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Novel Biobehavioral Methods for Assessing the Anxiety-Related Attention Bias

Samantha Denefrio

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NOVEL BIOBEHAVIORAL METHODS FOR ASSESSING THE ANXIETY-RELATED ATTENTION BIAS

by

SAMANTHA DENEFRIO

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in partial fulfillment of the requirements for the degree of
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2019
Novel biobehavioral methods for assessing the anxiety-related attention bias

by

Samantha Denefrio

This manuscript has been read and accepted for the Graduate Faculty in Psychology in satisfaction of the dissertation requirement for the degree of Doctor of Philosophy.

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ABSTRACT

Novel Biobehavioral Methods for Assessing the Anxiety-Related Attention Bias

by

Samantha Denefrio

Advisor: Tracy A. Dennis-Tiwary

Anxiety disorders will affect an estimated one in three Americans, significantly impacting emotional health and quality of life. High personal and economic costs make research on the etiology, maintenance, and treatment of anxiety a crucial public health goal. Selective and exaggerated attention towards threat, termed attention bias (AB), has been identified as a core behavioral and neurocognitive mechanism in anxiety. A novel treatment, attention bias modification training (ABMT), targets AB and aims to ameliorate anxiety. Rarely acknowledged, however, are the challenges in the conceptualization and measurement of AB. First, associations between anxiety and AB in anxious populations have been increasingly inconsistent. Second, traditional measurement relies on mean reaction times providing a static snapshot of attention. This ignores temporal variability in AB that may more accurately represent the dynamic nature of AB in anxiety and be a more informative measure of treatment-relevant individual differences. The goal of this study was to use innovative methods to identify pre-training individual differences that predict ABMT response. To do so, the current dissertation used temporally-sensitive behavioral (trial-level reaction times) and neurocognitive (event-related potentials; ERPs) metrics to measure AB in a clinically-anxious sample ($N = 93$) within the context of a larger ABMT randomized clinical trial (RCT). AB was assessed while EEG was simultaneously recorded in addition to anxiety and stress reactivity before and after one month of either ABMT or placebo training (PT). Furthermore, we measured training performance to track gains or losses during ABMT or PT. We hypothesized that ABMT would reduce AB and anxiety-related outcomes relative to PT and that pre-training individual differences in
temporally-sensitive metrics would predict ABMT outcomes above and beyond traditional AB. Overall, we found that contrary to predictions, ABMT and PT both led to improvements in training performance and stress reactivity. Consistent with predictions, individual differences in ERPs and TL-BS measured prior to training moderated the relationship between ABMT and clinical outcomes. Mean AB scores did not. Greater AB variability resulted in ABMT performance gains whereas an increase in AB resulted in higher anxiety following ABMT. In addition, larger pre-training P1 amplitudes (an ERP reflecting visual attention to threat) resulted in higher anxiety post-ABMT and an increase in N2 amplitudes (an ERP indexing cognitive control) was associated with lower post-ABMT anxiety but higher stress reactivity. Thus, results show that novel AB metrics revealed pre-training differences that were associated with better ABMT training performance and reduced anxiety. Current findings have the potential to advance the development of conceptually-sound behavioral and neurocognitive measures of AB. Such results can aid in the improvement of ABMT efficacy by identifying individual differences that predict for whom attention modification may be most beneficial. Implications for expanding measurement of AB and personalization of ABMT are discussed.

*Keywords:* Anxiety, AB, ABMT, ERPs, temporal dynamics, individual differences
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Novel biobehavioral methods for assessing the anxiety-related attention bias

One third of Americans will suffer from clinical levels of anxiety during their lifetime making anxiety and stress-related disorders the most common forms of mental illness and among the largest health burdens in society (Kessler et al., 2005). Anxiety significantly and negatively impacts quality of life, occupational productivity, and psychosocial functioning even at sub-clinical levels (Mendlowicz & Stein, 2014; Roy-Byrne et al., 2008) and ~ 42.3 billion insurance dollars are spent each year on its treatment (Kessler et al., 2009). Despite these personal and economic costs, rates of quality care using a combination of cognitive behavioral therapy (CBT) and pharmacological treatments are low (Stein et al., 2005) and symptom recurrence remains high with as many as 60% of patients symptomatic after one year (Olatunji, Cisler, & Tolin, 2007; Westen, Novotny, & Thompson-Brenner, 2004). Hence, additional research on targeted mechanisms that underscore anxiety disorders, and their relevance for the development and refinement of new treatment approaches is a crucial scientific and public health goal.

A promising new line of research has shown that a range of cognitive biases are associated with the etiology and maintenance of anxiety, and may be effectively targeted by interventions (Olatunji, Cisler, & Deacon, 2010). The anxiety-related attention bias (AB), characterized by selective and exaggerated attention towards threat, is among the most studied of these cognitive biases (Bar-Haim, Lamy, Pergamin, Bakermans-Kranenburg, & Van Ijzendoorn, 2007; Cisler & Koster, 2010). AB acts as an information filter that selects threat-relevant information at the expense of signals indicating positive outcomes or safety. This bias is thought to cause a cascade of cognitive, affective, and biological changes that give rise to and maintain symptoms of anxiety. For example, an exaggerated focus on threat disrupts attention available for other uses and interferes with productivity.
Early data from previous decades of research, using both behavioral and neurocognitive measures, has shown that anxious individuals show exaggerated AB measured as facilitated attention to threat via reaction-time based tasks in which threat and neutral cues compete for attention (MacLeod & Mathews, 1988; MacLeod, Mathews, & Tata, 1986). In fact, initial support for the correlation between anxiety and AB was so convincing that Bar-Haim and colleagues (2007) concluded that AB is a “robust phenomenon” in anxious populations and that only “diminishing returns could be expected from future studies that only focus on establishing the presence of a threat-related bias.”

Attention bias modification training (ABMT) is a novel treatment approach that aims to directly reduce AB, with the downstream effect of alleviating anxiety-related symptoms (Beard, Sawyer, & Hofmann, 2012; Hakamata et al., 2010; Hallion & Ruscio, 2011; MacLeod, Rutherford, Campbell, Ebsworthy, & Holker, 2002; Mogoase, David, & Koster, 2014). ABMT techniques create response demands that serve to shift the focus of attention away from threat and towards neutral or positive stimuli over many trials. There has been significant enthusiasm for ABMT as a novel intervention approach because it is both cost-effective and accessible with the potential to serve as adjunctive or stand-alone treatment to complement current treatment approaches.

However, initial excitement for the construct of AB and the clinical potential of ABMT has been tempered by a growing number of randomized ABMT clinical trials with null findings and placebo effects (Chen, Ehlers, Clark, & Mansell, 2002; Cisler & Koster, 2010; Fitzgerald, Rawdon, & Dooley, 2016; Mansell, Clark, Ehlers, & Chen, 1999; Morales, Pérez-Edgar, & Buss, 2014), which researchers have argued may be linked to several challenges in conceptualization and measurement of AB (Kappenman, Farrens, Luck, & Proudfit, 2014; Waechter, Nelson, Wright, Hyatt, & Oakman, 2014). First, growing documentation of heterogeneity in direction of
AB towards and away (avoidance) from threat has led some researchers to suggest that AB variability, or dynamic shifts in individual AB over time, are more clinically-relevant measures of AB and ABMT efficacy (Iacoviello et al., 2014; Zvielli, Bernstein, & Koster, 2014b). Second, the focus on AB variability coincides with increasing documentation that reaction-time-based measures of AB, which are averaged across trials before being computed as difference scores, not only fail to capture AB variability but also show poor psychometric properties. Third, given the neglect of temporal dynamics in studies of AB, relatively little research has capitalized on the use of neurophysiological tools with high temporal resolution, such as scalp-recorded event-related potentials (ERPs; Bar-Haim, Lamy, & Glickman, 2005; Dennis & O’Toole, 2014; Dennis-Tiwary, Denefrio, & Gelber, 2017; Dennis-Tiwary, Egan, Babkirk, & Denefrio, 2016; Eldar & Bar-Haim, 2010), which early studies suggest may also show superior measurement reliability compared to RTs (Kappenman et al., 2014).

The goal of the present dissertation was to use multiple, converging biobehavioral and temporally-sensitive measures of AB in the context of a large-scale, randomized clinical trial of ABMT with anxious adults. We tested the hypotheses that a) ABMT will modify temporally-sensitive measures of AB (AB variability and ERPs) more than mean AB scores and b) explored whether individual differences in these temporally-sensitive measures of AB at baseline influence anxiety-related ABMT outcomes (subjective anxiety and stress reactivity). We further explored the correspondence between behavioral and neurocognitive temporally-sensitive measures of AB, which is largely unknown. Thus, this dissertation aimed to advance development of psychometrically and clinically-relevant measures of AB and its variability. Findings have the potential to inform understanding of the temporal nature of AB and to refine interventions that directly target AB.
Theories of Anxiety Informing the Study of AB

_Cognitive Models._ Several foundational cognitive theories of anxiety have directly informed the conceptualization and measurement of AB. AB is considered an output of the threat detection and response system (MacLeod & Mathews, 1988). When faced with threat, the resulting fear and anxiety engages the sympathetic nervous system (SNS) and is accompanied by a set of physiological changes (e.g., increased blood flow to the brain, heart, and lungs) that prepare the body to respond to an emergency, allowing for a quick escape (Kreibig, 2010; LeDoux, 1995; Seligman, 1971; T Gross & Canteras, 2012) and increases the chances for survival. Therefore, from an evolutionary perspective, rapid and automatic detection of threat in the environment followed by sustained focus on the source of danger are highly adaptive attentional processes. However, humans do not only experience brief and context-appropriate fear and anxiety. Instead, anxiety can be elicited by aversive thoughts or unfounded expectations of danger in the absence of real threat (Levenson, 2014). Moreover, chronic and debilitating anxiety is associated with significant biological load, including sustained activity of the SNS, and accompanied by frequent uncomfortable and unwanted physical and cognitive symptoms such as sweating, rapid heart rate, and difficulty concentrating (Beck & Clark, 1988; Clark, 1986; Dieleman et al., 2015; Hoehn-Saric & McLeod, 1988; Mcewen, 2004). Thus, to understand how to combat the detrimental effects of inappropriate fear and anxiety, we must take a closer look at how attention is captured by and regulated to threat.

Attention can be defined as “any cognitive operation that results in the selection of some information over other information” (Weierich, Treat, & Hollingworth, 2008) and AB is the selection of threat. One aspect of threat selection is thought to reflect “bottom-up” processes that are relatively automatic and involuntary (Gray, 1978; McNaughton & Gray, 2000; Todd,
Cunningham, Anderson, & Thompson, 2012; Vuilleumier & Pourtois, 2007; White, Helfinstein, Reeb-Sutherland, Degnan, & Fox, 2009) aiding in prompt recognition of real or potential threat when time is of the essence (LeDoux, 2012; LeDoux, 2014; LeDoux & Hofmann, 2018). A second aspect of attention to threat is the top-down regulation of these initial responses that operate at a conscious level and are under the influence of the individual’s goals and motivations. This dual-processes perspective on attention suggests that these two sets of processes serve as and checks and balance system with bottom-up mechanisms maximizing costly physical resources when needed most and top-down mechanisms attenuating the threat response and limiting detrimental effects (Johansen, Cain, Ostroff, & LeDoux, 2011).

Several foundational cognitive theories of anxiety have informed the construct of anxiety-related AB (Beck & Clark, 1997; Eysenck, Derakshan, Santos, & Calvo, 2007; Mathews, Mackintosh, & Fulcher, 1997; Matthews & Mackintosh, 1998; Mogg & Bradley, 1998). These theories suggest that the difference between normal and pathological anxiety is not the existence of threat detection, but whether threat detection is chronically exaggerated, context inappropriate, and associated with individual maladaptive outcomes. Furthermore, they emphasize the role of dysregulated attention to and processing of threat at both bottom-up and top-down levels, thus laying the groundwork for conceptualizing AB as a temporally-sensitive cognitive mechanism. Below I review five models that discuss how anxiety impacts multiple stages of attention to threat and highlight their common focus on the temporally unfolding and dynamic nature of disrupted attention to threat in anxiety.

First, the Evaluative Map Network (EMNET) is a model put forth by Mathews, Mackintosh, & Fulcher (Mathews et al., 1997) that proposes an automatic system within each individual to evaluate all inputs and assign meaning, determine significance, and make associations with previous stimuli. This evaluation system is influenced by anxiety such that
stimuli with negative evaluations are assigned a greater meaning and result in biased attention (Fulcher, 1995). The EMNET model makes the important assumption that in order to see measurable differences in attention tasks between anxious and non-anxious individuals, indirect competition between neutral but task-relevant and threatening distractors (task-irrelevant) stimuli must be present such that distractors need to be ignored to respond accurately. For anxious individuals, attention to emotional distractors cannot be inhibited thus causing delays in response time and reduced performance. This idea of competing threat and neutral stimuli has become essential to the concept and measurement of AB and is the main design feature of the most-widely used AB assay, the dot probe in which threat and neutral cues appear simultaneously (MacLeod et al., 1986).

Second, the Threat Evaluation System (TES; Matthews & Mackintosh, 1998) model builds on the bottom-up perspective of the EMNET model. When threat and neutral stimuli occur simultaneously, both compete for attention and a choice must be made. Rather than being processed in parallel, one is prioritized over the other requiring a combination of bottom-up and top-down elements of responding (N. Amir et al., 1996; Broadbent & Broadbent, 1988). In the presence of real danger, this choice should be threat. However, in anxiety, the TES assigns heightened meaning to any internal or external threat. Specifically, anxiety lowers the threshold of the TES and therefore increases the likelihood that less threatening and innocuous stimuli will be negatively evaluated. In contrast, the TES for low trait-anxious individuals will only respond strongly to clear and substantial danger cues. Increased early activation present in anxiety can be inhibited by later stages of conscious and goal-directed efforts and the two influences of bottom-up and top-down processes ultimately determine attention selection and resource allocation (Mathews, Yiend, & Lawrence, 2004). Thus, non-anxious individuals can reduce the impact of initial exaggerated evaluation by recruiting goal-directed cognitive control.
Third, Beck and Clark’s (1997) three-step model of information processing in anxiety outlines three discrete stages: 1) threat registration 2) activation of threat response and 3) strategic evaluation of threat. Extending from Beck’s previous work (Beck, 1985), they propose that cognitive processing of threat at each stage is temporally dynamic, such that individuals shift back and forth from automatic to strategic stages. The first stage consists of entirely automatic and subliminal orientation to threat. Anxious individuals are primed to view negative information as relevant. The second involves a mix of stimulus-driven automaticity as well as early stages of interpretation of and responding to threat. This stage demands cognitive resources and constricts an individual’s view towards only negative information. The goal is to minimize danger by locating safety. In anxiety, this stage is thought to be rigid and constricted, focused on escape from threat and prohibiting a broader perspective (Beck, 2005). Lastly, the third stage is defined as the slow and effortful evaluation of the present threat in relation to one’s goals and motivations. In this stage, the anxious individual has difficulty identifying and engaging coping mechanisms. Instead, clinical anxiety is characterized by a tendency to avoid elaborative threat processing. Based on this model, anxiety can be treated by targeting both bottom-up and top-down stages.

Fourth, Mogg and Bradley’s (1998) cognitive-motivational model of attention to threat consists of two components (Garner, Mogg, & Bradley, 2006; Mogg & Bradley, 1999, 2002; Mogg, Bradley, De Bono, & Painter, 1997). Similar to the TES, the first component is a valence evaluation stage that involves the assigning of threat value to available stimuli. Anxiety vulnerability is the result of a bottom-up, reduced threshold for threat, not biased threat selection. In other words, subjective interpretation of stimuli favors threat over neutral in high anxious individuals and this leads to negative emotions even from mild stress events. The second component is a goal engagement stage in which attention allocation to the stimulus is enhanced.
because attending to threat is important and necessary for maintaining one’s safety. Therefore, attention allocation is driven by the motivation to stay safe and avoid danger. This is different for anxious and non-anxious individuals. In anxiety, motivation to attend to any degree of threat - mild or severe - is greater. Thus, the motivational system then has influence over earlier threat detection. Following this line of thought, treatment for anxiety should not target the low threshold for threat which may be acting outside of awareness but instead focus on the motivation system dictating the evaluation and appraisal of threat.

Lastly, attention control theory (ACT; (Derakshan, Smyth, & Eysenck, 2009; Eysenck & Derakshan, 2011; Eysenck et al., 2007) is a dual-system model proposing that anxiety disrupts two aspects of attention control: bottom-up attention inhibition and top-down attention shifting, which is the ability to direct attention towards and away from competing stimuli as needed. In high levels of trait anxiety, bottom-up attention shifting mechanisms are dominant as evidenced through faster threat detection and top-down control mechanisms of inhibition are weaker evidenced by difficulty disengaging from threat. The ACT proposes a more general theory for how anxiety differentially effects bottom-up and top-down attention systems not limited to threat stimuli. It expands on the previously discussed threat-specific models by delineating the ways in which anxiety places broad demands on available cognitive resources (Eysenck & Calvo, 1992). For example, worry, a cardinal symptom of anxiety, impacts cognitive efficiency by occupying working memory capacity. Then, compensatory mechanisms are recruited to reduce the predominate worry, further straining the system.

