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For whom the bell tolls: Neurocognitive individual differences in the acute stress-reduction effects of an attention bias modification game for anxiety

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ABSTRACT

The efficacy of attention bias modification training (ABMT) for anxiety is debated, in part because individual differences in task engagement and pre-training threat bias impact training efficacy. In the present study, an engaging, gamified ABMT mobile application, or "app," was utilized in 42 (21 females) trait-anxious adults. EEG was recorded during pre- and post-training threat bias assessment to generate scalp-recorded event-related potentials (ERPs) reflecting neurocognitive responses to threat. Following app play (ABMT versus placebo), subjective anxiety and stress responses (observed and self-reported) were measured. ABMT, versus placebo, resulted in improved behavioral performance during the stress task for females, and in potentiation of the N2 ERP to threat for males, suggesting increased attention control. Training groups did not differ in self-reported anxiety. ABMT also resulted in improved performance during the stress task among those evidencing specific pre-training ERP responses: decreased P1, suggesting less attention allocation, but potentiated N170, suggesting enhanced attention selection and discrimination. Differences in behavioral threat bias did not moderate training effects. Results suggest that efficient allocation of attention to threat combined with enhanced discrimination between threat and non-threat may facilitate stress-reduction effects of ABMT. Targeting neurocognitive responses to threat to personalize ABMT and develop more effective methods of treatment delivery, such as gamification, are discussed.

Over half of the U.S. population will suffer from a mental illness in their lifetime, but only a small fraction of this group will seek or receive effective treatment (Kessler et al., 2007; National Institutes of Health National Institute of Mental Health, 2005). This gulf between need and access to treatment (Corrigan, Druss, & Perlick, 2014; Greenberg et al., 1999; Kessler et al., 2008) has driven renewed investment in the development of alternative delivery strategies for mental health interventions (Harwood & L'Abate, 2010; Kazdin & Blase, 2011; Kazdin & Rabbitt, 2013; L'Abate, 2007; Mosa, Yoo, & Sheets, 2012; Rotheram-Borus, Swendeman, & Chorpita, 2012). To this end, particular attention has been paid to computerized and mobile interventions because they can serve as "disruptive innovations", which provide a qualitative leap in reducing cost and increasing accessibility of empirically-validated treatments (e.g., Kazdin & Rabbitt, 2013; Rotheram-Borus et al., 2012). The potential for such technologies to serve in this capacity as "disruptive innovations" is strengthened by the ubiquity of computers and mobile devices, which extends the reach of psychological services to those who might not otherwise have access (Dimeff, Paves, Skutch, & Woodcock, 2011; Kazdin & Rabbitt, 2013; Morris, Teevan, & Panovich, 2010).

Attention bias modification training (ABMT; Mathews & MacLeod, 2002; Van Bockstael et al., 2014) for anxiety may represent a model disruptive innovation. ABMT is a low-cost, computerized attention retraining protocol that targets a discrete cognitive mechanism in anxiety, the threat bias, or selective and exaggerated attention to potential threat (Hakamata et al., 2010; Hallion & Ruscio, 2011; Mathews & MacLeod, 2002). Threat bias is theorized to promote the continuity of anxiety by facilitating preferential processing of threat at the expense of cues for positive outcomes and safety (Bar-Haim, Lamy, Pergamin, Bakermans-

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Kranenburg, & van IJzendoorn, 2007; Eysenck, 1992). This preferential processing is a linchpin in the vicious cycle of anxiety, in which anxious distress is heightened and opportunities for disconfirmation of fear beliefs are minimized (e.g., Hofman, 2007; Ouimet, Gawronski, & Dozois, 2009). ABMT systematically redirects attention away from threat, thus modifying this dysfunctional pattern of attention (Mathews & MacLeod, 2002). A meta-analysis based on early randomized clinical trials showed that ABMT resulted in reduced threat bias with a large effect size ($d = 1.16$), and produced significantly greater reductions in anxiety ($d = 0.61$) and stress reactivity ($d = 0.77$) than placebo training (Hakamata et al., 2010).

Following the robust findings of these early clinical trials of ABMT with specific disorders such as generalized anxiety disorder (e.g., Amir, Beard, Burns, & Bomyea, 2009) and social phobia (e.g., Amir, Bomyea, & Beard, 2010), more recent clinical trials of ABMT document only modest to small effect sizes and null findings (Beard, Sawyer, & Hofmann, 2012; Hallion & Ruscio, 2011; Mogoase, David, & Koster, 2014) and suggest that this may be due to failure to successfully modify the threat bias (Cristea, Kok, & Cuijpers, 2015; Emmelkamp, 2012; Everaert, Mogoaşe, David, & Koster, 2014; Julian, Beard, Schmidt, Powers, & Smits, 2012; MacLeod & Clarke, 2015; McNally, Enock, Tsai, & Tousian, 2013). Moreover, the accessibility of ABMT has been recently questioned, leading several research groups to modify ABMT for use on mobile devices (Dennis & O'Toole, 2014; Enock, Hofmann, & McNally, 2014), or to be delivered via the internet (Amir & Taylor, 2012; Boettcher et al., 2013; Carlbring et al., 2012; Enock & McNally, 2013). These studies, too, have yielded mixed and null results. Notably, although the goal of delivering ABMT via the internet or a mobile device includes increasing accessibility and engagement, previous studies did not make ABMT more engaging through use of techniques such as gamification (Buday, Baranowski, & Thompson, 2012; Ferguson, 2012). The present study utilizes an empirically-supported gamified mobile ABMT application, or "app" (Dennis & O'Toole, 2014) with the aim of promoting greater engagement and adherence during training.

