate attention to threat, leading to the most common patterns of attention documented in research on anxiety: automatic and early attention capture by threat, and subsequent difficulty disengaging attention from threat once attention is captured (e.g. Armstrong & Olatunji, 2012; Cisler & Koster, 2010; Judah et al., 2016; Mogg et al., 1997; O'Toole & Dennis, 2012). On the other hand, when TD is compromised such that neutral or ambiguous signals are interpreted as potentially dangerous, low CC would result in the distinct, labile pattern of AB in which there is both exaggerated attention towards threat and towards safe/ambiguous signals.

Importantly, traditional AB metrics representing a single difference score reflecting the speed of responding to threat congruent versus incongruent probes may obfuscate the presence of labile AB because trials reflecting bias towards threat and away from threat will cancel each other out when they are averaged, leading to a score reflecting no or little bias. This highlights the importance of distinguishing between those evidencing a truly low bias score with little variability across trials from those with high-magnitude, high variability bias across trials.

Labile AB can only be documented using trial-by-trial bias scoring techniques (e.g. Egan & Dennis-Tiwary, 2018; Zvielli et al., 2014a; Zvielli, Bernstein, & Koster, 2015) as traditional methods of AB measurement that examine RT differences across an entire task would, as noted

above, likely show no bias. Labile AB refers to a pattern in which a given individual evidences both biases towards and away from threat on a trial-by-trial basis during a single assessment period. High trial-level AB variability has been associated with increased anxiety severity (Zvielli et al., 2015), stress reactivity (Egan & Dennis-Tiwary, 2018), and clinical anxiety (Zvielli et al., 2014a).

Evidence from task-based neuroimaging studies highlight the potential role of prefrontal cortical regions in under-regulation related to anxiety-related AB. For example, anxiety-related hypoactivation has been observed in the dorsolateral prefrontal cortex (DLPFC) during distractor and Go-NoGo tasks (in adults; Bishop et al., 2004; Bishop, 2009; Forster, Nunez Elizalde, Castle, & Bishop, 2013) and during error processing (in children; Fitzgerald et al., 2013), suggesting impaired ability to recruit this region to provide sufficient top-down attention modulation. Similar findings have been observed for the dorsal ACC (Blair et al., 2012). Disruptions in attentional control and disengagement from threat may result from altered iFC between these regions and the amygdala, as seen in GAD patients exhibiting hyperconnectivity between the amygdala and prefrontal regions at rest (in adults; Etkin, Prater, Schatzberg, Menon, & Greicius, 2009; in children; Roy et al., 2009) and during task (Spielberg et al., 2014; Wheelock et al., 2014). Hypoactivation of prefrontal regions, regardless of connectivity, could also account for reduced attentional control (i.e., a relative imbalance between prefrontal and limbic regions) and thus should also be investigated as a target neural mechanism (e.g. Bishop et al., 2004).

Over-regulation: Avoidant and no bias. The TDCM specifies two phenotypic expressions of over-control depending on level of discrimination between threat and non-threat. When TD is intact, high CC is expressed on the behavioral level as a bias away from, or avoidance of, threat-

related stimuli. In contrast, when TD is compromised and both signals of threat and neutral signals are interpreted as potentially dangerous, high CC would result in no discernable bias.

AB away from threat occurs when controlled avoidance of threat is enhanced and TD is intact. In other words, the avoidant subtype reflects the ability to avoid threat through high levels of CC (which contrasts with the relative difficulty in such attention control in the labile and vigilant groups). As detailed below, because bias away is posited to emerge from disruptions in fronto-parietal networks that support increased strategic control of threat, there may also be reduced variability in AB on a trial-level basis. This reasoning further suggests that those with high levels of CC but poor threat/safety discrimination will be the most likely to show no overall discernable bias, but also show little lability – that is, similar reaction times to threat and neutral cues across trials. Like the labile group, however, some low-magnitude trial-to-trial variability should remain due to difficulty distinguishing threat from safety, but high levels of CC would dampen the magnitude of this variability.