**Neurocognitive Models.** Models using the tools of cognitive neuroscience lend support to an integrative model of anxiety-related attention emphasizing both bottom-up attention selection and top-down cognitive control processes. These models provide anatomical locations for both sets of processes, emphasizing amygdala-cortical circuits and documenting a range of
temporally- and functionally-specific disruptions associated with exaggerated attention to threat.

Rodent studies have repeatedly implicated the amygdala located in the medial temporal lobe as a key location of rapid and initial threat detection. Indeed, visual representations of threat move immediately from the retina, to the thalamus, and then amygdala (LeDoux, Iwata, Cicchetti, & Reis, 1988; Phelps & LeDoux, 2005). Later stages involve projections from the amygdala to cortical regions for effortful and extended threat processing. Lang, Davis, & Ohman (2000) reviewed animal models of anxiety, highlighting the foundational role of reflexive and automatic motivational systems in both animals and humans. When faced with unpleasant stimuli, animals and humans alike experience a defensive response that drives withdrawal. For decades, basic animal neuroscience work on the neurobiology of fear have used fear conditioning principles that pair electric shock with an innocuous event to study the startle response following repeated exposure to and anticipation of pain to study fear, anxiety, and withdrawal (Carlsson et al., 2004). When applied directly to the amygdala, electric stimulation induces a state of fear (Davis & Whalen, 2001) providing neuroanatomical evidence for initial threat processing.

Later stages of threat processing extend to other regions of the brain outside of the amygdala, providing a network of structures to target when studying biased attention in anxiety. One additional structure that has been frequently studied in rodent models, the bed nucleus of the stria terminalis (BST) which receives direct projections from the central nucleus of the amygdala, is involved in more enduring and sustained responses to threat most similar to human anxiety and may serve to moderate the startle response (Walker & Davis, 1997). The central nucleus of the amygdala and the BST are tightly connected and responsible for moment to moment monitoring of threat and eliciting fear (Shackman & Fox, 2016). Next, secondary regions of interest are the anterior cingulate cortex (ACC) and the prefrontal cortex (PFC). Studies on nonhuman primates using neuronal tracing techniques have verified anatomical
bidirectional connections between the amygdala and the ACC (Ray & Zald, 2012). Both areas receive and send projections to the amygdala, thus suggesting a physical representation of how attention to threat is captured, prioritized, and modulated through communication of top-down and bottom-up systems (Davidson, 2002; Prater, Hosanagar, Klump, Angstadt, & Luan Phan, 2013).

Bishop’s neurocognitive model of anxiety-related biased selective attention (2007) extends from rodent and primate models and proposes a discrete neuroanatomical framework for systematically testing the involvement of both bottom-up and top-down attentional mechanisms in anxiety. The model is based on previous human imaging studies (Bishop, Duncan, Brett, & Lawrence, 2004a; Bishop, 2004) and identifies three brain regions of interest that underlie threat monitoring: the amygdala, which is associated with initial signaling of danger, the ACC, and the lateral prefrontal cortex (LPFC), both of which are associated with top-down mechanisms of conflict monitoring, decision-making, and attention control. When threat and neutral stimuli compete for available attention, bottom-up and top-down processes must coordinate the strength of the initial threat detection signal sent from the amygdala with the subsequent recruitment of attention control via the LPFC and ACC. Anxiety is thought to affect both processes in conflicting ways by heightening amygdala activation in the presence of threat and dampening the response of the LPFC and ACC (Bishop, 2009).

Consistent with this model, one study (Bishop, Duncan, Brett, & Lawrence, 2004b) asked participants to determine if two pictures of houses simultaneously presented were identical. Trials were delivered in a block design with one block using a random presentation of threatening faces as distractors alternating with neutral face distractors and the second block with frequent threat face distractors. In low levels of anxiety, recruitment of the LPFC was enhanced when threat distractors were present and the ACC when threat distractors were unpredictable. As
anxiety increased, broad reductions in both the ACC and LPFC activation were seen. These findings support the association between anxiety and reduced attention control to threat and provide neural substrates for evaluating experimental findings of selective attention to threat.

**Summary.** Taken together, cognitive theories of anxiety and neurocognitive models of anxiety-related attention suggest two key criteria for studying disrupted attention in anxiety. First, anxiety-related attention disruptions are best measured when threat and neutral stimuli compete for attention. In other words, for attention to be biased to threat then the individual must preferentially attend to and select threat over an innocuous alternative in the absence of any explicit direction and even if that threat is task-irrelevant. Second, threat detection is not a static process limited to one pattern of attention. Rather, attention to threat is a temporally-dynamic process involving multiple stages of attention and should be conceptualized and measured in ways that capture the broad time course of threat processing including bottom-up, more automatic selection of threat and later, more deliberative attention control. As discussed below, the construct of AB in particular has capitalized on creating and measuring biased attention when threat and neutral stimuli compete, but current measurement and conceptualization has not carefully delineated the dynamic time course of attention to threat.

**The Anxiety-Related Attention Bias (AB)**

Emerging from these foundational theories of anxiety-related attention and cognition, the construct of AB has been a focus of hundreds of empirical studies (Bar-Haim et al., 2007; MacLeod & Mathews, 1988; Mathews et al., 1997; Mogg, Mathews, & Eysenck, 1992; Pergamin-Hight, Naim, Bakermans-Kranenburg, van IJzendoorn, & Bar-Haim, 2015). AB, defined as selective and exaggerated attention to threat, is thought to cause and exacerbate anxiety by reducing the threshold for detection and processing of threat and by favoring threat at
the expense of reward or positive stimuli even when that threat is mild or irrelevant (Okon-Singer, 2018). As reviewed above in cognitive theories of anxiety, this preferential selection of threat creates a chronic state of anxious arousal that top-down goal-directed mechanisms fail to reduce and in turn exacerbates anxiety. In a lab setting, when threat and neutral-themed stimuli appear simultaneously, individuals high in anxiety (both clinical and sub-clinical) are faster to respond to a target that appears in the location of threat (MacLeod & Mathews, 1988; Wilson & MacLeod, 2003). As anxious arousal is increased, available cognitive resources are taxed, and the individual is primed towards feelings of uncertainty and fear creating a vicious cycle (Bar-Haim, 2010). Indeed, AB cuts across many variants of anxious pathology. The presence of AB has been measured across the full spectrum of anxiety diagnoses in adults and children (i.e. GAD, OCD, social phobia) and sub-clinical anxiety at an equal magnitude (see e.g. Amir, Beard, Burns, & Bomyea, 2009; Amir, Taylor, & Donohue, 2011; Bar-Haim et al., 2007; Fox, Russo, Bowles, & Dutton, 2001; Gilboa-Schechtman, Foa, & Amir, 1999; Mansell, Ehlers, Clark, & Yi-Ping Chen, 2002; Morales, Pérez-Edgar, & Buss, 2014; Yiend, 2010) making AB a candidate biological signature of and risk factor for anxiety.

The first published paper to use a novel version of the dot probe task with threat and neutral cues appearing simultaneously and competing for attention to measure AB showed that high anxious individuals showed facilitated reaction times to probes replacing the threat cues suggesting that attention was previously located on the threat image (MacLeod et al., 1986). This facilitation to threat was not seen in the low anxious control group. They concluded that anxious relative to non-anxious individuals direct attention to mild threat cues relative to neutral cues. Since then, results have been robust and far-reaching showing that both clinical and trait-anxious individuals selectively attend to threat in the environment and that this selection is particularly
enhanced in threat contexts (MacLeod & Mathews, 1988; Mogg et al., 1992; Williams, Mathews, & MacLeod, 1996).

A seminal meta-analysis (Bar-Haim et al., 2007) including 172 studies and covering over 2,000 anxious individuals found a moderate effect size (Cohen’s $d = 0.45$) for AB in anxiety and the absence of AB in non-anxious individuals. Similar subsequent meta-analyses showed moderate to large effect sizes for evidence of AB within groups of anxious individuals and across various conditions when compared to non-anxious control participants (Beard et al., 2012; Hakamata et al., 2010). Across these early studies, AB in anxiety has been reliably demonstrated with a series of task parameters (see Bar-Haim et al., 2007). First, AB has been well-documented using multiple reaction-time based tasks such as the dot probe task, emotion Stroop paradigm and visual search tasks (MacLeod & Mathews, 1988; Palmer, Ames, & Lindsey, 1993; Williams et al., 1996; Woodman & Luck, 1999). Second, AB is measured at an equal magnitude using both subliminal stimulus presentation in which threat faces or words are masked and supraliminal stimulus exposures that are above the level of conscious detection (Mogg & Bradley, 1999; Mogg, Bradley, & Williams, 1995). This finding suggests that AB occurs at automatic stages of attention. Third, measurement of AB has been successful using a variety of threat stimuli including words, faces, and images (Gilboa-Schechtman et al., 1999; Mansell et al., 2002; Pishyar, Harris, & Menzies, 2004). As a result of these collective findings, Bar Haim and colleagues put forth a multi-stage model the outlines the contributing role of AB in anxiety: Threat evaluation is followed by physiological arousal and cognitive resource allocation. AB can be the result of a disruption at any single stage causing sustained and heightened attention to threat and leading to feelings of anxiety (Bar-Haim, 2010).

In addition to the range of anxiety subtypes and the variety of conditions in which AB has been measured, neuroimaging research has revealed an important temporal component to AB.
Multiple and pervasive temporal disruptions in attention can be tracked at all stages of threat processing from initial capture (MacLeod & Mathews, 1988; Palmer, Ames, & Lindsey, 1993; Williams, Mathews, & MacLeod, 1996; Wilson & MacLeod, 2003; Woodman & Luck, 1999) to sustained engagement with threat, difficulty disengaging from threat (Fox, Russo, Bowles, & Dutton, 2001b; Fox, Russo, & Dutton, 2002) and avoidance (Heuer, Rinck, & Becker, 2007; Wald et al., 2011; Weinberg & Hajcak, 2011). Human imaging studies have supported temporal alterations, pointing to initial activation of the amygdala being associated with both behavioral AB and anxiety. Research in adults has shown a heightened amygdala activity and startle response in clinically-anxious populations (M. Davis, 2006). Developmental studies have paralleled these findings by showing that amygdala lesions disrupt emotional memory and learning (Blackford & Pine, 2012). Specific to AB studies, threat and fearful faces increase activation of the visual cortex and amygdala (Pessoa, Kastner, & Ungerleider, 2002; Pourtois, Schwartz, Seghier, Lazeyras, & Vuilleumier, 2006) signaling enhanced threat processing.

As noted above, AB is associated with alterations in cortical-amygdala neural networks showing early amygdala hyperactivity and a later reduced efficiency of the prefrontal cortex in dampening amygdala activation (Hardee et al., 2013) implicating the role of later cognitive control processes. Indeed, heightened activity of cortical regions has been associated with reduced activity in the amygdala (For review see Pine, Helfinstein, Bar-Haim, Nelson, & Fox, 2009). These correlations were stronger in non-anxious controls relative to anxious individuals suggesting both that the role of the prefrontal cortex and related structures is to modulate amygdala response and that this modulation is disrupted in anxiety. For example, Carlsson et al. (2004) used positron emission tomography (PET) imaging to show that although both phobic individuals and healthy controls showed increased amygdala activation in response to fear-relevant stimuli, only healthy controls showed a subsequent dampening of amygdala response.
coupled with a recruitment of executive control regions. Using fMRI during emotional Stroop task, Etkin and colleagues have shown that emotional conflict is resolved via ACC dampening of amygdala activation and that patients with clinical anxiety fail to recruit the ACC to the same degree as healthy controls (Etkin, Egner, Peraza, Kandel, & Hirsch, 2006; Etkin, Prater, Hoeft, Menon, & Schatzberg, 2010). When attention to threat is targeted by treatments such as ABMT and AB is effectively reduced, heightened PFC activity has been documented (Beard et al., 2012; Browning, Holmes, & Harmer, 2010; Browning, Holmes, Murphy, Goodwin, & Harmer, 2010; Taylor et al., 2014). Together, results suggest that the pathological brain response associated with anxiety is a reduction of cognitive control and a decreased ability to limit enhanced threat processing, highlighting the temporal dysregulation associated with AB and the interplay of bottom-up and top-down systems.

Taken together, research using neuroimaging techniques such as fMRI has aided in identifying the regions of the brain underlying AB and may provide more reliable measure of anxiety-related AB than RT-based measures (e.g. White et al., 2016). However, although fMRI has excellent spatial resolution, it lacks any reliable degree of temporal specificity and current standards have only begun to factor temporal characteristics into AB evaluation and measurement.

**Event-Related Potentials and the Measurement of AB**

At a time when methods used to measure AB have been challenged, the careful investigation of multiple AB metrics and the degree of convergence among these measures is not only warranted but crucial. Thus, a pivotal next step is to expand the tools used to measure the temporal qualities of AB beyond the limitations of behavioral and neuroimaging techniques.
Cognitive theories have emphasized multiple, temporally-unfolding stages of threat processing. RT-based metrics, while valuable, are a relatively indirect and down-stream measure of threat processes. They are a crude measure of response speed reflecting a culmination of hundreds of milliseconds and cannot directly capture more granular, extremely rapid and automatic stages of the threat detection and response system. In other words, although strong inferences can be made regarding the cognitive demands of a particular stimulus by measuring interference effects on downstream behaviors, such assays of AB as a measure of overt attention are unable to track the most rapid changes in neurocognitive responses to threat (Cisler & Koster, 2010). Scalp-recorded event-related potentials (ERPs), in contrast, are neural measures with millisecond precision that are sensitive to early processing of emotional faces, subtle shifts in threat processing, and distinct covert attentional mechanisms (Batty & Taylor, 2003). ERPs may be more reliable than behavioral measures of early attentional engagement with threat (Kappenman et al., 2014). For example, in one study directly comparing behavioral AB measures and ERPs, ERPs showed greater internal reliability and revealed a significant shift in attention towards threat not accounted for by averaged reaction times (Kappenman, MacNamara, & Proudfit, 2015).

As reviewed above, neurocognitive theories of AB emphasize a dual-process model: the interplay of automatic attention allocation to threat and later controlled stages of attention (Bar-Haim, 2010; Suway et al., 2013). The P1 and N2 ERPs, in particular, are excellent candidate components for dissociating these two attention processes.

The P1 component is a positive peak that is maximal at approximately 100 ms following stimulus presentation and occurring over posterior electrode sites that cover the lateral occipital lobe (Luck & Kappenman, 2011). The P1 signals early stages of attention allocation and is reliably observed in response to visual stimuli with larger amplitudes for stimuli presented in the
attended location (Hillyard & Anllo-Vento, 1998). It indexes enhanced activity of the extrastriate cortex with larger amplitudes correlated with increased blood flow to the ventrolateral occipital cortex (Heinze et al., 1994). When stimulus-locked to emotional faces during the dot probe task, it reflects early and automatic sensory processing of threat (Luck, Heinze, Mangun, & Hillyard, 1990; Mueller et al., 2009; Smith, Cacioppo, Larsen, & Chartrand, 2003) and attention capture of threat compared to neutral face cues in anxious populations (Bar-Haim, Lamy, & Glickman, 2005; Dennis-Tiwary, Denefrio, & Gelber, 2017; Dennis-Tiwary et al., 2016). The P1 has also been used to track attention to threat in anxiety. For example, it is enhanced to threat-themed stimuli in anxious relative to non-anxious groups (Li, Li, & Luo, 2005; Weinberg & Hajcak, 2011).

The later-emerging N2 is a negative deflection with a frontocentral location peaking at approximately 200 to 350 ms post-stimulus presentation (Folstein & Van Petten, 2008). It is associated with activity in the ACC and reflects a range of executive cognitive processes such as conflict monitoring (Nieuwenhuis, Yeung, Van Den Wildenberg, & Ridderinkhof, 2003; Van Veen & Carter, 2002). For example, the N2 is reliably elicited in the dot probe task following face cue presentation. Presumably because the different emotional faces create attentional conflict (Dennis-Tiwary et al., 2016) and in go/no-go studies, larger N2 amplitudes are generated following no-go relative to go trials because the no-go condition requires response suppression (e.g., Bruin & Wijers, 2002). Previous studies including anxious populations have further documented larger N2 amplitudes in anxious relative to non-anxious healthy controls during a go/no-go tasks, although between-group performance was comparable. This suggests that the N2 may signal increased levels of cognitive compensatory effort – in this case in order to maintain equal performance between the two groups (Ruchsow et al., 2007; Sehlmeyer et al., 2010). In a large sample of anxious youth, attentional avoidance was associated with larger N2 amplitudes to
threat cues as self-reported behavioral inhibition increased, consistent with the idea of increased compensatory cognitive control when participants have heightened social anxiety (Thai, Taber-Thomas, & Pérez-Edgar, 2016).

Behavioral research supports the link between attention control abilities and AB making the N2 a good ERP for exploring the nature of this relationship. For example, one study conducted by Derryberry & Reed (2002) found evidence of an initial AB toward threat relative to safety cues in trait-anxious individuals at 250 ms followed by a bias toward safety cues at 500 ms suggesting a shift away from threat following initial engagement. However, attention control moderated these effects. Anxious individuals who were low in self-control maintained an AB towards threat at 500 ms implicating increased cognitive control in directing attention away from threat.

