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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 morphologically similar to the N1, the N170 peaks in amplitude slightly later, between 150 and 200 ms, and occurs over posterior-occipital regions of the scalp (Vogel & Luck, 2000). The N170 reflects visual detection and discrimination in the context of facial processing (Batty & Taylor, 2003; Eimer, 2011; Wronka & Walentowska, 2011) and thus in part underlies early attention selection and facilitates further perceptual processing (Gauthier, Curran, Curby, & Collins, 2003; Luck, Woodman, & Vogel, 2000; Thierry, Martin, Downing, & Pegna, 2007). The N170 can be clearly distinguished from earlier-emerging attention-related ERPs, such as the P1 (Hillyard & Anllo-Vento, 1998; Luck, Heinze, Mangun, & Hillyard, 1990; Luck & Hillyard, 1995). The P1 peaks around 100 ms post stimulus over posterior regions of the scalp and reflects activity in the extrastriate area of the visual cortex (Clark & Hillyard, 1996). As more attention is allocated to visual stimuli, a greater number of extrastriate neurons are recruited and P1 amplitudes increase, thus reflecting degree of attention allocation and the cognitive "cost of attention" (Hillyard & Anllo-Vento, 1998; Luck et al., 1990; Smith, Cacioppo, Larsen, & Chartrand, 2003). Accordingly, the P1 has been used as a measure of facilitated or biased processing of unpleasant stimuli (Dennis & Chen, 2007; Smith et al., 2003), suggesting that larger P1 amplitudes prior to training may divert task-related cognitive resources and thus reduce ABMT potency. Thus, while both the P1 and N170 may reflect relatively automatic attention processes, they are functionally distinguishable (attention allocation versus discrimination) and may differentially predict ABMT effects.

The N2, in contrast, is thought to reflect the recruitment of later-emerging cognitive control capacities that support the strategic control of attention (Folstein & Van Petten, 2008; Nieuwenhuis et al., 2003; van Veen & Carter, 2002). Occurring over frontal-midline regions of the scalp from 200 to 350 ms after a stimulus is presented, the N2 is larger under conditions in which cognitive control is required, such as the presentation of incongruent response options (e.g., incongruent flanker displays in a visual flanker task) and during tasks that require inhibition of prepotent responses (Kopp, Rist, & Mattler, 1996; Nieuwenhuis et al., 2003; van Veen & Carter, 2002). Thus, the N2 is thought to signal the degree to which high-order cognitive control is recruited (Parasuraman, Warm, & See, 1998; Potts, Martin, Burton, & Montague, 2006; Yeung, Holroyd, & Cohen, 2005). In the context of the dot probe task, in which a threat and non-threat stimulus is simultaneously presented, the N2 is clearly detectable (Eldar & Bar-Haim, 2010; O'Toole & Dennis, 2012). Previous research documents increased N2 amplitudes following ABMT (Eldar & Bar-Haim, 2010), but to date has not examined whether an enhanced N2 *prior to* training bolsters effects. Another key individual difference that little research on ABMT has addressed is whether there are sex differences in ABMT response. Such differences may be particularly important to consider in the context of gamified mental health interventions (Veltri, Krasnova, Baumann, & Kalayamthanam, 2014). Overall, studies have shown that females play games less frequently, have less of a preference for games involving competition and a show a reduced motivation to play in a social context compared to male counterparts (Lucas & Sherry, 2004; Veltri et al., 2014; Yoon, Duff, & Ryu, 2013). Although gender difference in attention biases are poorly understood (Bar-Haim et al., 2007; Sass et al., 2010), one study showed that females with elevated mood symptoms, such as anxiety and depression, are more likely to show biased processing of threat and other negative information and less reduction of biases via training (Beshai, Prentice, Dobson, & Nicpon, 2014). In another study using behavioral and ERP measures of threat processing, anxious women versus men showed greater early visual processing (larger P1 amplitudes), whereas non-anxious men showed evidence of preferential processing of threat at an early stage (100 ms) and non-anxious women showed evidence of preferential processing of threat at a later stage (300 ms). Thus, there may be important gender differences both in neurocognitive processing of threat and plasticity of the threat bias, as well as responses to gamified ABMT.