This framework accounts for what seem puzzling or contradictory findings that a large percentage of anxious participants in studies of AB evidence no discernable bias (e.g. Heeren, Mogoașe, et al., 2015; Kruijt, Parsons, & Fox, 2018; Mogg, Waters, & Bradley, 2017). Indeed, a growing number of studies document that clinically-anxious individuals, screened to undergo ABMT, fail to show even a small bias towards threat measured via the dot probe (Eldar, Ricon, & Bar-Haim, 2008; Kruijt et al., 2018). Integrated consideration of individual differences in TD suggests that these anxious individuals do have disruptions in threat processing, but at the level of poor discrimination between threat and safety, and they may retain intact CC. As noted above, an individual showing the labile phenotype linked to low CC would also show little or no bias measured via traditional AB metrics. The magnitude of labile trial-level variability, however,

will be high, emphasizing the importance of measuring trial-level AB along with traditional average AB metrics to distinguish between the no bias and labile subtypes.

At the neural level, the frontoparietal network is implicated in monitoring conflict, attention discrimination, integration of sensory information with internal representations, and implementation of goal directed behavior (Vincent, Kahn, Snyder, Raichle, & Buckner, 2008). Thus, it is well-positioned as a target neural system underlying both strategic control required for threat avoidance, and the ability to monitor and discriminate between competing signals of threat and safety. This network is comprised of multiple regions including the ACC, DLPFC, and inferior parietal lobe (iPL) (Dosenbach et al., 2007; Thomas Yeo et al., 2011; Vincent et al., 2008). Previous resting state fMRI work has shown anxiety-related alterations in the connectivity of parietal cortex with prefrontal regions of this network (Liao et al., 2010). There is also some evidence supporting the role of the parietal cortex in avoidance of threat during the dot probe (Grimshaw, Foster, & Corballis, 2014; Pérez-Edgar et al., 2013; Schutter, Putman, Hermans, & van Honk, 2001). Volumetric studies further support a link between parietal function and avoidance in anxiety disorders (Irle, Barke, Lange, & Ruhleder, 2014). Together, these lines of research suggest unique disruptions in the function as well as the connectivity of frontoparietal networks among those showing under- and over-regulation of attention to threat, as well as threat detection and discrimination (Wang et al., 2017).

Clinical Implications

While the link between AB heterogeneity and specific clinical manifestations is the most conjectural part of the TDCM, there are several theoretically-driven predictions and implications for hypothesis generation emerging from TDCM. A small body of prior research suggests that AB towards and away from threat are associated with distinct anxiety symptom profiles, in particular that AB towards threat may be selectively linked to the experience of distress-related

symptoms and disorders (e.g., GAD, depression), whereas AB away from threat may be selectively linked with fear-related anxiety disorders (e.g., phobias; Stirling et al., 2006; Taghavi et al., 2003; Waters et al., 2014; Waters et al., 2012).

Yet, TDCM posits that, along with their contribution to AB heterogeneity, individual differences in TD and CC will likely predict patterns of clinical symptoms that are congruent with subtype of AB, rather than predict discrete diagnoses. Following this reasoning, the vigilant subgroup, associated with intact TD but disrupted CC, might be characterized by symptoms reflecting hyperarousal and difficulty regulating threat responses due to lower levels of CC (e.g., high sympathetic reactivity, poor attention and concentration in response to threat, and subjective feelings of fear and nervousness). The labile subgroup, associated with disruptions in both TD and CC, might be characterized by symptoms reflecting poorly regulated (low CC) and overgeneralized (low TD) fear (e.g., affective instability, intrusion symptoms like unwanted negative thoughts, and broad patterns of cognitive and behavioral dysregulation). The avoidant subgroup, associated with intact TD and CC, might be characterized by symptoms reflecting both sensitivity to threat given faciliated threat detection, but avoidance because CC resources can be marshalled to disengage (e.g., phobic avoidance and obsessive characteristics). Finally, the no bias subgroup, associated with disrupted TD but intact CC, might be characterized by symptoms reflecting autonomic restriction and chronic cognitive avoidance (e.g., worry, muscle tension, difficulty concentrating, and irritability; Borkovec & Hu, 1990; Borkovec et al., 2004). In other words, if TD is compromised, then both signals of threat and non-threat are interpreted as potentially dangerous or uncertain, but intact CC resources are chronically recruited across contexts leading to depletion, similar to some models of GAD (e.g. Borkovec & Hu, 1990;

Borkovec et al., 2004). While these predictions are consistent with TDCM, they remain to be tested and refined.