Given recent evidence of null and mixed effects of ABMT (e.g., Carlbring et al., 2012; Julian et al., 2012; Rapee et al., 2013; Reese, McNally, Najmi, & Amir, 2010), it has been argued that further advances in the development and clinical application of ABMT will be limited unless key individual differences impacting the efficacy of ABMT are identified (Clarke, Browning, Hammond, Notebaert, & MacLeod, 2014; Mogoase et al., 2014; O'Toole & Dennis, 2012). An individual differences approach has the potential to improve personalization of treatment and increase the ability to identify those for whom ABMT may be most effective.

Although few ABMT studies have taken an individual differences approach, recent emerging evidence suggests that pre-treatment patterns of threat bias predict ABMT efficacy. In one study, participants with social anxiety who evidenced a pre-treatment bias towards threat showed the greatest symptom reduction (Kuckertz, Gildebrant, et al., 2014), although in another study, participants with post-traumatic stress disorder who evidence a pre-treatment bias *away* from threat showed the greatest symptom reduction (Kuckertz, Amir, et al., 2014). In addition to the diagnostic diversity between the two studies, it is difficult to interpret this inconsistency given that behavioral reaction time measures are far downstream of neurocognitive responses to threat and may actually reflect a number of performance-related factors (Banaschewski & Brandeis, 2007). Indeed, some have argued that reaction-time based measures of threat bias are largely unreliable and imprecise measures of threat bias (e.g., Brown et al., 2014; Schmukle, 2005). Instead, several researchers have argued that threat bias might be best conceptualized and delineated in terms of discrete neurocognitive sub-processes underlying biased processing of threat (Cisler & Koster, 2010; Clarke, Notebaert, & MacLeod, 2014; O'Toole & Dennis, 2012).

Broadly, two discrete neurocognitive processes have been implicated in anxiety-related threat bias: those that reflect relatively automatic attention allocation and threat detection and those that reflect relatively later, cognitive control responses (Bishop, 2007; Cisler & Koster, 2010; Eldar & Bar-Haim, 2010; Heeren, De Raedt, Koster, & Philippot, 2013; Suway et al., 2013; Vuilleumier, 2005). This distinction is consistent with previous research and theory positing that relatively automatic and rapid deployment of attention towards potential threat is elevated in anxiety (Beck & Clark, 1997; Mogg & Bradley, 2002; Wilson & MacLeod, 2003), and is thought to reflect very early, limbic-driven threat detection and evaluation mechanisms (Vuilleumier, 2005). In addition, inhibitory, top-down cognitive sub-processes related to threat bias have been implicated. These refer to the relatively strategic, executive control of threat processing and reactivity, which is compromised in anxiety (Bishop, 2009; Bishop, Duncan, Brett, & Lawrence, 2004; Derryberry & Reed, 2002; Eysenck & Derakshan, 2011). From this dual-process viewpoint, ABMT may ameliorate anxiety via reduction of exaggerated, automatic threat detection mechanisms and/or via strengthening of top-down, controlled cognitive control and executive functions to inhibit amygdala-driven reactivity to threat (Heeren et al., 2013).

Consistent with this premise, several studies have used scalp-recorded event-related potentials (ERPs) to track relatively automatic and controlled neurocognitive responses implicated in ABMT (Eldar & Bar-Haim, 2010; O'Toole & Dennis, 2012; Suway et al., 2013). For example, in one study (Eldar & Bar-Haim, 2010) a single session of ABMT versus placebo resulted in increased magnitude of an ERP reflecting cognitive control, the N2 (Folstein & Van Petten, 2008; Nieuwenhuis, Yeung, van den Wildenberg, & Ridderinkhof, 2003; van Veen & Carter, 2002). Changes in the N2, however, were not related to efficacy of attention training or anxiety-related outcomes (Eldar & Bar-Haim, 2010) making it difficult to interpret the functional implications of this effect.

Although these early results are intriguing, an individual differences approach instead focuses on the question of whether variability in the response of either system can identify those for whom ABMT is most efficacious (Fox, Zougkou, Ridgewell, & Garner, 2011). For example, if executive control of attention to threat must be recruited for ABMT to be efficacious, then individual differences in these responses will predict ABMT effects. Emerging evidence supports this individual differences approach. In a study of cognitive control training in depressed patients, task-linked pupillary oscillations, a measure of task-related cognitive activity, prior to the intervention predicted which participants benefited most from the treatment (Siegle et al., 2014). ERPs may provide even more finely-grained analysis of the dual-process distinction between automatic and controlled neurocognitive processes implicated in ABMT. For example, in one study, trait anxious participants administered ABMT versus placebo training evidenced reduced negative mood following a stressor, but only if they also showed enhanced early visual detection within the first 100 ms after viewing complex emotional pictures (greater N1 amplitudes) prior to ABMT and showed flexible reductions in the magnitude of this response by completion of training (O'Toole, Quintero, Ahmed, Rieder, & Dennis, 2013). This finding suggests that engaging relatively automatic, early sensory gain mechanisms prior to training, and then reducing recruitment of these resources via training, may lead to a potent enhancement of the anxiolytic effects of ABMT.

When faces are target stimuli, such as in the majority of ABMT studies using the dot probe to assess threat bias, the first negative-going ERP to emerge is the N170 rather than the N1. Although