The goal of the current study was to use a single session of ABMT to identify individual differences in neurocognitive responses to threat that predict the magnitude of training effects. We embedded ABMT in an engaging mobile gaming application ("app") format (Dennis & O'Toole, 2014), and tested the hypothesis that a single session of ABMT, because it represents an acute experimental manipulation, should lead to moderate reductions in stress reactivity and anxiety. We also predicted that ABMT versus placebo would predict changes in ERP responses to threat, in particular increases in the N2 as previously documented (Eldar & Bar-Haim, 2010). The primary hypothesis, centering on individual differences, was that stress- and anxiety-reduction effects of ABMT will be amplified when *prior to ABMT*: ERP responses reflect reduced capture of attention allocation resources (P1), enhanced selection/discrimination (N170), and enhanced recruitment of cognitive control (N2). Comparison analyses examined whether pre-training individual differences in threat bias measured via the dot probe task predicted an enhanced positive impact of ABMT, as shown in previous studies (e.g., Kuckertz, Amir, et al., 2014; Kuckertz, Gildebrant, et al., 2014). Given potential gender differences in the use of games and in the expression of biased attention, we explored whether males or females showed increased responsiveness to the ABMT app.

1. Method

1.1. Participants

Participants were 50 adults recruited from an undergraduate research pool at an urban university in New York City, and also through Craigslist. Eight participants were excluded due to: EEG recording problems ($f = 3$), participant refusal ($f = 3$), excessive errors on the dot probe task ($f = 1$), and technical issues with the app ($f = 1$). The final sample consisted of 42 adults (21 females, 21 males) aged 18 to 38 ($M = 20.60$, $SD = 3.68$). There were 19 participants in the ABMT group (11 females, 8 males) and 23 participants in the placebo training (PT) group (10 females, 13 males). Self-reported race/ethnicity was as follows: 15 White, 6 Hispanic, 15 Asian, 1 African American, and 5 self-reported other race/ethnicity.

1.2. Procedure

The State-Trait Anxiety Inventory (STAI; Spielberger, 1983) was used as a screen to recruit participants who scored +1 standard deviation above the mean for college students on trait anxiety (a score of 49). This score was used only for screening purposes. Participants spent approximately 2 h in the laboratory. After a brief questionnaire period during which they completed demographic questions and self-report of state anxiety and depressed mood, EEG electrodes were applied and participants were seated in an EEG recording booth 65 cm from a 17 in monitor to complete the pre-training threat bias assessment using the dot probe. Following this, participants completed the ABMT or PT on an iPod Touch (fourth generation) in the EEG recording booth with the monitor switched off. After the training session, participants immediately reported on their state anxiety and completed the post-training threat bias assessment using the dot probe while EEG was recorded. Following the post-training assessment, EEG electrode caps were removed. Next, participants reported on positive and negative mood (Profile of Mood States, POMS; McNair, Lorr, Heuchert, &

Droppleman, 2003), completed the Trier Social Stress Test (TSST; Kirschbaum, Pirke, & Hellhammer, 1993), and again reported on positive and negative mood.

1.3. Measures

1.3.1. Baseline mood questionnaires

Trait anxiety was measured via the STAI; scores range from 20 to 80, with higher scores indicating greater anxiety (Spielberger, 1983). Depression symptoms were measured using the Beck Depression Inventory II (BDI-II; Beck, Steer, & Brown, 1996). Scores range from 0 to 63: 0–13 is minimal, 14–19 is mild, 20–28 is moderate, and 29–63 is severe.

1.3.2. The dot probe task and stimuli

The dot probe task (Bar-Haim et al., 2007; Mathews & Mackintosh, 1998) followed parameters of the Tel-Aviv University/National Institute of Mental Health protocol (http://www.tau.ac.il/~yair1/ABMT.html). Stimuli for the dot probe task are pictures of 20 different individuals (10 males, 10 females) from the NimStim stimulus set (Tottenham et al., 2009) with one female taken from the Matsumoto and Ekman (1989) set. 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 above and below a fixation cross, with 14 mm between them. The task included 120 trials (80 angry-neutral and 40 neutral–neutral). Each trial was comprised of: (a) 500 ms fixation, (b) 500 ms face-pair cue, (c) target (probe) in the 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 ITI. 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.