A recent meta-analysis specifically reviewing the use of ERPs in the measurement of AB via emotional faces cues found that collectively ERPs have been successful in detecting AB in anxious samples (Torrence & Troup, 2018). They suggest that when tracking AB via the dot probe, ERPs with a posterior scalp topography should be targeted for initial sensory-level attention allocation whereas ERPs with a frontocentral distribution are thought to reflect later stages of attentional disengagement. Larger P1 amplitudes to angry-neutral face pairs relative to happy-neutral face pairs have been documented in social anxiety as well as to threat faces relative to a low social anxiety group indexing enhanced visual processing of threat in anxiety (Helfinstein, White, Bar-Haim, & Fox, 2008; Mueller et al., 2009). Furthermore, ERPs have been used as both a neural index of AB and change in AB associated with ABMT. In two studies with non-clinical samples, we found that ABMT resulted in reduced P1 amplitudes, indicating reduced early attention capture and increased N2 amplitudes, indicating enhanced recruitment of top-down control (Dennis-Tiwary et al., 2016; O’Toole & Dennis, 2012). Most recently, we
found that training effects on anxiety were influenced by pre-training ERP biases (smaller P1 amplitudes) (Dennis-Tiwary et al., 2017). An earlier ERP study in another lab also found that training increased N2 amplitudes to face cues in the dot probe (Eldar & Bar-Haim, 2010).

Importantly, behavioral measures of threat bias (measured via the dot probe) changed inconsistently in these studies.

Thus, ERPs have been used to track alterations in both early attention to threat and later, more controlled processing of threat. ERP components with a posterior distribution such as the P1 can track sensory processing stages whereas components with a more central and anterior distribution such as the N2 can capture control and disengagement processes. In particular, the P1 and N2 have been used to characterize biased processing of threat at a very rapid timescale. Early attention allocation to threat, measured via the P1, is amplified in anxiety and has been modulated by ABMT (Mueller et al., 2009; O’Toole & Dennis, 2012). The later-occurring N2 reflects relatively controlled cognitive processing of threat and is increased via ABMT (Dennis-Tiwary et al., 2016; Eldar & Bar-Haim, 2010). It is difficult if not impossible for RT-based measures to directly differentiate these processes underlying AB.

Future AB investigation must continue to look for ways capitalize on the temporal specificity of ERPs. One area of AB research using ERPs that has yet to be explored is the temporal stability of ERP components across repeated measurements. For example, an increase in P1 and N2 amplitudes between multiple measurements might signal increased expenditure of neurocognitive resources [more robust attention allocation to threat (P1) or recruitment of cognitive control across two timepoints (N2)]. Whereas, a decrease in P1 and N2 amplitudes would reflect reduced resources [dampened attention allocation to threat (P1) or reduced recruitment of cognitive control (N2)]. No change between measurements would be evidence for neurocognitive stability. The advantage of multiple measurement would be to evaluate not only
ERPs but change in ERPs as a clinically-relevant and temporally-sensitive measure of neurocognitive stability and/or flexibility. In the current study, we test this assumption.

**Attention Bias Modification Training**

In light of the early success of AB research, it quickly became the target of a novel cognitive-based treatment for anxiety, namely ABMT. ABMT was developed with the assumption that AB is a feature of anxiety. Thus, directly manipulating attention away from threat should reduce anxiety. Remediation of the pathological fixed and exaggerated attention to threat should then have the downstream effect of alleviating the core symptoms of anxiety such as tension, worry, and apprehension. While correlational studies have been crucial for documenting the association between AB and clinical anxiety, it was the first ABMT study, showing both the causal link between AB and anxiety as well as the clinical intervention potential of AB that has driven innovation in the field. In a series of two experiments, Macleod and colleagues tested a simple modification of the dot probe task designed to train attention either towards or away from threat in a sample of people with normal levels of trait anxiety (MacLeod et al., 2002). Then, both training groups completed a difficult anagrams task to induce negative mood. Emotional vulnerability was assessed as individual differences in negative mood measured before and after the anagrams task. As predicted, negative mood in response to the stressor was attenuated for the train away from threat group relative to the train towards threat group within a single lab visit. Importantly, they introduced the use of the modified dot probe paradigm, known as ABMT, to effectively alter AB. Furthermore, they concluded that manipulation of AB altered emotional vulnerability after training thus supported a causal relationship between AB and anxiety. Mathews and MacLeod (2002) then selected participants
for high trait anxiety and trained attention either away from threat or control training over three weeks. Only the train away from threat group showed a significant reduction in trait anxiety from pre to post-training further lending support of a causal role of AB in anxiety.

The conception and study of ABMT is a direct response to this proposed link between AB and anxiety. Attention is systematically trained away from threat through a simple modification of the dot probe, and since pivotal studies, a growing body of research has examined it as a potentially powerful, cost-efficient and easily accessible treatment for anxiety (Dennis & O’Toole, 2014; Kazdin & Blase, 2011). The central tenet of ABMT is that when threat and neutral stimuli compete for attention, the tendency of threat to capture attention is an important factor in the development and maintenance of anxiety. This idea also stems from cognitive theories of attention that propose a range of temporal disruptions in anxious individuals from more top-down biased interpretation of ambiguous situations as threatening, an enhanced memory for threatening events, and more bottom-up initial attention selection of threat stimuli (Beck & Clark, 1988, 1997; Eysenck & Calvo, 1992; Mogg & Bradley, 1998; Williams, Watts, MacLeod, & Mathews, 1988). For example, if AB contributes to anxiety severity by directing and fixating attention on negative things then shifting attention away from threat and towards a neutral or positive stimulus repeatedly over trials and over time via ABMT may result in the reduction of symptoms.

Indeed, the first decade of clinical trials suggested that ABMT did in fact reduce AB and anxiety severity across several anxiety disorders such as social phobia and GAD and at levels comparable to cognitive behavioral therapy (Hakamata et al., 2010). However these robust effects were short-lived and as interest has flourished, treatment studies have become numerous and results have been mixed (Clarke, Notebaert, & MacLeod, 2014; Hallion & Ruscio, 2011; Mogoaşê, David, & Koster, 2014). One prominent meta-analysis reviewing the clinical efficacy
of ABMT treatment studies targeting AB in anxious people, found only small effect sizes in symptom reduction post training (hedge’s g = .160; Mogoâse et al., 2014). Moreover, a growing selection of studies have also reported null findings (Boettcher et al., 2013; Carlbring et al., 2012; Fitzgerald et al., 2016; Schoorl, Putman, & Van Der Does, 2013) calling efficacy of ABMT into question. Other reviews have shown that ABMT fails to reduce symptoms of anxiety when selective attention to threat via AB remains unchanged and that remediation of anxiety-related outcomes can only be accurately detected if AB has been measurably altered (MacLeod & Clarke, 2015). In addition, most studies that do report ABMT success tend to measure only the immediate effects of ABMT on acute outcomes and are limited in terms of evaluating the long term and real-world desired effects on anxiety (MacLeod et al., 2002). Furthermore, there are important differences in dosing parameters and training protocols across studies that should be considered. Both single-session ABMT and multiple ABMT sessions over days and/or weeks have reduced a range anxiety-related symptoms and clinical severity at similar rates but only when AB has also first been reduced (for review see Mogoas, David, & Koster, 2014).

One important candidate moderator for ABMT success is the existence of a pre-training AB. Successful ABMT studies have shown that the magnitude of AB at baseline moderated the relationship between training group and reduction in anxiety symptoms (i.e., Amir, Taylor, & Donohue, 2011; Kuckertz et al., 2014). Lazarov and colleagues (2018) completed a randomized clinical trial (RCT) for PTSD comparing attention control training (ACT) to ABMT that was contingent upon the direction of pre-training AB either towards or away from threat. ACT consisted of completing dot probe trials with an equal probability of the probe replacing threat or neutral cues. Although ACT was more effective at reducing PTSD symptoms relative to ABMT, bias-contingent ABMT did successfully alter AB. Specifically, training was effective at altering AB when an individual with a pre-training bias towards threat was trained away from threat.
Furthermore, two more recent meta-analyses have identified a number of specific conditions and individual differences that support the desired effects of ABMT on AB and anxiety. Price and colleagues (2016) found that ABMT was most effective when changes in anxiety were assessed by a clinician and attention training took place in a laboratory or clinic setting. Mogg, Waters, and Bradley (2017) examined 34 ABMT studies of high trait anxious individuals and found that anxiety reduction often occurs in both active and placebo training conditions and more importantly that 1) high trait anxiety is not associated with a pre-training AB and that 2) anxiety reduction is not consistently accompanied by reductions in AB. Lastly, there has been conflicting support for a causal impact of AB on anxiety (see Van Bockstaele et al., 2014 for review). In particular, some evidence has shown that anxiety and fear are present prior to AB and in the absence of AB. Further, changes in fear and anxiety have impacted AB suggested a bidirectional rather than causal relationship. This has important clinical implications for ABMT because training protocols designed to alter AB and reduce anxiety rely on the role of AB in the maintenance and expression of anxiety.

ABMT remains a novel treatment, still in its infancy in terms of research and development. Yet, the field’s ability to evaluate and refine this emerging treatment approach has been complicated by debate and concerns over the measurement of AB, along with the demonstrated need to consider individual differences in AB prior to its remediation. Indeed, a growing number in the field have called for “taking a step back in order to take a step forward” (Koster & Bernstein, 2015; Roy, Dennis, & Warner, 2015). A special issue devoted to exactly this cause calls for an emphasis on the science of AB measurement through “innovation and refinement” of current methodology (Koster & Bernstein, 2015) in order to evaluate the use of AB as 1) a risk factor for anxiety and 2) a target for the treatment of anxiety. Below, I summarize
key problems in the conceptualization and measurement of AB that influenced the clinical literature on anxiety-related cognitive biases and ABMT.

**Challenges in the Conceptualization and Measurement of AB**

*Heterogeneity and Variability in AB.* Recent evidence increasingly documents inconsistent associations between AB and anxiety across the full range of disorders. A significant proportion of anxious adults (Chen et al., 2002; Heuer et al., 2007; Mansell et al., 1999; Salum et al., 2013) and children (Morales et al., 2014; Waters, Bradley, & Mogg, 2014) evidence a bias away from threat reflecting avoidance as the predominant mode of threat processing or fail to show evidence of any attentional bias (Moritz & von Mühlenen, 2008; Schofield, Coles, & Gibb, 2007). For example, Mansell and colleagues (1999) using a modified dot probe, found that individuals with social anxiety showed a bias away from both negative and positive faces relative to images of household objects. Another study found that trauma-exposed participants who showed AB away from threat, rather than a bias towards threat, were more likely to have symptoms of PTSD one year later (Wald et al., 2011). Together, findings suggest that both patterns of AB (towards and away from threat) represent clinically-relevant variability and may provide valuable insight into the mechanisms underlying anxiety. In contrast to AB towards threat, avoidance of threat may maintain certain symptoms of anxiety by limiting exposure to triggering stimuli and therefore reducing opportunities to disconfirm distorted views of others and of the world. Furthermore, the absence of any bias in an anxious sample may signal the true lack of a directional bias or may be a signal of measurement error - a critical difference - but this cannot be determined based on current standards.

*Behavioral Assays of AB.* Emerging from cognitive theories of AB, behavioral assays measuring AB were designed to isolate subtle discrepancies in information processing.
Specifically, both threat and neutral cues are presented simultaneously creating competition for attention or interference of threat is measured relative to another type of stimulus. Multiple reaction-time-based assays such as the emotional Stroop paradigm, visual search task, and the dot probe have been used to measure AB. They measure the degree to which threatening stimuli capture attention faster than non-threat stimuli by comparing mean reaction times across each type of trial. In this section, I review these measures and highlight their psychometric strengths and several critical limitations.

In the emotional Stroop paradigm (Williams et al., 1996), threatening and positive words do not compete for attention. Instead, each type of word is presented separately, and the participant is asked to identify the color in which the word is written. Longer response times to one type of word over another indicates that the meaning of that word distracted from identifying the color, measured via a delay in naming the color. Because this task lacks direct competition, one criticism is that the delays in color naming may be better explained by avoidant behavior towards the threat stimuli rather than an indication of attention capture by the threat.

The visual search paradigm (Öhman, Flykt, & Esteves, 2001; Palmer et al., 1993; Woodman & Luck, 1999) requires participants to quickly locate a target image presented simultaneously within a variety of similar distractor images. AB is interpreted as faster responses when the target image was threatening relative to when the target image was positive or neutral. However, studies have shown that the level of arousal of the target image is more important than the valence when looking at differences between angry and happy faces (Palmer et al., 1993). Thus, this task cannot fully dissociate arousal from valence and AB must be measured independent of arousal.

Among extant behavioral assays, the dot probe task is arguably the gold-standard in AB measurement. In this task, preferential threat selection is most directly measured, as threat and
neutral cues compete for attention (MacLeod et al., 1986). Both cue types (e.g., faces, words) appear simultaneously for approximately 500 ms, and then at offset, the location of one cue is replaced with a probe (an arrow or asterisk). Shorter cue durations allow for overt visual processing while limiting the occurrence of multiple saccades (typical timescale of 300 ms) (Henderson & Hollingworth, 1998). Although 500 ms is the typical presentation duration used in the dot probe, much shorter cue durations of 300 ms and 150 ms have been successful at documenting initial attention allocation to threat relative to neutral stimuli (Torrence, Wylie, & Carlson, 2017). Participants are then asked to respond by indicating a characteristic of the probe (e.g., direction of the arrow). AB is calculated as the mean difference between reaction times (RTs) to each cue type providing a snapshot of attention preference (Bar-Haim et al., 2005). A positive score is indicative of facilitated attention to threat (vigilance) as RTs are faster on trials where the probe was replaced by threat cue. Negative scores indicate RTs faster on probes that follow the location of neutral faces and thus are thought to reflect threat avoidance. Because the dot probe task relies on attentional competition, attention is allocated to one face at the expense of the other. When the duration of face cue presentation is shorter than 500 ms, it can provide some evidence for vigilance towards threat, whereas longer durations of 1000 or 1500 ms can be used to track avoidance of threat cues in anxiety (Mogg, Bradley, Miles, & Dixon, 2004). However, avoidance or difficulty disengaging from threat cannot be ruled out, particularly when only one stimulus duration is used (Bradley, Mogg, Falla, & Hamilton, 1998). Therefore, using RTs on the dot probe to interpret AB can vary widely according to task parameters. One recent study presenting a range of SOAs found evidence for AB towards fearful relative to neutral faces only at SOAs under 300 ms (Torrence et al., 2017).

Together, all three tasks provide only a limited picture of threat detection. The dot probe is considered to be superior and is the most-widely used because neutral and threat stimuli are
pitted against each other creating competition for attention and forcing the participant to make a choice. The dot probe design allows for testing the hypothesis that threat can have either facilitating or impairing effects on probe detection. For example, a positive bias score via dot probe scoring indicates a facilitation of threat on attention to probes that replace threat faces and an impairing effect of threat on attention to probes that replace neutral faces. Despite this strength, averaged reaction times lack any degree of temporal specificity because scores are generated by averaging over many trials. Therefore, there are a range of temporal qualities of and individual differences in AB that are not accounted for by the available RT measurement approaches.

**Poor Psychometric Properties of the Dot Probe.** Dot probe scoring, relying only on averaged RT difference scores occurring hundreds of milliseconds post-face presentation, is a static snapshot of attention and may be inadequate for characterizing clinically-relevant change in AB across time and context. These RTs reflect a cascade of events that can vary greatly based on task parameters. AB measured this way assumes that biased attention towards threat emerges consistently in the same way throughout the task. Any trial-level variability in attention is dampened by averaging performance across all trials. The resulting bias score is either positive or negative indicating a mean AB in one direction: either towards or away from threat. This assumption fails to allow for the same individual to show both a bias both towards and away from threat within a single task, a phenomenon that has been increasingly documented using temporally-sensitive measures of AB (Iacoviello et al., 2014; Zvielli et al., 2014b).

Because it has become the most widely-used task, the dot probe has been under some scrutiny and this has revealed a number of psychometric problems. The first AB meta-analysis (Bar-Haim et al., 2007) reported that studies using dot probe-based measures of AB had smaller effect size (Cohen’s $d = 0.37$) relative to overall effect size for AB (Cohen’s $d = 0.45$). Since
then, studies on the psychometric properties of the dot probe have shown poor internal consistency and poor split-half and test-retest reliability (Kappenman et al., 2014, 2015; Rodebaugh et al., 2016; Schmukle, 2005; Waechter et al., 2014). Chapman, Devue, and Grimshaw (2017) systematically tested dot probe reliability in a series of experiments under varying stimulus onset asynchronies (SOA) in which the time between the cue and the probe presentation differed. In the first experiment, with SOAs greater than 100 ms, internal reliability of AB was not significantly different from zero and even at 100 ms reliability was poor. In the second experiment, after doubling the number of trials in an effort to improve task reliability, AB measurement with an SOA of 100 ms was no longer significantly different than zero. Furthermore, AB was not correlated with either self-reported anxiety or attention control and AB measured at different SOAs was also unrelated. These results highlight both poor internal reliability and lack of temporal specificity of the dot probe.

The dot probe also shows poor stimulus generalization and cross stimulus-convergence. For example, Zvielli, Bernstein, and Koster (2014) measured AB across five stimulus categories (threat faces, angry dogs, weapons, snakes, and violent scenes) in a large trait-anxious sample. They found that only one third of participants showed a positive AB for at least one stimulus category. More surprisingly, they found that one third of participant also showed a bias towards threat in one category and away from threat using another stimulus group. Taken together, findings reflect the understudied variability in AB and instigate a call to improve the psychometric properties of the dot probe.