The TDCM guides hypothesis generation for research examining both mechanisms of AB and the clinical utility of treatments that aim to reduce AB, such as ABMT (Folstein & Van Petten, 2008). For instance, ABMT may be sensitive to changes in threat context which could potentiate or dampen training effects (Shechner, Pelc, et al., 2012). Indeed, there have been increasing attempts to improve upon and develop more effective forms of ABMT, including "adaptive" (Bernstein & Zvielli, 2014), "next generation" (Zvielli, Amir, Goldstein, & Bernstein, 2016), idiographic (Amir, Kuckertz, & Strege, 2016), and gamified (Dennis & O'Toole, 2014) approaches. A small number of studies have examined the efficacy of training attention to a non-biased state by providing real-time adaptive feedback, rather than only training attention away from threat without any tracking of individual level of bias before or during training. Other research has embedded ABMT in more engaging or gamified formats, such as mobile applications (Dennis & O'Toole, 2014; Enock, Hofmann, & McNally, 2014), and web-based approaches. TDCM provides a framework for examining mechanisms underlying AB heterogeneity, with direct implications for future evidence-based personalization of ABMT.

Theoretical and Research Implications

As noted above, the interplay between relatively automatic, valence-sensitive processes like disrupted TD and more deliberative, executive processes like CC has been articulated in several theories of anxiety (e.g., Eysenck et al., 2007), and have been explored in working models of AB (e.g., Heeren et al., 2013; Cisler & Koster, 2010). TDCM, however, is unique in several ways. First, in TDCM, we specifically highlight the interactive contribution of TD and CC to AB. Prior research on AB has neglected learning processes related to anxiety, such as fear and safety

learning, which contribute to TD. TDCM therefore can be used for generating hypotheses regarding the role of these processes and integrate with a significant body of translational research on anxiety (Armony, Servan-Schreiber, Romanski, Cohen, & LeDoux, 1997; Lissek, 2012). Second, TDCM identifies four subtypes of AB documented in the literature but rarely examined as potential expressions of anxiety-related dysregulation of attention to threat. TDCM therefore provides a theoretically- and empirically-informed framework for expanding the conceptualization and measurement of AB. Third, TDCM integrates emerging neuroscience research to explain why AB might be expressed in these heterogenous ways while still reflecting core disruptions in the threat detection and response system.

Cognitive theories have long postulated that anxiety is characterized by anomalies in attention selection that result in the increased processing of threat, and that this disruption directly influences performance on attention competition paradigms like the dot probe that are used to assess AB. Given this rich clinical and empirical literature, we believe attention-level measures like reaction-time based metrics of AB should be retained at this stage in the research, at the least to allow for drawing connections with and building upon past research. However, one potential implication of the model is that empirical findings over time might point to the utility of focusing measurement on individual differences in TD and CC, with no need to consider AB. Because ours is a working model, however, we are not prepared to recommend throwing out the construct of AB before the model is tested, or before the field as a whole can examine whether these individual differences have unique or overlapping clinical predictive power when compared to measures of AB. AB may indeed remain an independent and clinically-meaningful construct (Baker et al., 2019).

Related to this, an assumption of TDCM is that AB is a downstream output of more fundamental and basic processes underlying dysregulated attention to threat. That is, while TD requires recruitment of arguably "higher order" discrimination detection and monitoring processes, it is also anchored in basic fear and safety learning mechanisms that are meaningfully studied at the molecular level in animal models. Meanwhile, the construct of AB is largely conflated with current gold-standard measurement approaches, including reaction time-based metrics derived from tasks such as the dot probe, Posner cuing paradigm, and eye tracking. These measures are indeed downstream from processes that can be measured at the level of brain and basic perception. Yet, a crucial direction for future research is to test the degree to which AB is an output as well as a higher-order input of the threat detection and response system. For example, Basanovic and MacLeod (2017) measured AB when participants were given the attentional goal of either attending towards more negative (vigilance) or more benign (avoidance) emotional stimuli. AB was observed only for the vigilance goal-setting condition, suggesting that AB is embedded in higher-order goal states rather than in the selective execution of these goals.