1.3.3. Quantifying behavioral attention bias

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. The average response time was 494.61 ($SD = 110.84$) and the overall accuracy rate was 0.98 ($SD = 0.03$). The *attention bias* score was calculated as the average RTs for neutral probes (when the target replaces the neutral face from a pair of angry and neutral faces) minus RTs for angry probes (when the target replacing the angry face from a pair of angry and neutral faces). Higher scores indicate an attention bias toward threatening information, such that participants respond faster when the probe appears in the location of the angry versus neutral face.

1.3.4. Electrophysiological recording and data reduction

A Biosemi system (BioSemi; Amsterdam, NL), was used to record EEG activity continuously during the pre- and post-training dot probe tasks using 64 Ag/AgCl scalp electrodes. Electrodes were fixed into an elasticized nylon cap and arranged according to the international 10/20 system. Eye movements were monitored by electro-oculogram (EOG) signals from electrodes placed 1 cm above and below the left eye (to measure vertical eye movements) and 1 cm on the outer edge of each eye (to measure horizontal eye movements). Preamplification of the EEG signal occurred at each electrode which improves the signal-to-noise ratio. EEG was recorded at a sampling rate of 512 Hz. During EEG acquisition, the voltage from each of the 64 electrodes from which data was collected was referenced online with respect to the common mode sense active electrode and driven right leg electrode, which produces a monopolar (nondifferential) channel. Brain Vision Analyzer (Version 2.2, GmbH; Munich, DE) was used to prepare the data. Offline, all data were re-referenced to the average of the scalp and filtered with a high pass frequency of 0.1 Hz and a low pass frequency of 30 Hz. Data was then segmented 200 ms prior to face-pair cue onset (during the fixation period, used for baseline correction) and continued for 500 ms until face-pair cue offset. Trials with incorrect responses were excluded from further processing and analyses.

The Gratton, Coles, and Donchin (1983) ocular correction method was used to identify and remove blinks. Artifacts were identified using the following criteria and removed from analyses: voltage steps greater than 50 μV, changes within a given segment greater than 300 μV, and activity lower than 0.5 μV per 100 ms. In addition to this method of artifact identification, trials were visually inspected for artifacts, which were removed on a trial-by-trial-basis.

Electrodes were chosen via visual inspection of the topographical distribution of the pre-training dot probe task data, grand averaged across all stimulus conditions and participants (see Fig. 1). ERPs were quantified as the mean amplitude for each cue condition: the P1 was generated from 80 to 150 ms over P5/P7/PO7 and P6/P8/PO8; the N170 was generated from 140 to 200 ms over CP5/P5/P7 and CP6/P6/P8; the N2 was generated from 290 to 350 ms over FCz.

For each component, difference scores were generated to the threat versus the non-threat cues to index neurocognitive processing of threat. *These difference scores were used in all ERP analyses reported below*.

Trial counts were grand averaged across all stimulus conditions and participants. The average trial count for P1 was 38.45 ($SD = 2.02$), for N170 was 38.46 ($SD = 2.02$), and for N2 was 38.45 ($SD = 2.02$). There were no significant group differences in the average trial counts between the ABMT and PT groups, all $ts < 1.01$, $ps > 0.31$.

1.3.5. ABMT and PT conditions of the app

Participants received either the ABMT or PT condition of the app. The ABMT version of the app was available at the time on the App Store under the name Personal Zen. Participants reported no previous familiarity with the app and were blind to the purpose of the app. Both experimenters and participants were blind to whether assignment was to the ABMT or PT condition. Participants sat comfortably at a table, and were given an iPod Touch. They were instructed by the experimenter, “In this game two animated characters will appear on the screen. Shortly after, they will burrow into a hole. One of them will cause a path of grass to rustle behind it. With your finger, trace the path of the rustling grass, beginning from the burrow. Try to complete this task as quickly and as accurately as possible.” Then, they were given one practice screen in which the swiping motion on the touch screen was demonstrated and they were able to practice. The screen did not advance to the game until the swiping was correctly executed. Experimenters remained to answer any questions about the game. After each block of trials (40 trials) experimenters recorded the accrual of points and end-of-round feedback (see below).