**Summary.** Despite the breadth of early findings supporting a link between AB and anxiety, recent findings have called into question the robustness of this association and highlighted psychometric problems with the gold-standard measurement, the dot probe, including its failure to capture clinically-relevant temporal variability in AB. First, there is
significant heterogeneity in the direction of AB. This may be the result of averaged scores that provide one direction of attention to threat (either towards or away). Second, although current reaction-time based methods capitalize on creating competition between threat and neutral cues, they lack temporal specificity of biased attention. Third, the dot probe task is considered to be an unreliable and inconsistent AB assay. Rather than reflecting measurement error, this inconsistency provides an opportunity to re-evaluate the current state of AB research and standards in the conceptualization and measurement of AB.

**Temporally-Sensitive Behavioral Metrics of AB**

In addition to temporally-sensitive ERP metrics of AB, there has been significant progress in the development of temporally-sensitive behavioral metrics that have the potential to advance the way in which AB in conceptualized and how ABMT efficacy is evaluated (Koster & Bernstein, 2015). Novel methods for the measurement of AB have focused on measuring within-person variability and movement in AB across one task and between tasks. In addition, innovative approaches for tracking performance gains or losses during ABMT have been used both as an individual difference to predict treatment response and as an outcome measure of AB flexibility and ABMT efficacy. The newly available approaches reviewed below more accurately reflect the concept of AB as multiple and unfolding disruptions in attention to threat over time. They may be capable of capturing anxiety-related changes missed by traditional approaches and the capacity to resolve conflicts between AB theory and measurement.

**Repeated Measurement of RTs.** Over the past decade, several labs have measured AB variability repeatedly within a single dot probe task (N. Amir, Najmi, & Morrison, 2009; Iacoviello et al., 2014). The first studies showed that AB significantly differed from the beginning to the end of the dot probe task highlighting the value of temporally-sensitive
measurement. For example, Iacoviello and colleagues found that within-task AB variability from a dot probe task using trauma-related versus neutral words was larger in a PTSD group relative to healthy controls and was positively correlated with PTSD symptoms (Iacoviello et al., 2014). Thus, AB variability or the degree of change in AB an anxious individual displayed over one task was not only measurable but also clinically-relevant. Rather than computing one mean RT difference score, Zvielli, Bernstein & Koster (2014) took this idea a step further and were the first to systematically calculate AB multiple times across trials by pairing temporally contiguous trial types and computing a difference score for each pair, termed trial level bias scores (TL-BS). TL-BS, plotted over the course of the dot probe, reflects changes in AB across individual trials within a given individual. This approach challenges two important assumptions of mean AB scores. The first is that the random order of threat-cued and neutral-cued trials does not impact AB expression. The second is that AB is expressed either towards or away from threat for each AB measurement and each individual. When tracking individual variability using TL-BS, they observed phasic bursts in AB expression (both towards and away from threat) that could be quantified. This supports the notion that AB is not static, but instead changes moment to moment. From these TL-BS, they quantified five metrics to represent the full range of AB movement. Peak Positive and Mean Positive TL-BS indicate the degree of TL-BS towards threat and Peak Negative and Mean Negative TL-BS indicate the degree of TL-BS away from threat. Lastly, an overall measure called Variability encompasses the four previous metrics and reflects the amount of movement in negative and positive TL-BS with a larger value indicating large and frequent shifts in attention and a smaller value reflecting consistent AB expression. Collectively, these metrics provide a much more complete picture of how attention was allocated during the dot probe task.
Results of this first study showed that these temporally sensitive TL-BS were a better predictor of phobic status than traditional AB scores. Larger mean positive and peak positive TL-BS metrics significantly predicted spider phobic status versus controls using the dot probe task. In addition, more variability also predicted phobic status. Traditional mean AB scores only marginally predicted phobic status. When both mean AB and TL-BS derived metrics were included in the same regression models, TL-BS metrics significantly predicted phobic status above and beyond mean AB. Thus, sampling AB repeatedly within a single task provides a clinically-relevant measure of AB variability and provides a promising addition to behavioral AB measurement following the dot probe task.

Since its development, multiple studies have documented that these metrics show improved reliability relative to traditional mean AB score (Caudek, Ceccarini, & Sica, 2017; Rodebaugh et al., 2016) and are more sensitive to clinical status (Badura-Brack et al., 2015; Zvielli et al., 2014b), symptoms of anxiety severity (Schäfer et al., 2016), and emotion dysregulation (Bardeen, Daniel, Hinnant, & Orcutt, 2017). TL-BS are also effectively reduced via CBT (M. L. Davis et al., 2016) and, in non-clinical samples, are sensitive to mood inductions (Caudek et al., 2017) and predict increased stress reactivity following a brief lab stressor in trait-anxious individuals (Egan & Dennis-Tiwary, 2018).

A second clinically-relevant approach to measuring within-person variability is the assessment of between-context changes in AB. Heeren, Philippot & Koster (2014) assessed AB at two distinct timepoints to evaluate change in AB as an important pre-training individual difference. Trait-anxious participants first completed the dot probe task at an initial lab visit, then at a second visit two weeks later. Both timepoints took place prior to completing ABMT. The authors measured the amount of shared variance in AB - suggesting greater stability - between the two visits and found that more stability in AB between the two visits predicted
worse training performance gains during ABMT. The authors interpreted this as suggesting that temporal variability *between time points* in AB reflects healthy flexibility and thus may signal more malleable AB. Results suggest that measuring between-context change in AB measured is an important individual difference when evaluating the clinical potential of ABMT. However, this prior research does not clarify the direction of change in AB that the measure of variance represents. In the present study, we directly measure change in AB between two baseline, pre-training visits through a difference score that indicates an increase in AB, a decrease in AB, or no change in AB. Based on the aforementioned finding, we would expect that an increase in AB or stability in AB represented by no change between visits would both signal a more rigid and fixed expression of AB that would be more resistant to modification via ABMT. In contrast, a decrease in AB would reflect a reduction in attention towards threat signaling flexibility in attention and may be a desirable individual difference influencing training performance.

Taken together, these studies suggest that temporal variability in AB - either measured multiple times within a single task or between two time points - may provide powerful and relatively new means for capturing clinically-relevant individual differences while avoiding the pitfalls of traditional measures of AB. First, multiple indices of AB per individual allows for a calculation of temporal variability by quantifying the degree to which attention shifts in both directions (towards and away) within a single task (Amir, Zvielli, & Bernstein, 2016; Egan & Dennis-Tiwary, 2018; Zvielli et al., 2014b). Second, between-context change in AB may be a useful pre-training measure of AB flexibility and ABMT potential (Heeren et al., 2014; Price et al., 2015). If AB is in fact not a stable trait, then AB should not be assumed to be same from one day to the next or one moment to the next and measured using only static measures. In contrast to traditional methodology, both of these approaches measure attention dysregulation and allow
for within-person directional changes in AB and divergent patterns of either rigid expression of AB or dynamic movement and flexibility/instability. Importantly, measures of temporal AB characteristics more accurately reflect the concept of AB as multiple and unfolding disruptions in attention to threat over time, which is a better measure of anxiety-related changes.

**Training Performance.** In addition to evaluating temporally-sensitive measures as pre-training individual differences, another emerging temporally-sensitive behavioral measure focuses on changes in attention during ABMT as a novel ABMT-related outcome. When considering how to measure the efficacy of ABMT, one important outcome that has been absent from the large majority of ABMT intervention studies is the evaluation of training performance. Indeed, how and if attention changes specifically during ABMT trials had been widely ignored. Instead, ABMT efficacy is assessed solely by changes in AB before and after training and by tracking subsequent reductions in anxiety. As the dearth of ABMT meta-analyses have shown, anxiety reduction is not consistently accompanied by alterations in AB and anxious adults often do not show a pre-training AB. Thus, assumptions about directly manipulating attention to threat via ABMT should be called into question by asking whether a significant change in AB equals successful attention training.

The measurement of reaction times during ABMT training trials is a simple way to evaluate how effectively individuals have implicitly learned the contingency rule that probes will always replace neutral cues. Over training trials, reaction times should decrease and this documentation of an increase in the speed of responding to neutral-cued trials should directly correlate to a decrease in AB on post-training AB assessment and predict reductions in anxiety-related outcomes. Therefore, ABMT performance is a temporally-sensitive measure of learning. Furthermore, training performance is also a potentially powerful measure of individual differences in many performance-related factors. For example, the available research on learning during ABM
discusses two processes that should be considered, online learning tracked within session and offline learning or consolidation between sessions (Abend et al., 2013). In addition to tracking reaction times during ABMT sessions, consolidation can be assessed by measuring change in RTs following a rest period such as between ABMT sessions. Abend and colleagues found that in multiple sessions of ABMT, consolidation was greater when participants had a rest period of either one hour or 24 hours relative to no rest (Abend, Pine, Fox, & Bar-Haim, 2014). Interestingly, they also found that significant gains in reaction times during all training conditions (towards threat, away from threat, control) occurred within the first 200 trials. Most recently, Abend et al., (2018) found that age moderated the relationship between learning during ABMT and symptom reduction. In a combined sample of children and adults with social anxiety disorder, they found that learning improved with age and that with age, learning resulted in decreased self-reported anxiety. Importantly, this relationship was not significant for mean AB scores suggesting that training performance may be a more sensitive to important individual differences.

Of the handful of studies that have examined training performance, it has proven to be a clinically-relevant outcome. For example, Heeren, Philippot, and Koster (2014) quantified training gains during ABMT by tracking the change in speed of RTs to neutral-cued dot probe trials from the beginning to end of training. They computed a percentage of gain in response speed. Results showed that anxious participants with a more stable and rigid AB between two pre-training visits had decreased training gains relative to participants with a more variable pre-training AB. Other studies have demonstrated that anxiety may blunt the efficacy of ABMT through disrupted learning during training (Abend et al., 2013, 2014). Abend and colleagues (2014) found that trait-anxious relative to non-anxious individuals showed reduced training gains during ABMT away from threat but not towards threat. Therefore, results suggest that training attention away from threat is more difficult in the presence of anxiety. Taken together, these studies show that rich and clinically-
relevant data may be missed when ABMT is treated as a black box. Rather, as clinical outcome, training performance can confirm whether or not learning has occurred and detect patterns of changing attention that may not yet be reflected in post-training AB assessment.

**Overall Summary**

In sum, research reviewed above suggests that initial enthusiasm for construct of AB – both in terms of its potential causal role in anxiety and its targeted remediation by ABMT - has been slowed by inconsistent and null findings. This has revealed two major empirical gaps that limit the full understanding of the association between AB and anxiety. The first is that the traditional view of AB as a stable trait has been replaced with mounting evidence of AB temporal variability that predicts clinical outcomes above and beyond static measures of AB. The second is that available measures have poor reliability, limiting our ability to infer that we are directly measuring the construct of interest. Therefore, there is a need for new metrics for AB assessment and ABMT efficacy that are designed to account for this variability and improve reliability. The current findings represent a crucial next step towards this goal by first, clarifying measurement of AB and its variability and second by identifying what pre-training individual differences are important for predicting target ABMT outcomes.

**The Current Study**

The current study tested a novel conceptual and methodological framework for AB using multiple, converging methods to measure temporal variability and evaluate its clinical relevance in the context of an experimental intervention targeting AB, ABMT. Temporally-sensitive behavioral and neurocognitive measures of pre-training individual differences (TL-BS, between-context AB, ERPs, between-context ERPs), ABMT outcomes (training performance), and
traditional AB metrics (mean difference scores) were examined in relation to each other and to predict ABMT outcomes: training performance, self-ratings of anxiety, and stress reactivity.

**Aims and Hypotheses.** Because this dissertation was embedded in a randomized, placebo-controlled clinical trial of ABMT, Aim 1 was to test the effects of ABMT on AB, self-reported anxiety, stress reactivity, and training performance. Hypothesis 1 was that ABMT relative to PT would reduce behavioral measures of AB (mean and temporally-sensitive), anxiety-related ABMT outcomes (anxiety and stress reactivity), and alter neurocognitive measures of AB (reduce P1 and increase N2). Hypothesis 1a was that ABMT vs PT will show greater training performance gains, with the largest gains occurring in the second half of the month reflecting compounded effects of time and consolidation on learning.

**Aim 2** was to test whether individual differences in temporally-sensitive measures of AB prior to training predict anxiety-related ABMT outcomes above and beyond mean AB. AB variability will be computed in two ways: 1) TL-BS, and 2) between-context AB change score. **Hypothesis 2** was that greater TL-BS variability and an increase or stability in AB between two baseline measurement context points will be associated with worse anxiety-related outcomes and training performance losses.

**Aim 3** was to test whether individual differences in neurocognitive measures of AB (ERPs and between-context change in ERPs prior to training) predict anxiety-related ABMT outcomes. Two ERPs were targeted: 1) P1 (reflecting attention allocation) and 2) N2 (recruitment of cognitive control). The P1 and N2 were examined in two ways: 1) mean amplitudes to threat and 2) the change score for P1 and N2 amplitudes between-context prior to training to mirror the between-context behavioral measure of AB. **Hypothesis 3** was that greater P1 and N2 mean amplitudes to threat and a between-context increase or stability in ERPs would predict worse anxiety-related ABMT outcomes and training performance losses. **Exploratory**
Hypothesis 3a was that neurocognitive measures of AB and temporally-sensitive behavioral measures of AB would be positively intercorrelated.

Method

Participants

One hundred and twenty-five adults [83 (66 %) female] were recruited from a community-based survey center and selected for moderate to severe symptoms of anxiety and stress. Potential participants were screened using the Depression, Anxiety and Stress Scale (DASS 21; Henry & Crawford, 2005) and were invited to participate if they reported moderate to severe symptoms on either the anxiety or stress subscales. The mean score on the anxiety subscale was 18.70(6.98) and 25.53(7.61) on the stress subscale. One hundred and twenty-one individuals agreed to participate. Upon arrival to the lab, the Mini International Neuropsychiatric Interview (MINI; Sheehan et al., 1998) was administered. One participant was excluded due to a past manic episode that included psychotic features, and 10 participants due to substance and/or alcohol dependence. Individuals using medication were only included if there were no changes in pharmacological treatments and if there was a stable history of concurrent psychotherapy for a minimum of six weeks prior to study entry. One participant was excluded due to recently starting an SSRI within two weeks of the first lab visit. Fourteen participants did not complete all study visits and two participants had incomplete data due to experimenter error (see Figure 1 for enrollment flow diagram).

The final sample was 93 adults (64 female), aged 18-41 (M = 25.14, SD = 6.38) who completed both Time 1 (pre-ABMT) and Time 5 (post-ABMT) assessments and were randomly assigned to either the ABMT (n = 46) or placebo (PT; n = 47) group that required five weekly visits. Mean education was college level and mean household income was 63,833.11 with a
range of $0.00 to $400,000.00. Self-reported race/ethnicity was: 49 White (52.7%), 18 Asian (19.4%), 8 African American (8.6%), 9 more than one race (9.7%), and 9 choose not to answer (9.7%). Of these, 17 identified as Hispanic/Latino. Participants were compensated with $100.00 for Visits 1 and 5 and $50.00 for Visits 2, 3, and 4 totaling $350.00.

**Materials and Procedure**

The larger RCT study consisted of six visits taking place over the course four months with Visit 6 being a three-month follow-up. The present dissertation consisted of the first five visits with the following schedule: (a) Visit 1 was the pre-training bias assessment with simultaneous EEG recording, diagnostic interview, measures of anxiety, and brief stressor (b) Visits 2 through 4 were training visits (c) Visit 5 was the final training visit followed by post-training bias assessment with simultaneous EEG recording, diagnostic interview, measures of anxiety, and brief stressor. For the purposes of this dissertation, a second pre-training bias assessment with simultaneous EEG recording was completed at the beginning of Visit 2.

**Diagnostic Interview.**

The MINI is a short (approximately 15 to 30 minutes) and reliable structured diagnostic interview for current and past DSM-IV disorders (Sheehan et al., 1998). The MINI was used to identify specific anxiety diagnoses and comorbidities. Visit 1 diagnoses can be found in Table 1.

**Trait-Level Measures of Anxiety.**

All questionnaires were administered at Visits 1 and 5.

*The Depression, Anxiety, and Stress Scale (DASS-21).* The DASS-21 (Henry & Crawford, 2005) is a 21-item questionnaire that measures the degree of severity of symptoms across three domains: depression, anxiety, and stress. On each item, the participant is asked to rate how much the statement has applied to them over the past week on a scale from zero (“Did not apply to me at all”) to three (“Applied to me very much or most of the time”). Each subscale
contains 7 items with raw sum scores with a range from 0 to 21. Raw scores are then multiplied by two for a final subscale score ranging from 0 to 42. Higher scores indicate increased severity. Items in the DASS-Depression subscale assess symptoms such as anhedonia and hopelessness with a moderate severity range of 14-20. Items in the DASS-Anxiety subscale assess symptoms such as autonomic arousal and situational anxiety with a moderate severity range of 10-14. The DASS-Stress subscale assesses symptoms such as non-specific arousal and agitation with moderate severity scores in the range of 19-25 (Brown, Chorpita, Korotitsch, & Barlow, 1997).