Moreover, prior theories of affect-biased attention (e.g. Myruski, Bonanno, Gulyayeva, Egan, & Dennis-Tiwary, 2017; Todd, Cunningham, Anderson, & Thompson, 2012) integrate consideration of how attentional biases recursively tune and modulate bottom-up and top-down components of TD and CC. In one model of affect-biased attention as a form of emotion regulation, for example, Todd et al. (2012) argue that AB serves to "pre-tune" sensory systems to favor perception of some affectively salient stimuli over others. In the case of anxiety-related AB, if AB serves to bias perception towards threat-related stimuli, TD could be directly affected or work in concert with AB to create more entrenched patterns of habitual responses to threat

(e.g., arousal, cognitions, and behavior). Indeed, a recent study with adolescents (Baker et al., 2019) examined whether AB, overgeneralized fear, and attention control accounted for unique or interactive variance in anxiety symptoms. They found that avoidant AB combined with impaired attention control and exaggerated fear generalization together predicted greater variance in anxiety symptoms than each variable in isolation. In addition, speaking to the impact of AB on these processes, avoidant AB predicted variability in self-report of overgeneralized fear, and overgeneralized fear was associated with heightened anxiety only among those with self-report of poor attention control. Although the use of self-report measures limits the conclusions that can be drawn from this study, these results highlight the importance of examining mutual interactions among these factors.

Methodological Challenges and Opportunities

Challenges. TDCM faces several conceptual and methodological challenges. Heterogeneity of AB may in part reflect the impact of the specific context in which it is assessed. For example, drawing on both developmental (Buss, 2011) and functional emotion theory (e.g. Campos, Frankel, & Camras, 2004), Shechner, Britton, et al. (2012) describe context-sensitive reactions to threat that signal healthy versus anxious responses. Healthy responses to threat are context sensitive to both the danger level in the environment and whether a cue indicates threat or safety (flexible). This means that in dangerous environments, the individual evidences appropriate vigilance and discriminates well between threat and safety in order to move from the former to the latter. When danger is minimal, degree of vigilance needed is low. Clinically-anxious individuals, while vigilant for present threats are also more likely to show high, context-insensitive levels of AB (Notebaert, Tilbrook, Clarke, & MacLeod, 2017) and vigilance in safe environments – also expressed as overgeneralized fear (Arnaudova et al., 2013; Cha et al., 2014;

Jovanovic, Kazama, Bachevalier, & Davis, 2012; Kong, Monje, Hirsch, & Pollak, 2014; Lissek et al., 2008; Lissek et al., 2014). While the TDCM model of AB explicitly integrates consideration of overgeneralized fear responses and related problems in TD, future research based on the model must examine the degree to which these proposed trait-like patterns of AB heterogeneity may also be sensitive to context- and state-related changes, as well as to individual differences in motivation (Notebaert et al., 2017; Shechner & Bar-Haim, 2016).

A focus on specific stimuli or context of assessment also applies to measurement of TD and CC. For example, AB following fear conditioning is influenced by threat-related context (Shechner, Pelc, et al., 2012), and the nature of stimuli used in fear conditioning influences the measurement of TD, such that perceptually-similar conditioned stimuli facilitate over-generalization (Lissek et al., 2005; Lissek, Rabin, McDowell, et al., 2009). At the same time, TD assessed during discrimination testing paradigms reflects the gradient of discrimination as the clinically-relevant individual difference, even among perceptually-similar stimuli (e.g. Likhtik & Paz, 2015; Lissek et al., 2008). This highlights the importance of assessing TD independently of AB since AB stimuli used to represent threat and non-threat tend to be perceptually similar (e.g., angry and neutral faces).

TDCM cannot yet specify what qualifies as adaptive or healthy levels of CC and TD. For example, the model posits that those anxious individuals evidencing avoidant AB (AB away) will show relatively high or intact levels of both CC and TD. The same, however, might be said of non-anxious individuals who could be considered the "baseline" healthy comparison group in terms of these underlying processes. In research testing this model, it will be important to clarify (a) whether and/or how CC and TD functioning differs between anxious individuals with avoidant AB and non-anxious individuals; and (b) how other key risk factors, such as cognitive

processes (e.g., intolerance of uncertainty), exposure to stress or trauma, or biological abnormalities (e.g., neuroendocrine or neurobiological) differentiate anxious from non-anxious individuals who show similar levels of CC and TD.