For every trial, two cartoon characters (sprites), one showing an angry expression and one showing a neutral/mildly pleasant expression, appeared simultaneously on the screen for 500 ms. Next, both sprites simultaneously “burrowed” into the grass field (Fig. 2). In the ABMT condition, a trail of grass appeared in the location of the non-threat character for every trial, whereas in the PT condition, a trail was equally likely to appear in the location of

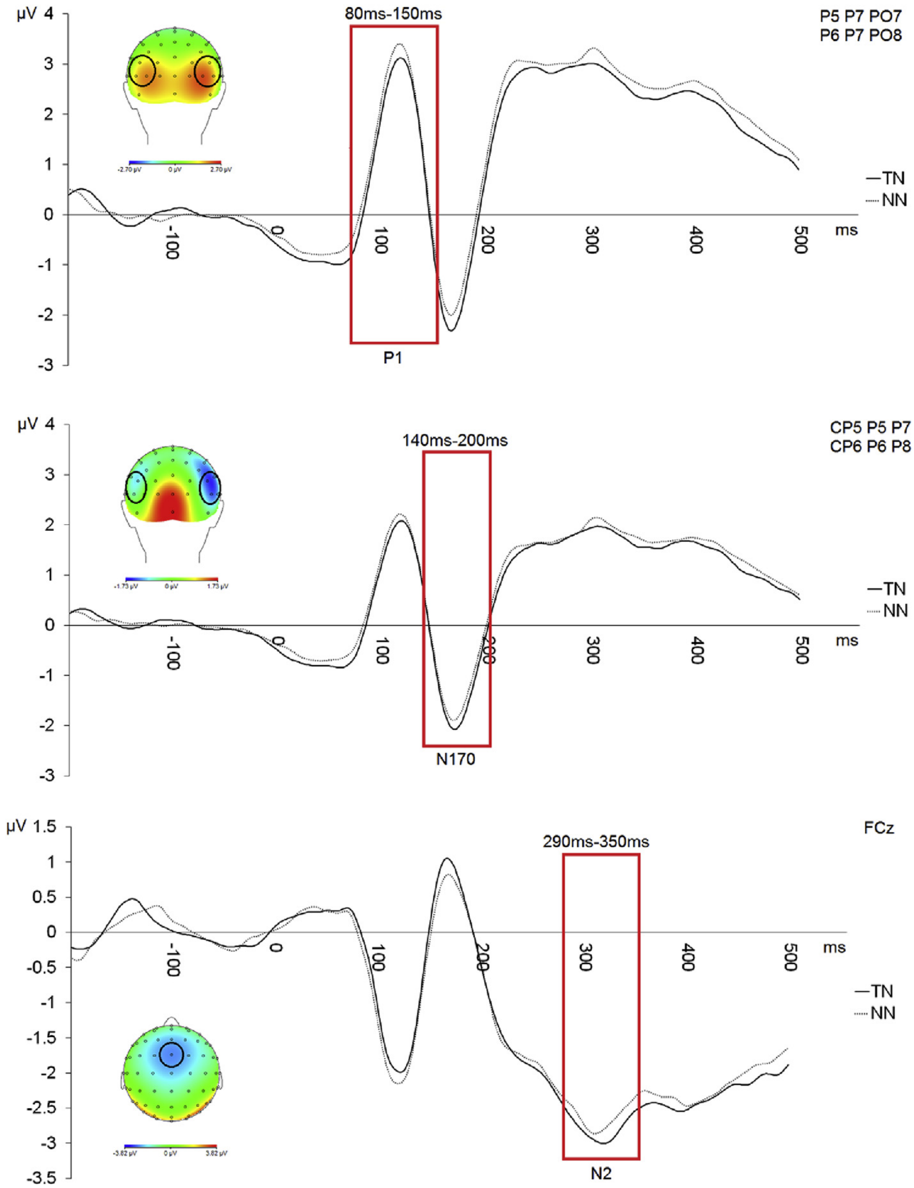

Fig. 1. Grand averaged scalp topographies and waveforms for ERP components (P1, N170, N2) generated to the face pair cues during the pre-training dot probe task.

the angry or neutral sprite. The grass remained until the participants responded. Paths were divided into separate "tufts" of grass (randomly varying between five and eight tufts), and when a tuft was correctly traced it was illuminated. Points were accrued based on speed and accuracy. Participants were given additional feedback after each trial via fixation "jewels" varying in color and accompanying sound to denote level of performance (see Dennis & O'Toole, 2014 for scoring and feedback details). When errors were made, a feedback sound was given (a high pitched "huh?"). Throughout game play, relaxing instrumental music played in the background.