The Hamilton Anxiety Scale (HAM-A). The HAM-A (Hamilton, 1959) is a clinician-administered measure of anxiety severity consisting of 14 items. Symptoms such as tension, anxious mood, fears, somatic complaints, and behavior at interview are rated on a 5-point scale from 0 (“not present”) to 4 (“severe”). The number endorsed on each item is summed resulting in scores that range from 0 to 56. Higher scores indicate increased anxiety severity with moderate scores within the range of 18-24. The HAM-A is a tool recommended for repeated administration to track response to a given treatment.

Lab-Based Stressor and State-Level Stress Reactivity.

During Visits 1 and 5, the Trier Social Stress Test (TSST; Kirschbaum, Pirke, & Hellhammer, 1993) was administered. The TSST requires participants to complete a difficult 3-minute arithmetic task in front of two trained judges. Participants stood in front of both judges and were asked to count backwards by 13 from either 1999 or 1022. If a mistake was made, participants were instructed to begin again starting at the first number. After five minutes, the judges stopped the task. Two different versions of the task (different number used as the starting point) were given, counterbalanced across pre- and post-ABMT to avoid order effects.

Self-reported changes in state anxiety was assessed using the State-Trait Anxiety Inventory (STAI; Spielberger & Gorsuch, 1983). The STAI is a 40-item questionnaire that
measures participants’ perceptions of their state and trait levels of nervousness and anxiety. State anxiety and trait anxiety are each measured using 20 items. For state anxiety (STAI-State) items are statements such as “I am worried” and participants are asked to rate them on a 4-point scale from 1 (“not at all”) to 4 (“very much so”) based on how they are feeling “right now at this moment”. Some items (i.e., “I am relaxed”) are reverse coded. Scores for state anxiety range from a minimum of 20 to a maximum of 80, with higher scores indicating greater anxiety. STAI-State was obtained before and after each TSST (Visit 1 and Visit 5). Stress Reactivity was calculated as the difference score of STAI-State post-TSST minus STAI-State pre-TSST with positive scores indicating an increase in state anxiety and negative scores indicating a decrease in state anxiety.

**Attention Bias (AB) Assessment and Attention Bias Modification Training (ABMT).**

*The Dot Probe.* The dot probe task (MacLeod & Mathews, 1988; MacLeod et al., 1986) followed parameters of the Tel-Aviv University/National Institute of Mental Health protocol. Stimuli for the dot probe task are photographs of 20 different individuals (10 males, 10 females) from the standardized NimStim stimulus set (Tottenham et al., 2009) with one female taken from the Matsumoto and Ekman (1989) set. Faces were placed on a background presented in color with each photograph subtending 45mm in width and 34 mm in height. In each trial, pairs of angry-neutral or neutral-neutral faces of the same actor were displayed. Stimuli were programmed using E-Prime version 2.0 (Schneider, Eschman, & Zuccolotto, 2002).

During each trial, two pictures were presented, either angry-neutral face pairs or neutral-neutral face pairs (depicting the same individual). The pictures were shown with equal distance above and below a fixation cross, with 14 mm between them. The task included 120 trials [80 TN trials (threat-neutral face pairs) and 40 NN control trials (neutral-neutral face pairs)]. Each trial comprised: (a) 500 ms fixation, (b) 500 ms face-pair cue, which then disappeared, (c) arrow
(target) in the former location of one of the faces until a response is made via the left or right mouse button to indicate the direction in which the arrow is pointing, and (d) 500 ms inter-trial interval (see Figure 2). Participants were asked to respond as quickly and as accurately as possible whether the arrow was pointing to the left or the right. Probes were equally likely to appear on the top or bottom, in the location of the angry or neutral face cues and pointing to the left or the right.

**AB (Mean AB).** An attention bias score was calculated from each dot probe assessment: Visits 1 and 2 (pre-training dot probe); Visit 5 (post-training dot probe). Trials with incorrect responses were excluded from further processing and analyses. Responses faster than -3SD from an individual’s mean and slower than +3SD from an individual’s mean were removed. Furthermore, all participants had an accuracy rate of 85% or above. The average response time was 570.72 (SD = 75.91) at Visit 1 was and the task accuracy rate was .98 (SD = .018). Mean AB was calculated as the average RTs for neutral probes on TN trials (TN-Neutral) minus RTs for threat probes on TN trials (TN-Threat) with positive scores indicating a bias towards threat and negative numbers indicating a bias away from threat. NN Trials were baseline trials where threat was not present. These trials were not used for AB calculation.

**Trial-Level AB Variability (TL Variability).** To quantify trial-level variability in attention bias, temporally-contiguous pairs of TN-Threat and TN-Neutral trials were matched across Visit 1 and Visit 5 AB assessment tasks separately (see Egan & Dennis-Tiwary, 2018). First, TN-Neutral trials were paired with the next closest TN-Threat trial. Second, TN-Threat trials were paired with the next closest TN-Neutral trials. A distance rule was applied such that paired trials were no further than five trials apart (before or after) and redundant pairings were discarded. This approach allows for the maximum number of temporally contiguous pairs of trials across the length of the dot probe task (120 trials). Within each pair of matched trials,
reaction times were subtracted according to the Mean AB score previously outlined. From the resulting group of trial-level bias scores (TL-BS) calculated per individual, five distinct measures were quantified: Mean Positive; Mean Negative; Peak Positive; Peak Negative; and TL Variability (see Figure 3). TL Variability was calculated as the sum of the distance between each sequential TL-BS divided by the number of pairs. This score provides a measure of the “length” of the plotted TL-BS line. Thus, the higher the summed value, the greater the variability seen towards and away from threat over time.

The average number of pairs created for each participant was 58.71 (3.06) and average trial distance between pairs was 1.95 (0.17). Furthermore, the average number of trials with no pair was 22.59 (7.50) and the average number of trials removed due to outlier criteria was 1.08 (0.54).

**Between-Context AB Variability (ΔAB).** To measure pre-training AB variability between two distinct timepoints, the difference between Mean AB scores at Visit 1 and Visit 2 (Visit 2 – Visit; ΔAB) was calculated. This method provides a measure of three levels of variability. A positive number indicates more variability via an increase in AB between visits or amplified expression of AB. Zero would reflect no variability or no change in AB between visits. A negative number indicates an increase in variability via a decrease in AB between visits or dampened expression of AB between visits. Thus, both positive and negative numbers reflect increased variability.

**ABMT or PT.** Participants were randomly assigned to complete four sessions of ABMT or placebo (PT) attention training that took place each week over one month. ABMT was designed to train attention away from threat via a modified dot probe in which the probe always replaces the neutral face cue with 100% contingency (TN-Neutral trials). In the modified dot probe for PT, there was an equal likelihood of the probe replacing either the threat or neutral face
cue designed to not directly train attention either towards or away from threat (50% TN-Neutral trials and 50% TN-Threat trials). Each session consisted of four blocks of 160 trials [120 TN training trials (threat-neutral face pairs) and 40 NN baseline trials (neutral-neutral face pairs)] for a total of 640 trials. In each block, there is a break offered every 40 trials. If accuracy falls below 70%, a warning was provided in the break slide. Each participant completed one session per week for four consecutive weeks. As with the AB task, reaction times to the probe on each trial were recorded.

*Training Performance (Gains and Losses).* Training performance was tracked by measuring whether or not mean reaction times to probes replacing neutral faces decreased (a training gain) or increased (a training loss) over the entire month of four training sessions. As outlined above, four blocks of training trials were completed per session for a total of 16 blocks (Session 1: 1, 2, 3, 4; Session 2: 5, 6, 7, 8; Session 3: 9, 10, 11, 12; Session 4: 13, 14, 15, 16). Within each block, the mean reaction time across trials in which the probe followed neutral face cues was computed. Thus, 16 mean RTs were computed per participant and plotted (see Figure 4). In addition, we computed an average RT for each session of training. Both block-level and session-level mean RTs were used in subsequent analyses. A reduction in RTs between sessions or blocks represents a gain whereas an increase in RTs between sessions or blocks represents a loss or increase in RTs during training. Only TN-Neutral trials with correct responses and with RTs greater than 150 ms but less than 2000 ms were included.

*Electrophysiological Recording and Data Reduction.*

EEG activity was recorded continuously during each AB assessment via 64 Ag/AgCl scalp electrodes embedded in an elasticized nylon cap (BioSemi; Amsterdam, NL). Electrodes in this system are arranged in accordance with the international 10/20 system. Eye movements were monitored by electro-oculogram (EOG) using four flat-type facial electrodes placed one cm
above and below the left eye (vertical eye movements) and one cm to the outer corner of each eye (horizontal eye movements). Electrodes preamplified the EEG signal to improve the signal-to-noise-ratio. EEG was recorded at a sampling rate of 512 Hz. During EEG acquisition, the voltage from each electrode was referenced online with respect to the common mode sense active electrode and the driven right leg electrode, which produces a monopolar (nondifferential) channel. Offline data processing was conducted using Brain Vision Analyzer (Version 2.2, GmbH; Munich, DE). All data were re-referenced offline to an average reference and filtered with a high pass frequency of .1 Hz and a low pass frequency of 30 Hz.

Stimulus-locked EEG to faces were segmented into epochs from 200 ms before stimulus presentation to 500 ms after stimulus onset, with a 200 ms (-200 ms to 0 ms prior to face onset) baseline correction. Following ocular correction (Gratton, Coles, & Donchin, 1983) and baseline correction, artifacts were identified using the following criteria and trials removed from analyses: data with voltage steps greater than 50 µV, changes within a given segment greater than 300 µV, and activity lower than .5 µV per 100 ms. Electrodes used for ERP components were selected via visual inspection of the topographical distribution of the first AB assessment data, grand averaged across all stimulus conditions and participants. Artifact-free EEG trials were used to calculate ERPs for each individual as follows: the P1 was calculated as the average amplitude between 90 ms and 120 ms at O1, PO3, PO7, P5, P7, O2, PO8, PO4, P6, and P8. The N2 was calculated as the average amplitude between 270 ms and 330 ms at Fz (see Figure 5 for ERP waveforms and scalp distributions)\(^1\). Both components were quantified on NN trials and averaged across TN-Threat and TN-Neutral trials.

Trial counts were averaged across stimulus conditions and participants for each Visit.

\(^1\) There were no significant differences in N2 amplitudes when averaging across Fz and Cz electrodes.
The average trial count at Visit 1 for P1 was 38.53 (SD = 1.62) and for N2 was 38.63 (SD = 1.83). The average trial count at Visit 2 for P1 was 38.52 (SD = 1.67) and for N2 was 38.47 (SD = 2.86). Lastly, the average trial count at Visit 5 for P1 was 37.66 (SD = 2.39) and for N2 was 38.03 (SD = 2.29). There were no significant differences in the average trial counts between ABMT and PT groups at any visit, all t’s < 1.54, p’s > .13. Furthermore, a small selection of participants were excluded from P1 analyses due to error in recording file or low trial counts (< 20 trials per condition) at any electrode site (four at Visit 1; eight at Visit 2; eight at Visit 5). For N2 analyses, participants were excluded from analyses if trial counts at Fz was below 20 trials per condition equivalent to 50% of trials (one at Visit 1; four at Visit 2; two at Visit 5).

**ERP to Threat**. For each component, mean amplitudes were generated on TN trials (TN-Threat and TN-Neutral) and NN trials. ERPs averaged across TN trials were used in all ERP analyses reported below (Rossignol, Philippot, Bissot, Rigoulot, & Campanella, 2012) to reflect brain activity while both threat and neutral faces appeared simultaneously. To account for brain activity when threat was not present, all analyses were conducted controlling for ERPs on NN trials. Trial counts were grand averaged across stimulus conditions and participants. Larger P1 amplitudes on TN trials (TN-Threat, TN-Neutral) reflect increased attention allocation whereas larger N2 amplitudes (more negative) reflect increased recruitment of cognitive resources.

**Between-Context ERPs (Δ P1 and ΔN2)**. To measure pre-training ERP variability between two distinct time points, the difference between P1 and N2 amplitudes to threat at Visit 2 minus Visit 1 was computed (Δ P1 and ΔN2). This difference score represents the change in neurocognitive responses to threat on the dot probe task over one week. This method provides a

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2 We first attempted to quantify within-task ERP variability by dividing the AB assessment task into multiple blocks of sequential trials- thirds or halves. Because ERPs are based on signal to noise reduction, components are typically quantified using an average value across a minimum number of trials (Luck & Kappenman, 2011). After artifact rejection, mean trials counts averaged across halves at Time 1 was 14.71(4.39) a with a range of 2 to 20. Thus, we were not able to maintain a suitable number of trials per component per block.
measure of three levels of ERP variability. For $\Delta P_1$, a positive number represents an increase in or amplified $P_1$ to threat from Visit 1 to Visit 2. A zero indicates no change or stability in $P_1$ and a negative number is a decrease in or dampened $P_1$ from Visit 1 to Visit 2. Because the N2 is a component with a negative deflection, a positive $\Delta N_2$ represents a decrease in or dampening of N2 to threat from Visit 1 to Visit 2. A zero indicates no change or stability in N2 and a negative $\Delta N_2$ is an increase in or amplified N2 from Visit 1 to Visit 2. EEG recording at Visit 2 was added to the study design after the start date. Therefore, Visit 2 ERP data was collected for a subset of individuals ($n = 72; 77\%$).

Procedure.

Visit 1. Participants were in the laboratory for approximately three hours. After consent, demographics and a self-reported anxiety measure (DASS) was completed. Then, EEG electrodes were applied, and participants were seated in an EEG recording booth 65 cm from a 17 in monitor. AB assessment 1 was completed via the dot probe task while EEG was continuously recorded. Following EEG removal, a trained lab member conducted the MINI and assessed anxiety severity (HAM-A). Lastly, participants completed the TSST with stress reactivity measured and the schedule of Visits 2-5 was reviewed.

Visit 2. One week later, participants returned to the lab for approximately 1.5 hours. After EEG application, AB assessment 2 was completed via the dot probe task while EEG was continuously recorded. Then EEG was removed and after a short break, participants completed ABMT Session 1.

Visits 3 and 4. The next two weeks following Visit 2, participants returned for 1 hour each week to complete Session 2 and Session 3 of ABMT.

Visit 5. Participants returned to the lab one more time, 1 week after Visit 4 and approximately five weeks after Visit 1. First, ABMT Session 4 was completed. Then, post-
training self-report anxiety (DASS) was measured. AB assessment 3 was completed via the dot probe task while EEG was continuously recorded. Following EEG removal, post-training MINI was conducted, and anxiety severity (HAM-A) was assessed. Lastly, participants completed the TSST with stress reactivity measured.

Results

Pre-Training Group Differences and Lab Stressor Manipulation Check

Statistical analyses were conducted using SPSS (Version 21). Age, baseline AB metrics (Mean AB, TL-BS), ERPs (P1, N2), measures of anxiety and depression, and stress reactivity are presented by training group in Table 2. There were no training group differences in any demographics or self-report measures (p’s > .08). Groups also did not differ across AB metrics or ERPs with the exception of P1 amplitudes on TN trials (p = .024) with the ABMT group showing significantly larger amplitudes.

As a measure of stress reactivity, we looked at changes in state anxiety via STAI-State from pre-TSST to post-TSST. To confirm that the TSST significantly increased state anxiety, we used a paired-samples t-test. At Visit 1, participants reported significantly higher levels of post-TSST state anxiety (M = 51.99, SD = 13.61) compared to pre-TSST (M = 39.45, SD = 11.42), t(91) = -12.03.

Pre-Training Correlations

Because the present study included multiple measures of anxiety and AB, we examined pre-training intercorrelations by conducting bivariate correlations between AB metrics (Mean AB, TL-BS), ERPs (P1, N2), self-reported measures of anxiety and depression, and stress reactivity. Mean negative (r = 0.37, p < .001) and peak negative (r = 0.26, p = .01) TL-BS
metrics were both positively correlated with Mean AB. All TL-BS metrics were inter-correlated (ranging between -0.89 - .85, all p’s < .001). DASS subscales (anxiety, depressions, and stress) were also highly positively inter-correlated (ranging between 0.59 - 0.74, all p’s < .001; see Table 3). In addition, independent self-report measures (DASS, HAM-A) were positively intercorrelated (ranging between 0.57 - 0.72, all p’s < .001). Correlations between ERPs and self-report measures show that higher stress was associated with larger P1 amplitudes to threat, $r(87) = 0.23, p = .033$.

Importantly, at baseline, behavioral AB metrics did not correlate with any self-report measures of anxiety, depression, or stress reactivity. ERPs and AB metrics were not significantly related, and no other correlations reached significance.

**Aim 1: Main Effects of Training on ABMT-Related Outcomes**

**Hypothesis 1.** First, we tested the hypothesis that ABMT relative to PT would be associated with reduced behavioral measures of AB (mean and temporally-sensitive) and anxiety-related outcomes (self-reported anxiety and stress, stress reactivity), and altered neurocognitive measures of AB (reduced P1 and enhanced N2). A series of 2 (Time: pre-training Visit 1 and post-training Visit 5) x 2 Training Group (ABMT or PT) repeated-measures ANCOVAs were conducted with overall mean RTs by trial type (TN-threat, TN-neutral, and NN), AB metrics (Mean AB, and TL Variability), self-reported anxiety and stress (DASS, HAM-A), stress reactivity (ΔSTAI-State), and ERPs on TN trials (P1, N2) as the dependent variables. Because of the robust relationship between measures of anxiety with depression in the current sample reported above and the importance of assessing the effects of comorbid depression on AB (see Bar-Haim et al., 2007), depression was entered as a covariate. For ERP analyses only, post-

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3 Scatterplots indicated an outlier participant for both mean negative and peak negative values. Correlations with this participant removed remained significant ($p < .001$ and $p = .03$).
training amplitudes on NN trials were also entered as a covariate to account for amplitudes on trials when threat was not present. To control for multiple comparisons, Bonferroni correction was applied.