Finally, while heterogeneity in AB may be shaped by individual differences in TD and CC, it is difficult to assess this possibility when much of the research reviewed above relies upon measures, such as the dot probe task, that yield AB metrics with poor reliability and high measurement error (Rodebaugh, Scullin, Langer, Dixon, Huppert, et al., 2016). While some studies show that reaction times show acceptable split-half and test-retest reliability, bias scores calculated as reaction time differences between threat and non-threat cueing conditions yield reliability coefficients near zero (Brown et al., 2014a). In a review, Schmukle (2005) further showed that the dot probe in anxious adults using both images and words showed poor internal consistency and poor test-retest reliability, as have other studies with the dot probe task (Kappenman, Farrens, et al., 2014; Staugaard, 2009). In a study of non-anxious children, the dot probe was administered three times over a two week period and showed close to zero reliability across the three measurement points (Brown et al., 2014a). A lack of stability in AB was also reported in a study of 12 healthy adolescents who completed the dot probe during two fMRI scans approximately 3 months apart (Brown et al., 2013).

It is unclear whether this poor reliability is inherent in the dot probe task, and/or reflects the impact of context sensitivity on reaction time-based measurement approaches making it difficult to identify stable individual differences (Brown et al., 2014b; Price et al., 2015; Rodebaugh, Scullin, Langer, Dixon, Juppert, et al., 2016; Roy et al., 2015; Schmukle, 2005; Weierich, Treat, & Hollingworth, 2008a; Zvielli, Bernstein, & Koster, 2014b; Zvielli et al., 2014c). Because sources of unreliability in difference scores include individual measurement error and high

collinearity between measures used to calculate the difference score, current work suggests that reliability may be improved through minimization of these factors, such as through the use of idiographic stimuli that are personally-relevant to the individual (Amir et al., 2016) or through alternative statistical modeling (Roy et al., 2015).

One challenge impacting further examination of TDCM is that, despite preliminary methodological progress in attempts to capture the dynamic quality of AB through trial-level metrics (e.g. Egan & Dennis-Tiwary, 2018; Zvielli et al., 2015), these measure have significant limitations. For example, variability scores themselves are calculated as average scores, or difference scores from averages across trials. Moreover, this analytic approach fails to consider the temporal sequence in which variability is expressed, such as patterns of change over time that time series analyses would capture. In a study using simulations, Kruijt, Field, and Fox (2016) found that group differences in variability metrics derived from RT-based measures can occur even in the absence of an identified AB.

Taken together, the field is ripe for methodological and analytic innovations that address issues of assessment context, measurement reliability, and clinical benchmarks for adaptive versus maladaptive AB.

Opportunities. Several methodological "best practices" are becoming apparent in the field, and will be needed to identify the proposed heterogeneity outlined by TDCM. First, given the methodological concerns about current trial-level scoring methods such as TLBS (e.g. Egan & Dennis-Tiwary, 2018; Zvielli et al., 2015), there is an opportunity to import trial-level metrics used in other areas of study, such as neural "quenching" during perceptual processing. Neural quenching, which reflects the dampening of neural variability following stimulus presentation,

may offer innovative new methods for tracking trial-level individual differences relevant to dysregulated attention to threat in anxiety (Arazi, Gonen—Yaacovi, & Dinstein, 2017).

It will also be crucial to expand analytic approaches to characterizing AB. Recent work suggests that computational modeling holds promise for improved characterization of attentional biases in anxious individuals (Raymond, Steele, & Seriès, 2017; White, Ratcliff, Vasey, & McKoon, 2010a; White, Skokin, Carlos, & Weaver, 2016). Tools based in decision theory, such as sequential sample modeling, and specifically the drift-diffusion model (DDM), are designed to apply to two-choice decision tasks with RTs under 1- 1.5 seconds (e.g. White, Ratcliff, Vasey, & McKoon, 2010b), and thus, are ideally suited to dot probe and eye tracking data. DDM improves upon traditional analyses focused on RT and accuracy by incorporating both variables, resulting in quantification of multiple, independent components including response bias, non-decision time, and stimulus evidence. Previous work supports the utility of DDM to identify threat-related AB in high anxiety participants and suggests that this modeling approach has greater power to assess these biases than traditional methods (Price, Brown, & Siegle, 2018; White et al., 2010a; White et al., 2016). In addition to characterizing and measuring AB, machine learning techniques are increasingly being used to identify biobehavioral profiles that predict treatment response and clinical severity and phenotype (e.g. Reggente et al., 2018).

Given concerns about reaction time-based measures highlighted above, an increasing number of studies have shifted to eye-tracking methods to assess AB (Armstrong & Olatunji, 2012), with four primary advantages. First, eye-tracking provides a relatively direct measure of overt visual attention and has more proximity to attention than manual reaction-time assays. Second, eye movements are less susceptible to confounds, such as overall response slowing typically caused by threatening stimuli (McNaughton & Corr, 2004; Nummenmaa, Hyönä, & Calvo, 2006).

Third, eye-tracking measures of AB are correlated with anxiety symptoms even when associations with reaction-time are absent (e.g. Stevens, Rist, & Gerlach, 2011). Finally, eye movements can be tracked continuously during stimulus presentation (Armstrong et al., 2010) allowing a dynamic assessment of attention to threat. Eye-tracking studies have successfully documented AB towards threat as reflected in increased vigilance and dwell-time on threat relative to neutral stimuli among anxious youth (Gamble & Rapee, 2009).

While use of eye-tracking allows for careful examination of the timescale of attentional vigilance and avoidance in anxious individuals, the utility of eye tracking in distinguishing between engagement and disengagement of attention remains dependent on the assessment task (Clarke et al., 2011) and may fail to yield metrics that converge with reaction-time based AB measures. In youth, there is significant phenotypic diversity in expressions of AB depending on measurement type (Gamble & Rapee, 2009; In-Albon, Kossowsky, & Schneider, 2010; Price et al., 2013; Shechner, Britton, et al., 2012). For example, Price et al. (2013) found that both anxious and non-anxious groups showed a bias away from threat assessed based on eye movements but no bias using traditional reaction time measures. According to TDCM, this apparent lack of convergence may actually reflect AB heterogeneity or dynamic variability that additional measures of CC and TD could clarify. Therefore, methodological advantages afforded by eye tracking will be strengthened through the use of rigorous assessments and multiple measures.

Behavioral assessments (i.e., reaction times or eye movements) of AB are valuable as low-cost and clinically-relevant measures of AB, but cannot reveal the full-time course of neural responses to threat from relatively automatic detection to later, more deliberative engagement and disengagement (Roy et al., 2015). Neural assays, such as ERPs, may be among the most

important methods for the next era of AB research. ERPs have the advantage of being sensitive to the full "cascade" of cognitive responses to threat, as well as specific brain activities underlying that response (Shechner, Britton, et al., 2012). With millisecond precision, ERPs reflect multiple and discrete neurocognitive responses to threat stimuli (Dennis-Tiwary et al., 2016; Eldar & Bar-Haim, 2010; O'Toole & Dennis, 2012), and ERPs show greater internal reliability and predictive power in comparison to reaction time measures of AB (Dennis-Tiwary, Denefrio, & Gelber, 2017; Eldar & Bar-Haim, 2010; Kappenman, Farrens, et al., 2014).

Summary

Drawing on clinical, neuroscience, and animal models of anxiety, we propose TDCM, a working model of clinically-relevant AB heterogeneity. We argue that this model has the potential to integrate the broader literature on cognitive disruptions in anxiety, strengthen the conceptualization, measurement, and modification of AB, and provide a meaningful framework for interpreting existing findings and generating hypotheses for future studies. Initial enthusiasm for AB (e.g. Hakamata et al., 2010), and a broader scientific shift towards the development of targeted interventions focused on core psychopathological processes (e.g. Kapur, Phillips, & Insel, 2012; Wittchen, Höfler, & Merikangas, 1999) has been tempered by the realities of mixed and null clinical trials for ABMT (Clarke et al., 2014) and by evidence for AB heterogeneity (e.g. Koster, Crombez, Verschuere, Van Damme, & Wiersema, 2006; Monk et al., 2006; Salum et al., 2013). Yet, we believe that these apparent road blocks actually reflect the field's entry into a stage of maturity and opportunity (Roy et al., 2015), in which innovative new approaches and emerging technologies and methodologies will allow researchers and practitioners to push the boundaries of past research and move towards greater understanding of AB and its role in the development of targeted and personalized treatment approaches.

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