There was a main effect of Time on stress reactivity measured, $F(1, 86) = 8.51, p = .01$, partial $\eta^2 = .09$. Pairwise comparisons revealed that self-reported change in state anxiety after the lab-based stressor decreased from Visit 1 ($M = 12.65, SE = 1.08$) to Visit 5 ($M = 5.92, SE = .98$).

In addition, there was a main effect of Time on N2 amplitudes, $F(1, 83) = 6.90, p = .01$, partial $\eta^2 = 0.08$. Pairwise comparisons revealed that N2 amplitudes increased from Visit 1 ($M = -2.28, SE = .19$) to Visit 5 ($M = -2.93, SE = .15$).

No other analyses reached significance. To further assess why AB was not reduced by ABMT as predicted, we tested whether ABMT versus PT differed in mean reaction times to each trial type. Since Mean AB is computed as the difference score of mean reaction times on TN-threat trials subtracted from TN-neutral trials, RTs, RTs on TN-neutral should be selectively faster when AB to be reduced via ABMT.

There was a significant main effect of Time on mean reaction times for each ANCOVA on all three trial types (TN-Threat, TN-Neutral, NN). For trials in which the probe replaced threat faces, [TN-Threat; $F(1, 87) = 38.73, p < .001$, partial $\eta^2 = 0.31$], pairwise comparisons revealed that RTs decreased from Visit 1 ($M = 571.12, S = 8.26$) to Visit 5 ($M = 510.81, SE = 6.43$), $p < .001$. For trials in which the probe replaced neutral faces, [TN-Neutral; $F(1, 87) = 54.69, p < .001$, partial $\eta^2 = 0.39$], pairwise comparisons revealed that RTs decreased from Visit 1 ($M = 571.85, SE = 8.07$) to Visit 5 ($M = 510.38, SE = 6.38$), $p < 0.001$. Lastly, for control trials

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4 Because there was a baseline group difference in P1 amplitudes on TN trials, we also conducted a one-way ANCOVA with Training Group as the independent variable and P1 amplitudes TN trials as the dependent variable and controlling for P1 amplitudes on TN trials. Results remained insignificant ($p = .50$).
Hypothesis 1 Summary. Counter to prediction, in both ABMT and PT, reaction times significantly decreased from pre to post-training visits for all trial types. In addition, stress reactivity decreased in both groups, and the N2 increased, the latter suggesting enhanced recruitment of neural resources associated with cognitive control. Null effects emerged. AB (Mean AB, \( p = .08 \); TL Variability, \( p = .66 \)) and anxiety (DASS-Anxiety, \( p = .12 \); DASS-Stress, \( p = .40 \); HAM-A, \( p = .24 \)) were not significantly reduced via ABMT or PT. Importantly, there were no significant interactions of Training Group x Time, suggesting that although participants showed reductions in stress reactivity and an increase in N2 amplitudes, these effects were comparable across ABMT and PT conditions.

Hypothesis 1a. Next, we tested the hypothesis that ABMT vs PT will show greater training performance gains, with the largest gains occurring in the second half of the month reflecting compounded effects of consolidation on learning. To do so, we conducted a 2 (Training Session: 1 and 4) x 2 (Training Group: ABMT and PT) repeated-measures ANCOVA with training performance as the dependent variable. As with other target outcomes above, depression was entered as a covariate. To control for multiple comparisons, Bonferroni’s correction was applied.

Contrary to predictions, the interaction effect of Training Group X Training Session on performance was not significant (\( p = .94 \)). Instead, there was only a main effect of Training

\[ F(1, 87) = 44.13, \quad p < .001, \quad \text{partial } \eta^2 = 0.34, \]

pairwise comparisons revealed that RTs decreased from Visit 1 (\( M = 572.04, \quad SE = 8.10 \)) to Visit 5 (\( M = 509.10, \quad SE = 6.22 \)), \( p < .001 \).

\[ F(1, 87) = 37.54, \quad p < .001, \quad \text{partial } \eta^2 = 0.30, \]

\[ F(1, 87) = 15.01, \quad p < .001, \quad \text{partial } \eta^2 = 0.15, \]

\[ F(1, 87) = 21.11, \quad p < .001, \quad \text{partial } \eta^2 = 0.20, \]

\[ F(1, 91) = 20.44, \quad p < .001, \quad \text{partial } \eta^2 = 0.18 \] were significantly reduced from pre to post-training visits.

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5 Post hoc paired-samples t-tests showed that the change in RTs across trial types were not significant, \( p \)'s > .41.
6 When DASS-Depression was not entered as a covariate, main effects of Time were significant across all measures of anxiety and depression. Scores on DASS-Anxiety \( [F(1, 87) = 37.54, \quad p < .001, \quad \text{partial } \eta^2 = 0.30] \), DASS-Depression \( [F(1, 87) = 15.01, \quad p < .001, \quad \text{partial } \eta^2 = 0.15] \), DASS-Stress \( [F(1, 87) = 21.11, \quad p < .001, \quad \text{partial } \eta^2 = 0.20] \), and HAM-A, \( [F(1, 91) = 20.44, \quad p < .001, \quad \text{partial } \eta^2 = 0.18] \) were significantly reduced from pre to post-training visits.
Session, $F(1, 87) = 18.17, p < .001$, partial $\eta^2 = 0.17$. Pairwise comparisons showed training performance improved (faster RTs) equally for ABMT and PT groups from Session 1 ($M = 533.12, SE = 6.47$) to Session 4 ($M = 515.38, SE = 5.71$), $p < .001$ (see Figure 6). Thus, for both sessions, no group differences emerged ($p$’s > 0.44). Furthermore, depression was not significantly related to training performance ($p = .54$).

To examine whether the largest gains in performance would be evident in the second half of the month, we focused in on the first blocks of the last two training sessions and conducted a 2 (Training Block: 9 and 13) x 2 (Training Group: ABMT and PT) repeated-measures ANCOVA with training performance as the dependent variable and controlling for training performance during the first two training sessions (Block 1 and Block 5). Blocks 9 and 13 were used due to previous findings that performance improves during the first 200 trials (Abend et al., 2014) and Blocks 1 and 5 were entered as covariates to account for performance in the first half of training. There was an interaction of Training Block X Training Group, $F(1, 89) = 4.79, p = .03$, partial $\eta^2 = .05$. Consistent with predictions, performance improved for the ABMT group but not the PT group in the second half of training. During ABMT, performance in Block 13 ($M = 504.49, SE = 3.68$) was significantly better (faster RTs) than in Block 9 ($M = 514.36, SE = 4.08$), $p = .03$. This effect was not significant in the PT group ($p = 0.38$), see Figure 7.

**Hypothesis 1a Summary.** The ABMT group showed significantly more training performance gains relative to the PT group, but only in the second half of the training period. Based on these findings, we used the following approach to measure training performance as a target ABMT outcome in all subsequent regression analyses: performance on Block 13 when controlling for performance on Block 9.

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7 Because depression was not related to training RTs, it was removed as a covariate for subsequent training performance ANCOVAs.
**Aim 2: Individual Differences in Temporally-Sensitive Behavioral Measures of AB**

_Hypothesis 2._ To test the hypothesis that greater TL variability and an increase or stability in AB between measurement contexts will be associated with worse anxiety-related outcomes and training performance losses, we used a series of hierarchical regressions. Pre-training TL Variability and ΔAB were independently examined as moderators of the effect of ABMT on anxiety, stress reactivity, and training performance above and beyond the traditional mean AB metric. TL Variability reflects the range of temporal stability of attention within a single task with larger numbers indicating more pronounced and or frequent shifts in attention and smaller numbers indicating a more consistent pattern of attention. ΔAB reflects the direction of change of Mean AB when measured between two pre-training visits. A positive number indicates an increase or amplified AB between visits. Zero indicates no change or stability in AB between visits. A negative number indicates a decrease or dampening in AB between visits.

Each post-training anxiety and clinical measure was entered separately as the dependent variable with the following variables entered in separate steps: 1) the corresponding pre-training measure and DASS-Depression 2) Mean AB; 3) TL Variability or ΔAB; 4) Training Group; 5) interaction between Training and AB (e.g. ABMT Group X TL Variability). There were five dependent variables [DASS-Anxiety, DASS-Stress, HAM-A, stress reactivity, and training performance] X two moderators (TL Variability, ΔAB) for a total of 10 regressions. Based on recommendations for probing interaction effects (Aiken, West, & Reno, 1991; Finney, Mitchell, Cronkite, & Moos, 1984), interaction terms’ contributions to R² that approached significance (p ≤ 0.10) were followed up with the PROCESS macro for SPSS (Hayes, 2013) using simple regression equations. Moderators (TL Variability, ΔAB) were mean centered and three levels of
each moderator were generated (mean value and +/- one standard deviation from the mean). Due to the comorbidity between anxiety and depression (Kessler et al., 2005) and the strong significant correlation in the current sample between anxiety and depression (see section on Baseline Correlations), depression scores were entered in Step 2 as a covariate in all regression analyses (see Dennis-Tiwary, Denefrio, & Gelber, 2017). See supplement for full model statistics of regressions reported below.

**Trial-Level AB Variability (TL Variability).** A significant Training Group effect and Training Group X Trial-Level Variability interaction effect emerged on training performance. The main effect of Training Group on training performance showed that the PT group evidenced worse performance (more losses) than the ABMT group \[\beta = .12; t(83) = 2.09, p = .04\]. The interaction showed that ABMT was associated with better training performance than PT, but only when individuals showed high levels of pre-training variability. The same trend emerged for individuals at moderate levels of variability [Full model: \(F(6, 83) = 41.56, p < 0.001, R^2 = 0.75\); interaction step change statistics: \(F(1, 83) = 5.54, p = 0.02, R^2 = 0.02\); see Figure 8].

**Between-Context AB (ΔAB).** First, there was a main effect of Mean AB such that a larger Mean AB score was related to lower stress reactivity \[\beta = -.38; t(62) = -2.00, p = .05\]. Second, a significant Training Group X ΔAB interaction effect on stress reactivity emerged showing that ABMT was associated with greater stress reactivity than PT, but only for participants who showed an increase in AB between two pre-training visits [Full model: \(F(6, 62) = 3.98, p = 0.002, R^2 = 0.28\); interaction step change statistics: \(F(1, 62) = 3.93, p = 0.05, R^2 = 0.05\); see Figure 9].

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8 As a follow-up to Aim 2 regressions and because there was one significant main effect of Mean AB, all 10 models were repeated using ABMT x Mean AB interactions in Step 6. All interactions failed to reach significant (all p’s ranging from .13 - .93). Therefore, moderation effects of TL Variability and ΔAB were above and beyond Mean AB effects.
**Hypothesis 2 Summary.** Temporally-sensitive measures of AB at baseline moderated the relationship between training group and training performance and stress reactivity. Contrary to predictions, pre-training trial-level variability predicted greater training performance gains, for the ABMT group relative to PT. As predicted, a pre-training increase in AB predicted increased stress reactivity in the ABMT group relative to PT. In addition, a larger mean AB predicted less post-training stress reactivity regardless of training group.

**Aim 3: Individual Differences in Neurocognitive Measures of AB**

**Hypothesis 3.**

*ERPs to Threat (P1 and N2).* To test the hypothesis that greater P1 and N2 amplitudes to threat at baseline would predict worse anxiety-related ABMT outcomes and training performance losses, we used a series of hierarchical regressions. Each post-training anxiety and clinical measure was entered separately as the dependent variable with the following predictors entered in separate steps: 1) the corresponding pre-training measure, corresponding ERP amplitudes on NN trials, and DASS-Depression; 2) ERPs to threat at Visit 1; 3) Training Group; 4) interaction between Training Group and ERP (e.g., ABMT x N2). Larger P1 amplitudes to threat reflect increased attention allocation whereas larger N2 amplitudes (more negative) reflect increased attention control. There were five dependent variables [DASS-Anxiety, DASS-Stress, HAM-A, stress reactivity, and training performance] X two ERP moderators (P1, N2) for a total of 10 regressions. Based on recommendations for probing interaction effects (Aiken & West, 1991; Finney, Mitchell, Cronkite, & Moos, 1984), interaction terms’ contributions to $R^2$ that approached significance ($p \leq .10$) were followed up with the PROCESS macro for SPSS (Hayes, 2013) using simple regression equations. Moderators (P1, N2) were mean centered, and three levels of each moderator were generated (mean value and +/- one standard deviation from the
P1. One significant Training Group X ERP interaction effect emerged. Anxiety was higher following ABMT vs PT, but only for participants who showed larger pre-training P1 amplitudes to threat [Full model: $F(6, 80) = 8.64, p < .001, R^2 = 0.39$; interaction step change statistics: $F(1, 80) = 2.91, p = .09, R^2 = 0.02$; see Figure 10].

*Between-Context ERPs (ΔP1 and ΔN2).* To test the hypothesis that a between-context increase or stability in ERPs at baseline would predict worse anxiety-related ABMT outcomes and training performance losses, we again used a series of hierarchical regressions. Each post-training anxiety and clinical measures were entered separately as the dependent variable with the following predictors entered in separate steps: 1) the corresponding pre-training measure, corresponding Δ ERP amplitudes on NN trials, and DASS-Depression; 2) Between-Context ERP (ΔERP amplitudes on TN trials); 3) Training Group; 4) interaction between Training and Between-Context ERP (e.g., ABMT x ΔN2). ΔERP was calculated as the difference score of amplitudes on TN trials at Visit 2 minus Visit 1. An increase in amplitudes to threat between visits is thought to reflect increased recruitment of neurocognitive resources. Whereas, a decrease in amplitudes to threat between visits is interpreted as a reduced neurocognitive response to threat. Zero indicates no change or stability in threat responding. There were five dependent variables [DASS-Anxiety, DASS-Stress, HAM-A, Stress Reactivity, and Training Performance] X two Between-Context ERP moderators (ΔP1, ΔN2) for a total of 10 regressions. Based on recommendations for probing interaction effects (Aiken & West, 1991; Finney,
Mitchell, Cronkite, & Moos, 1984), interaction terms’ contributions to $R^2$ that approached significance ($p \leq .10$) were followed up with the PROCESS macro for SPSS (Hayes, 2013) using simple regression equations. Moderators were mean centered, and three levels of each moderator were generated (mean value and +/- one standard deviation from the mean). $\Delta$P1 and $\Delta$N2 amplitudes on NN trials of the dot probe were entered in Step 2 to control for any variance in ERPs not specific to threat processing. Depression was entered in Step 3 to control for the high correlation between depression and anxiety symptoms. See supplement for full model statistics of regressions reported below.

$\Delta$N2. Two significant Training Group X $\Delta$N2 interaction effects emerged, one for anxiety and one for stress reactivity. When anxiety was the dependent variable, anxiety was lower following ABMT vs PT, but only for participants who showed an increase in N2 amplitudes between the two pre-training visits (negative $\Delta$N2) [Full model: $F(6, 56) = 12.37, p < .001, R^2 = 0.57$; interaction step change statistics: $F(1, 56) = 4.92, p = .03, R^2 = 0.04$; see Figure 11].

When stress reactivity was the dependent variable, there was significant main effect of $\Delta$N2, such that a decrease in pre-training N2 amplitudes to threat (positive $\Delta$N2) was related to lower stress reactivity [$\beta = -.91; t(56) = -2.33, p = .02$]. Next, there was a significant Training Group X $\Delta$N2 interaction for stress reactivity. The interaction revealed that stress reactivity was greater following ABMT vs PT, but only for participants who showed an increase in pre-training N2 amplitudes (negative $\Delta$ N2), [Full model: $F(6, 56) = 2.28, p = 0.05, R^2 = 0.20$; interaction step change statistics: $F(1, 56) = 5.14, p = .03, R^2 = 0.07$; see Figure 12].

No Training Group x $\Delta$P1 interactions reached significance.

**Hypothesis 3 Summary.** Pre-training ERPs to threat and $\Delta$ERPs to threat moderated the relationship between ABMT and anxiety and stress reactivity. Larger P1 amplitudes prior to
training, a neurocognitive measure of early visual threat processing, predicted greater post-
training anxiety in the ABMT group relative to PT. For ΔN2, an increase in N2 between pre-
training visits, reflecting increased recruitment of cognitive control, predicted lower anxiety and
increased stress reactivity in the ABMT group relative to PT.

**Exploratory Hypothesis 3a.** To test the hypothesis that neurocognitive measures of AB
and temporally-sensitive behavioral measures of AB would be positively intercorrelated,
bivariate correlations were performed between behavioral AB measures (TL Variability, ΔAB),
ERPs (P1, N2), and between-context ERP measures (ΔP1, ΔN2). For the whole sample, less TL
variability was correlated with larger P1 amplitudes to threat at the level of a trend, $r(89) = -1.99,$
$p = .06$. In addition, greater ΔAB (increase in pre-training AB) was associated with negative ΔN2
(increase in pre-training N2) at the level of a trend, $r(72) = -.209$, $p = .078$. No other correlations
reached significance.

**Hypothesis 3a Summary.** There were trend level associations between temporally-
sensitive behavioral and neurocognitive measures of AB.

**Discussion**

Traditionally, anxiety has been associated with an attentional bias (AB) towards threat,
which has informed development of innovative treatments like attention bias modification
training (ABMT) (Beard et al., 2012; Hakamata et al., 2010). Recent documentation of AB
heterogeneity and variability, including AB away from threat in anxious populations and null and
mixed findings regarding the efficacy of ABMT, have prompted reevaluation of how to
conceptualize and measure AB in order to better predict anxiety-related outcomes and
personalize ABMT (Koster & Bernstein, 2015). The current study tested the predictive power of
pre-training individual differences in temporally-sensitive neurophysiological (ERPs) and novel
reaction-time (TL-BS) metrics within the context of an ABMT treatment study. These metrics target poorly-understood, but clinically-relevant, variability in the anxiety-related AB. Overall, we found that contrary to predictions, ABMT was not superior to PT and both led to improvements in clinical outcomes. Stress reactivity was reduced, training performance improved, and the N2 was boosted equally across groups. Consistent with predictions, individual differences in ERPs and TL-BS metrics measured prior to training moderated the relationship between ABMT and anxiety-related and clinical outcomes. Mean AB scores did not. These findings not only highlight the value of expanding on traditional behavioral methods but more importantly, support the use of ERPs as a neurocognitive index of visual attention to threat (P1) and cognitive control recruited in the presence of threat (N2). Because of their millisecond precision, new and innovative ways to evaluate individual differences in ERPs prior to ABMT can help to clarify discrete attentional processes underlying AB and its remediation via ABMT. 

First, individual differences in trial-level AB variability predicted ABMT effects. When pre-training TL variability was high, those in the ABMT vs PT group showed enhanced training performance measured via faster reaction times on active training trials during the second half of the month. Previous studies have shown that anxiety is associated with greater TL variability (M. L. Davis et al., 2016; Iacoviello et al., 2014; Schäfer et al., 2016; Zvielli et al., 2014b) and attributed this to the idea that TL variability reflects disorganized attentional shifts and dysregulated attention both towards and away from threat. However, no study we know of has looked at TL variability in relation to training performance. One plausible interpretation of this finding is that the ability to shift attention both towards and away from threat signals a malleable AB and primes the participant for training protocols designed to focus attention consistently in one direction. PT participants who showed high levels of variability did not have a consistent training pattern to benefit from. Thus, high levels of TL variability prior to training may indicate
a disorganized pattern of attention to threat that is both associated with anxiety and trainability. As such, TL variability may be an important individual difference prior to training that can indicate ABMT responsiveness, and the potential to benefit from ABMT.

Individual differences in between-context change in AB were also associated with anxiety-related outcomes. As predicted, an increase in AB (positive ΔAB) between two pre-training visits resulted in more state anxiety following an acute lab stressor, but only for those in the ABMT group. This effect on stress reactivity was not evident at no change (stability) or a decrease in AB. Therefore, increased responsiveness to threat via dot probe cues prior to training signaled a larger response to stress after ABMT. This result extends beyond TL variability as a measure of dynamic AB, showing that change (either increase or decrease) across assessment contexts is also predictive of ABMT-related outcomes. The degree of AB change did moderate the relationship between training group and stress reactivity. One explanation is that a more rigid and exaggerated AB between visits may reflect pathologically fixed attention to threat that drives anxiety symptoms. Rather than demonstrating learning effects, attention to threat increased the second time participants completed the dot probe. Indeed, stress manipulation tasks prior to AB have been shown to increase AB suggesting that AB is not fixed but instead sensitive to shifts in mood and anxiety. For example, Mogg and colleagues (1990) found that participants had a larger AB following a stressor and that this was not influenced by trait anxiety. Thus, variability in AB can be conceptualized in multiple ways and this is among the first studies to include a range of different approaches.

In addition, mean AB scores predicted stress reactivity such that larger AB was associated with less stress reactivity regardless of training. This finding is important because it was the only significant finding using mean AB scores. It supports recent meta-analyses that underscore the importance of starting with a pre-training AB and the need to test for such
individual differences when exploring non-significant ABMT reductions in AB (Mogg et al., 2017).

Taken together, findings suggest that temporally-sensitive behavioral AB measures moderated the relationship between ABMT and training performance and stress reactivity. Individual differences in these measures should be fully evaluated as prerequisites for successful training and post-training AB modification. In particular, variability in AB may signal the capacity for change inherent to the success of ABMT. For between-context changes in AB, a pattern of stability in mean AB between visits would be most consistent with the standard and static way that AB is typically measured. But rather, we show that instability in AB was significant individual difference that influenced stress reactivity. This reflects the recent recommendation for improving reliability of the dot probe by averaging scores across multiple timepoints (Price et al., 2015). Furthermore, these findings support the importance of looking at a combination of both trait and state-related ABMT outcomes. Stress reactivity was reduced overall and was sensitive to both mean AB and between-context change in AB. Thus, both state-level changes in anxiety and stable measures of anxiety should be used as ABMT outcomes.

In addition to behavioral temporally-sensitive measures, ERPs were used in the current study as a neurocognitive measure of AB with precise temporal detail. Specifically, the P1 and N2 components were used to characterize biased processing of threat at a very rapid timescale and, as predicted, both components moderated the relationship between training and anxiety-related ABMT outcomes. Consistent with Hypothesis 3, larger P1 amplitudes prior to ABMT, not PT, resulted in higher post-training anxiety. Thus, pre-training attention allocation to threat disrupted ABMT. One possible explanation for this effect is that fewer ABMT active training trials (as seen in the PT condition) are more beneficial when attention allocation to threat is already enhanced – as indexed by a larger P1. In contrast, the large number of training trials in
the ABMT condition in which threat was present but participants had to repeatedly disengage from only exacerbated anxiety. Indeed, multiple studies have suggested that AB is associated with a difficulty disengaging from threat-themed stimuli (Derryberry & Reed, 2002; Fox et al., 2001b, 2002). Furthermore, a larger baseline P1 to threat may be part of a threat-reactive neurocognitive profile that reflects a more potent AB, resistant to effects of ABMT. This result is in line with previous work in our lab using a gamified version of ABMT. Recently, we found that those in the ABMT versus PT condition showed more self-reported anxiety when they also showed larger pre-training P1 amplitudes (Dennis-Tiwary, Denefrio, & Gelber, 2017) which was replicated in the present study.

The N2 is a later-emerging ERP that reflects relatively controlled cognitive processing of threat. Although previous studies have documented that ABMT boosts the N2, in the current sample, N2 amplitudes increased overall across both ABMT and PT groups (CITE) and contrary to predictions, the N2 did not predict anxiety-related outcomes. However, individual differences in pre-training change in N2 between two visits did predict two target outcomes. Regardless of training group, a decrease in pre-training N2 amplitudes to threat predicted less stress reactivity. When N2 amplitudes increased from Visit 1 to Visit 2, the ABMT group showed lower levels of anxiety. One possible explanation for this effect is that an elevated recruitment of cognitive control between two separate dot probe tasks reflects a threat-reactive profile, similar to a larger P1 as discussed above. If cognitive control is increased the second time the participant is exposed to the dot probe, then it may suggest inefficiency such that that more effort is needed to shift attention towards and away from threat when threat and neutral cues compete. In ABMT, there is a high degree of repetition of neutral-cued trials only creating a learning environment that allows for a participant with elevated cognitive control to engage only with neutral stimuli and practicing directing attention away from threat. In addition, an increase in N2 amplitudes
between two visits prior to ABMT predicted increased stress reactivity relative to PT. This finding is consistent with the idea that state-level responsiveness of the N2 to threat is related to state-level response to stress at the level of behavior. Thus, increased recruitment of the N2 may signal both threat processing inefficiency and stress response inefficiency.

A small number of previous ERP studies have shown that ABMT increases N2 amplitudes from pre to post training (Eldar & Bar-Haim, 2010; for review Torrence & Troup, 2018) suggesting that the ability to boost N2 is beneficial and that attention control maybe one mechanism underlying how ABMT reduces AB. In one such study, authors measured attention control with a questionnaire and then assigned individuals to either ABMT or control training (Paulewicz, Blaut, & Kłosowska, 2012). They found that attention control was an important individual difference that predicted a reduction in attention to threat following ABMT. This effect was not influenced by trait anxiety. However, there is little research available on individual differences in the N2 predicting outcomes and no research similar to the present design of looking at between-context change in N2 as a precursor for training potential. Therefore, the present findings suggest that more work is needed to understand how N2 stability and variability may index an individual’s ability to harness cognitive control towards the task at hand versus inefficient recruitment of cognitive control in response to threat. Further, it is unknown whether variability in these discrete cognitive responses to threat is related to anxiety and behavioral measures of AB. Thus, a major goal of the current study was to begin to develop parallel metrics that measure variability in ERP responses to threat.

Finally, we found trend-level evidence that these novel neurocognitive measures of AB were related to behavioral measures AB variability and between-context change. Less trial-level AB variability was associated with larger P1 amplitudes to threat consistent with the view that a more consistent and rigid pattern of attention towards threat is associated with enhanced visual
threat processing. Furthermore, an increase in pre-training AB was associated with an increase in pre-training N2. One possibility this trend suggests is that an increase in behavioral attention to threat was related to a neurocognitive recruitment of cognitive control resources in an attempt to compensate and/or regulate biased attention towards threat. A second and alternative interpretation is that the N2 is indexing greater attention capture by angry faces. However, training overall boosted the N2 and reduced stress reactivity implicating the N2 as possible mechanism by which attention to threat is shifted. Thus, further investigation is needed to clarify whether N2 is indexing threat processing inefficiency or whether any form of attention training (ABMT or PT) that boosts N2 is beneficial.

**Null Findings**

The current findings, including null findings, highlight the importance of future ABMT research taking an individualized and personalized approach. One month of ABMT failed to reduce mean AB, TL-BS metrics of AB, and self-report measures of anxiety. Furthermore, stress reactivity decreased and N2 amplitudes increased regardless of receiving ABMT or PT.

Contrary to predictions, ABMT did not reduce AB. The behavioral measurement of AB requires competition between threat and neutral stimuli and is defined as a response speed advantage to threat relative to neutral. In the current study, reaction times across all three trial types (TN-Threat, TN-Neutral, NN) significantly decreased from pre to post-training visits. Therefore, Mean AB, or the difference between TN-Threat and TN-Neutral trials, remained unchanged. Moreover, consistent with previous ABMT vs PT treatment studies, remediation of anxiety symptoms was not evident in the absence of reductions in AB at post-training assessments (see MacLeod & Clarke, 2015 for review). Since AB was not altered, the lack of ABMT group effects (e.g., anxiety) is not surprising.
Failure to replicate initial support for the causal link between ABMT and anxiety reduction have caused doubt about the clinical implications of ABMT (Emmelkamp, 2012). One of the most recent ABMT meta-analyses reviewed 34 studies and found that anxiety reduction frequently occurs across both ABMT and PT conditions (Mogg et al., 2017) and that anxious participants often do not exhibit a pre-training AB. Our data supports both of these conclusions. We saw a decrease in stress reactivity across both training groups and our clinically-anxious sample had a mean AB score of .81(20.44) indicating less than a 1 ms facilitation to threat relative to neutral-cued probes. The current failure to reduce AB adds to a growing number of ABMT studies reflecting a trend toward small effect sizes that are driven by a large proportion of insignificant findings within clinically anxious samples (Cristea, N Kok, & Cuijpers, 2015; Fitzgerald et al., 2016) and should prompt more careful consideration of how ABMT RCTs can be improved.

One such area for improvement is the quality of placebo conditions used for ABMT comparison. Across randomized control ABMT trials, the PT condition looks very much like the AB assessment task with an equal distribution of trials in which probes replace neutral and threat cues. As a direct comparison to ABMT with 95% to 100% contingency of probes replacing neutral cues, PT has no reliable repetition of any one type of trial. What is noticeably absent from studies that report null finding in particular is any type of measure of training performance. Here, the lack of ABMT vs PT effects on targeted outcomes may be best explained by fully considering training performance results. In line with other standard control conditions, the PT condition used in the current study involved half the trials with probe replacing threat and half the trials with probe replacing neutral cues (active ABMT training trials). In other words, participants assigned to PT received half the number of ABMT training trials relative to the ABMT condition. Although there was no implicit learning that the probe would follow the
neutral stimulus location, PT participants still completed 240 per session for a total of 960 neutral-cued active training trials over the month of training sessions. In addition, some of the newest available data looking at ABMT protocol characteristics has shown that the sheer total number of trials matter. Specifically, Price and colleagues (Price et al., 2017) pooled datasets from available ABM RCTs and found that studies administering more that 1,280 training trials did not find significant group differences in target outcomes. In the current design, ABMT consisted of 1,920 trials training attention away from threat suggesting. In light of this finding, it is possible that we exceeded optimal ABMT dosing and that learning effects from the high number of similar trials in the PT condition washed out any group difference. Thus, the possibility that PT participants benefited from practice directing attention away from threat on these trials cannot be ruled out.

There are several findings to support the hypothesis that PT was beneficial for participants. First, RTs across all assessment trial types were equally reduced. Second, recruitment of cognitive control resources via the N2 was equally boosted. Third, both training conditions showed an equal reduction in stress response to an acute lab stressor. Finally, overall training performance on active training trials improved equally. Because PT conditions such as the one used here have many of the same characteristics of active training, the present results should be carefully considered. In line with this suggestion, Enock and colleagues (Enock, Hofmann, & McNally, 2014) tested the effects of three different training conditions (ABMT, control, and waitlist) on a socially anxious sample. They also found significant symptom reduction effects equal in magnitude across ABMT and control training groups. Only the waitlist comparison group did not benefit. Furthermore, recent meta-analyses have shown that in some studies, PT results in better outcomes relative to ABMT, in particular for individuals showing a pre-training AB away from threat (Price et al., 2016). This may be due to a poor fit between
ABMT and participants that do not have a pre-training AB to reduce. In fact, it has been suggested that PT conditions similar in design to the present one may even be indicated over ABMT for the treatment of anxiety disorders characterized by attentional avoidance such as PTSD and social phobia (Badura-Brack et al., 2015).

In sum, not only do these recent effects demand a further critique of categorizing pre-training AB as *either* towards or away from threat with a single static mean difference score but also that personalizing ABMT requires a much more detailed look at placebo training conditions that are meant to serve as a true control comparison.

**Limitations**

The present study was an important first step in understanding how temporally-sensitive AB metrics may interact with ABMT to predict anxiety-related outcomes. Many ABMT RCTs only test for main effects of training on anxiety and associated symptoms. In contrast, our aims were to specifically examine individual differences in pre-training AB and AB variability that may moderate the effects of ABMT on clinically-relevant outcomes. However, we did not investigate the mechanisms by which ABMT shifts attention and alters anxiety as it was beyond the scope of this dissertation. That is, we did not look at whether changes in AB or ERPs mediated changes in anxiety. Studies looking at mechanism have shown that there are different components of attention underlying AB such as orienting to threat and disengagement from threat and that in order to modify ABMT protocols, mechanism of change must be further understood (Cisler & Koster, 2010; Yiend et al., 2015). A recent pooled individual-level meta-analysis of ABMT explicitly looked at AB as a mechanism of change in anxiety remediation (Price et al., 2016). They found that change in AB mediated the effects of ABMT on anxiety ratings when optimal training conditions were met which included participants who were younger than 37 years old and trained in a laboratory setting. These findings help to clarify the
conditions under which reductions in clinical symptoms via ABMT may be boosted by establishing firm evidence of mechanism for change and contextual factors that will maximize this change.

The present sample was clinically comorbid by design and showed a range of clinical severity in order to better understand the dimensional aspect of anxiety symptoms and serve as a valuable comparison to single-disorder studies. At the same time, we acknowledge that this heterogeneity might have introduced some unintended variance in the remediation of anxiety-related and clinical outcomes. Almost one fourth of our sample met criteria for a primary diagnosis of MDE based on clinical interview. Although little is known about how comorbid anxiety and depression impact AB and its remediation via ABMT, some studies have shown that depressed patients do not display an AB (Mogg, Bradley, Williams, & Mathews, 1993). Although, recent studies have shown that ABMT is not contraindicated for depression and that using active training protocols to training attention toward positive face stimuli reduced depressive symptoms and waking cortisol (Browning, Holmes, Charles, Cowen, & Harmer, 2012; Lazarov & Bar-Haim, 2016). To account for possible effects of comorbidity, we controlled for self-reported levels of depression in all main outcome analyses and regression models. Depression and anxiety were robustly correlated, and when depression was not accounted for, all self-report measures of anxiety severity were reduced over from Visit 1 to Visit 5. Interestingly, ABMT did not influence this change.

Using a selection of novel temporally-sensitive behavioral and neurocognitive measures is a strength of current design but also comes with certain limitations. First, we have a limited basis of previous research from which to generate predictions. In particular, between-context change in AB and in ERPs are two approaches that are being tested together for the first time in this study. First, we wanted to expand on Hereen et al.’s (2014) previous work quantifying a
variance metric between two visits and instead measure the direction of change in AB as a pre-training individual difference. Second, we wanted to mirror directional changes at the behavioral level by evaluating between-context changes in the P1 and N2. By doing this, we were able to further evaluate the dynamic nature of attention to threat. Results add value to the field in supporting the unstable nature of AB as a phenomenon. However, we are also limited in our interpretations until more work has been done. We also intended to measure ERP variability during the dot probe by dividing the task into multiple sections and comparing variability across sections. However, we were limited by the number of trial counts available after artifact rejection. Because ERPs are based on signal to noise reduction, components are typically quantified using an average value across a minimum number of trials (Luck & Kappenman, 2011). Thus, we were not able to maintain a suitable number of trials per component. Lastly, we took the novel approach of evaluating training performance which gave us the opportunity to track change in reaction times over of four training sessions, each encompassing four blocks of training trials. Thus, we have a wealth of training data to analyze in new and exciting ways. The two approaches used in the current study represent an initial inquiry into how to measure performance during ABMT as an important indicator of intended change.

**Future Directions**

As the most common mental illness, anxiety disorders pose a significant challenge to Americans (Whiteford et al., 2013). Remarkably, most individuals in need of mental health counseling receive no treatment. This is in part because current standards in anxiety treatment have depended widely on lengthy and expensive interventions designed to identify conscious obsessions and restructure the cognitions and behaviors that surround those obsessions and negative thoughts (Insel, 2012). Thus, treatment options are limited, expensive, and symptom remission is far too low (Griебel & Holmes, 2013). One meta-analysis of CBT randomized
control trials found that although CBT was more effective compared to placebo conditions, results differed significantly by disorder with Obsessive Compulsive Disorder (OCD) having the greatest benefit and Generalized Anxiety Disorder (GAD) and Panic Disorder (PD) benefiting the least (Hofmann & Smits, 2008). However, more recently effort has shifted to develop affordable and accessible alternatives designed to address this gap between need and care and treat more unconscious elements of anxiety (e.g., Kazdin, 2015, 2017). Hence, investigation of cognitive biases in anxiety such as AB and novel treatments such as ABMT is a timely endeavor.

The present study worked towards a better understanding of how to measure within-person variability and stability in AB in order to use these concepts to inform interventions designed to modify AB, such as ABMT. We acknowledge that this is only the start of promising new methods of analysis that have potential to improve current AB conceptualization and measurement without abandoning the dot probe task or ABMT, despite the current impediments and conflicting findings reviewed here.

Some of the most promising new research in AB has been the development of non-invasive neuromodulation techniques. One innovative and safe approach to interrogate underlying neurocognitive mechanisms of AB is transcranial Direct Current Stimulation (tDCS). In tDCS, electrodes are placed on the scalp, carefully positioned over the areas of interest and a weak but constant current (~ 2 mA) is delivered (Brunoni et al., 2012; Nitsche et al., 2007). The current alters polarization of the resting membrane potential, stimulating brain areas below. This allows the researcher to effectively target areas of the prefrontal cortex that are suspected to control top-down mechanisms of AB during ABMT and test the effects of current-induced alterations (P. J. F. Clarke, Browning, Hammond, Notebaert, & MacLeod, 2014; Heeren, Baeken, Vanderhasselt, Philippot, & de Raedt, 2015). When compared to a sham condition, tDCS applied to the dorsolateral PFC (dIPFC) while participants with social anxiety completed
ABMT, resulted in a significant decrease in AB (Heeren et al., 2017) suggesting that ABMT can be boosted via top-down attention control.

A novel approach to EEG data analysis, called neural quenching, capitalizes on the finding that variability is inherent in cortical activity underlying sensory functions even over repeated exposure to a stimulus. Neural quenching is a measure of the amount of reduction in variability prior to stimulus presentation compared to post-presentation with more quenching thought to reflect processing efficiency (Arazi, Censor, & Dinstein, 2017). Remarkably, quenching has been shown to very reliable across cognitive tasks and is thought of as a stable individual trait that influences behavior (i.e., performance) (Arazi, Gonen-Yaacovi, & Dinstein, 2016, 2017). In AB research, this would be an improved method for measuring variability across the dot probe task as a measure of individual differences in threat processing efficiency in anxious populations and how that relates to AB measured via reaction times. Indeed, these recent and exciting approaches represent the future of ABMT research.

Finally, although the measurement of ABMT performance gains and losses was a novel outcome, we did not explore the full range of possible learning trajectories. The next step for evaluating performance would be to apply the phenomenon of sudden gains seen in depression and anxiety research (Bohn, Aderka, Schreiber, Stangier, & Hofmann, 2013; Deschénes & Dugas, 2013; Shalom et al., 2018; Z Tang, DeRubeis, Beberman, & Pham, 2005). Sudden gains are defined as a brief period of large and enduring gains that occur rapidly between two treatment visits (Tang, Luborsky, & Andrusyna, 2002). The drastic jump in symptom improvement is associated with better outcomes and has been seen with multiple treatments such as pharmacotherapy, CBT, and family therapy (Gaynor et al., 2003). Sudden gains can be tracked as an alternative to and in addition to relying on more gradual trends across of the full treatment period (Kelly, Roberts, & Ciesla, 2005). Most recently, variability in symptom
expression over the course of treatment has been identified as a potential robust predictor of who will show sudden gains lending continued validity to the investigation of variability metrics (Shalom et al., 2018). In the current study, we saw that trial-level variability in AB did in fact predict ABMT performance gains. We measured differences in performance at the start of each visit in order to avoid fatigue effects and we looked at overall speeding of RTs. However, we did not evaluate individual trajectories to identify the potential for sudden gains. Future data analysis will include plotting individual RT trajectories and selecting for individuals who display an early but significant increase in performance between the first and second training visits. This approach might provide some clarity for our lack of a significant group difference in overall training performance. Ultimately, once the best methods for quantifying training gains and losses have been established, they can be used to set individualized goals for a participant and track shifting reaction times in real time.

Conclusion

Prior research has assumed that anxiety is associated with an AB towards threat (Bar-Haim et al., 2007; MacLeod & Mathews, 1988; MacLeod et al., 2002). Recent evidence of heterogeneity and methodological questions have challenged this simplistic view, instead suggesting that AB is dynamic and context-sensitive rather than static and trait-like in nature (Egan & Dennis-Tiwary, 2018; Zvielli et al., 2014b). In order to evaluate treatments that aim to reduce AB- namely ABMT- and ameliorate anxiety, innovative methods are needed to capture variability and more accurately reflect the dynamic nature of AB that may be missed by traditional measures (Zvielli, Amir, Goldstein, & Bernstein, 2015). The temporally-sensitive behavioral and neurocognitive methods presented in this dissertation revealed important pre-training individual differences that moderated the relationship between training and the target outcomes of performance, anxiety, and stress reactivity. In contrast, mean AB scores failed to
predict all target outcomes but stress reactivity. With a growing interest in ABMT as a cost-effective and accessible treatment, individual differences such as this presented here can be used to not only predict treatment response but more importantly to monitor an individual’s progress and modify training protocols in real time. The current study was successful in challenging the use of one averaged reaction time score at a single timepoint and offers a set of potential candidate biobehavioral measures with improved temporal sensitivity and specificity. Thus, the proposed new metrics have the potential to improve AB assessment without changing gold-standard measurement (dot probe). This provides a significant opportunity to encourage new analyses within a wealth of data previously collected across multiple labs to identify clinically-relevant variability in the expression, maintenance, and treatment of anxiety.
Table 1.

*Mini International Neuropsychiatric Interview (MINI) Primary Diagnoses at Visit 1*

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generalized Anxiety Disorder (GAD)</td>
<td>21</td>
</tr>
<tr>
<td>Major Depressive Episode (MDE) – Past</td>
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</tr>
<tr>
<td>Major Depressive Episode (MDE) – Recurrent</td>
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</tr>
<tr>
<td>Comorbid GAD/MDE</td>
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</tr>
<tr>
<td>Panic Disorder (PD)</td>
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<tr>
<td>Agoraphobia</td>
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</tr>
<tr>
<td>Social Phobia</td>
<td>9</td>
</tr>
<tr>
<td>Obsessive Compulsive Disorder (OCD)</td>
<td>3</td>
</tr>
<tr>
<td>Post Traumatic Stress Disorder (PTSD)</td>
<td>3</td>
</tr>
<tr>
<td>Bulimia Nervosa</td>
<td>2</td>
</tr>
<tr>
<td>Did Not Meet Criteria for a Diagnosis</td>
<td>20</td>
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Table 2.

Descriptive Statistics for Age, AB Metrics, ERPs, Pre-Training Anxiety, and Stress Reactivity

<table>
<thead>
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<th>Variable</th>
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<th>PT</th>
</tr>
</thead>
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<td></td>
<td>M</td>
<td>SD</td>
</tr>
<tr>
<td>Age</td>
<td>24.35</td>
<td>7.18</td>
</tr>
<tr>
<td>Mean AB</td>
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</tr>
<tr>
<td>TL Variability</td>
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<td>.65</td>
</tr>
<tr>
<td>ΔAB</td>
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<td>27.40</td>
</tr>
<tr>
<td>P1*</td>
<td>2.91</td>
<td>1.93</td>
</tr>
<tr>
<td>N2</td>
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</tr>
<tr>
<td>ΔP1</td>
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</tr>
<tr>
<td>ΔN2</td>
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<tr>
<td>DASS-Anxiety</td>
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<td>8.31</td>
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<tr>
<td>DASS-Stress</td>
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<td>9.17</td>
</tr>
<tr>
<td>DASS-Depression</td>
<td>12.27</td>
<td>8.13</td>
</tr>
<tr>
<td>HAM-A</td>
<td>19.36</td>
<td>7.36</td>
</tr>
<tr>
<td>Stress Reactivity</td>
<td>13.36</td>
<td>11.05</td>
</tr>
</tbody>
</table>

*Note. ABMT = attention bias modification training. PT = placebo training.
**Significant group difference at .05 level.
Table 3.

Correlation Matrix for Pre-Training Measures

<table>
<thead>
<tr>
<th>Measure</th>
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<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
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<tr>
<td>1. DASS-Anxiety</td>
<td>___</td>
<td>.74**</td>
<td>.62**</td>
<td>.72**</td>
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</tr>
<tr>
<td>2. DASS-Stress</td>
<td>.74**</td>
<td>___</td>
<td>.59**</td>
<td>.63**</td>
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</tr>
<tr>
<td>3. DASS-Depression</td>
<td>.62**</td>
<td>.59**</td>
<td>___</td>
<td>.57**</td>
<td></td>
</tr>
<tr>
<td>4. HAM-A</td>
<td>.72**</td>
<td>.63**</td>
<td>.57**</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note. ** Correlation is significant at the .01 level (2-tailed).
Figure 1. Enrollment and participation flow diagram
Figure 2. An example of a non-threat cued trial of the dot probe used for AB assessment.
Figure 3. Trial-level bias scores (TL-BS) plotted in sequential order by trial-level pairing for a sample participant. The variability measure is an index of the length of the line, with higher scores indicating more dynamic shift in attention and greater variability in threat bias over the course of the assessment. The horizontal line represents the mean bias score.
Figure 4. Training performance plotted by group for each of the 16 training blocks.

ABMT = attention bias modification training. PT = placebo training.
Figure 5. The P1 and N2 were segmented between -200 pre-stimulus onset and 500 ms post-stimulus onset. The topographic map and waveform represent grand average amplitudes averaged across TN trials of dot probe (TN-threat, TN-neutral) and training group during Visit 1.
Figure 6. Training performance improved from Session 1 to Session 4 comparably for the whole sample overall.
Figure 7. Training performance improved from the beginning of the third session of training (Block 9) to the beginning of the fourth session of training (Block 13) for the ABMT but not the PT group. ABMT = attention bias modification training. PT = placebo training.
Figure 8. Training performance was better in the ABMT versus PT group, but only for individuals with high pre-training trial-level variability. ABMT = attention bias modification training. PT = placebo training.
Figure 9. Stress reactivity was greater in the ABMT versus PT group, but only for individuals with an increase in pre-training mean AB scores between Visit 1 and Visit 2. ABMT = attention bias modification training. PT = placebo training.
Figure 10. Self-reported anxiety was greater when ABMT participants showed larger P1 amplitudes to threat. ABMT = attention bias modification training. PT = placebo training.
Figure 11. Self-reported anxiety was lower in the ABMT versus PT group, but only for individuals with an increase in pre-training N2 amplitudes to threat between Visit 1 and Visit 2. ABMT = attention bias modification training. PT = placebo training.
Figure 12. Stress reactivity was greater in the ABMT versus PT group, but only for individuals with an increase in pre-training N2 amplitudes to threat between Visit 1 and Visit 2. ABMT = attention bias modification training. PT = placebo training.
Supplement: Regression Results

### TL Variability predicting Training Performance in Block 13

<table>
<thead>
<tr>
<th>Source</th>
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<th>t</th>
<th>p</th>
<th>Cohen’s f</th>
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<td>Constant</td>
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<tr>
<td>Training Performance (Block 9)</td>
<td>0.759</td>
<td>0.061</td>
<td>0.827</td>
<td>12.439</td>
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<tr>
<td>Depression</td>
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<td>0.294</td>
<td>0.034</td>
<td>0.615</td>
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<tr>
<td>Mean AB</td>
<td>-0.016</td>
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<td>-0.006</td>
<td>-0.110</td>
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<tr>
<td>TL Variability</td>
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<td>-0.328</td>
<td>-1.634</td>
<td>0.334</td>
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<tr>
<td>Training Group</td>
<td>11.814</td>
<td>5.667</td>
<td>0.115</td>
<td>2.085</td>
<td>0.040</td>
<td>0.04</td>
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<tr>
<td>Training Group x TL Variability</td>
<td>14.029</td>
<td>5.958</td>
<td>0.446</td>
<td>2.355</td>
<td>0.021</td>
<td>0.06</td>
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### Between-Context ΔAB predicting Stress Reactivity

<table>
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<tr>
<th>Source</th>
<th>B</th>
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<th>β</th>
<th>t</th>
<th>p</th>
<th>Cohen’s f</th>
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<tr>
<td>Constant</td>
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<td>4.027</td>
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<tr>
<td>Stress Reactivity (Visit 1)</td>
<td>0.279</td>
<td>0.102</td>
<td>0.302</td>
<td>2.727</td>
<td>0.008</td>
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<tr>
<td>Depression</td>
<td>-0.028</td>
<td>0.108</td>
<td>-0.029</td>
<td>-0.263</td>
<td>0.793</td>
<td></td>
</tr>
<tr>
<td>Mean AB</td>
<td>-0.170</td>
<td>0.085</td>
<td>-0.381</td>
<td>-1.997</td>
<td>0.050</td>
<td>0.39</td>
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<tr>
<td>ΔAB</td>
<td>0.226</td>
<td>0.136</td>
<td>0.716</td>
<td>1.659</td>
<td>0.102</td>
<td></td>
</tr>
<tr>
<td>Training Group</td>
<td>-2.112</td>
<td>2.115</td>
<td>-0.109</td>
<td>-0.999</td>
<td>0.322</td>
<td></td>
</tr>
<tr>
<td>Training Group x ΔAB</td>
<td>-4.266</td>
<td>2.150</td>
<td>-0.756</td>
<td>-1.985</td>
<td>0.052</td>
<td>0.10</td>
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### P1 predicting Anxiety

<table>
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<tr>
<th>Source</th>
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<th>β</th>
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<th>p</th>
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<tr>
<td>Anxiety (Visit 1)</td>
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<td>.104</td>
<td>.519</td>
<td>4.676</td>
<td>.000</td>
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<tr>
<td>P1 on NN Trials</td>
<td>.915</td>
<td>.755</td>
<td>.226</td>
<td>1.211</td>
<td>.229</td>
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<tr>
<td>Depression</td>
<td>.141</td>
<td>.092</td>
<td>.169</td>
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<td>.127</td>
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<tr>
<td>P1 on TN Trials</td>
<td>1.425</td>
<td>2.828</td>
<td>.172</td>
<td>.504</td>
<td>.616</td>
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<tr>
<td>Training Group</td>
<td>-1.530</td>
<td>1.483</td>
<td>-.094</td>
<td>-1.032</td>
<td>.305</td>
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<tr>
<td>Training Group x P1</td>
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<td>-490</td>
<td>-1.705</td>
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<td>.05</td>
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### Between-Context ΔN2 predicting Anxiety

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<th>β</th>
<th>T</th>
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<td>.626</td>
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<td>.345</td>
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<td>ΔN2</td>
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### Between-Context ΔN2 predicting Stress Reactivity

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<td>ΔN2 on NN Trials</td>
<td>-.613</td>
<td>.718</td>
<td>-.137</td>
<td>-.854</td>
<td>.397</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>.149</td>
<td>.128</td>
<td>.146</td>
<td>1.167</td>
<td>.248</td>
<td></td>
</tr>
<tr>
<td>ΔN2</td>
<td>-8.703</td>
<td>3.733</td>
<td>-.905</td>
<td>-2.332</td>
<td>.023</td>
<td></td>
</tr>
<tr>
<td>Training Group</td>
<td>-3.312</td>
<td>2.478</td>
<td>-.171</td>
<td>-1.337</td>
<td>.187</td>
<td></td>
</tr>
<tr>
<td>Training Group x ΔN2</td>
<td>5.586</td>
<td>2.464</td>
<td>.906</td>
<td>2.267</td>
<td>.027</td>
<td>.09</td>
</tr>
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References


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