Participants completed 12 blocks of 40 trials for a total of 480 trials (25 min of game play with 20 min of breaks given consisting of a 10-min break after round 160 and a 10-min break after round 320). The number of training trials were selected based on ABMT studies showing significant reductions in threat bias, anxiety, and stress reactivity following a single (Eldar & Bar-Haim, 2010; Klumpp & Amir, 2009) and multiple sessions of 480 trials (Eldar et al., 2012; Li, Tan, Qian, & Liu, 2008).

1.3.6. Pre- and post-training state anxiety

State anxiety was derived from the STAI; scores range from 20 to 80 with higher scores indicating greater anxiety (Spielberger, 1983). State anxiety was measured immediately prior to and following completion of app training.

1.3.7. Behavioral performance and self-report of mood during the stress task

Following the app training, report of state anxiety, and post-training threat bias assessment, the Trier Social Stress Test (TSST) was administered (Kirschbaum et al., 1993). The TSST included both a social-evaluative threat (giving a speech for three minutes) and a lack of control task (three minute arithmetic task). Both tasks were video-recorded and completed in front of two researchers who were described as judges. Participants were informed that their performance would be compared to others in the study and that a voice-frequency analysis and analysis of non-verbal behaviors would be conducted. The TSST was not administered prior to attention training because acute stress may induce shifts in threat-

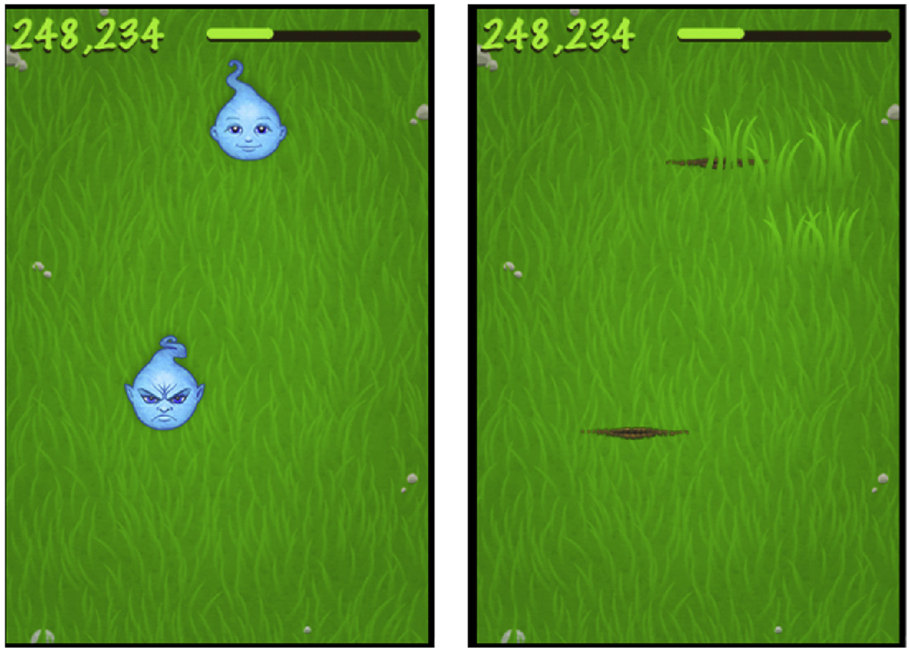

Fig. 2. App screenshots depicting sprites with angry and neutral/mildly pleasant expressions (left) and trail of grass appearing after sprites burrow into the grass field (right).

related attention (Bar-Haim, 2010) thus distorting the measurement of pre-training bias. Stress reactivity was measured in terms of observed behavioral performance and anxiety-related behaviors and self-report of mood as described below:

1.3.7.1. Behavioral performance. Observed behavioral performance during the TSST was coded based on three domains: global behaviors (e.g., content was understandable, appeared confident), non-verbal behaviors (e.g., kept eye contact with the audience, fidgeted), and verbal behaviors (e.g., stuttered, voice quivered). Within these three domains, any anxiety-related behaviors (e.g., fidgeted, stuttered, voice quivered) were reverse-coded prior to summing scores from a five-point Likert scale (0 = not at all, 1 = slightly, 2 = moderately, 3 = much, 4 = very much). Scores were summed across domains and across the speech and arithmetic tasks to generate a single Behavioral Performance score. Thus, lower Performance scores indicate signs of stress reactivity. Videos were coded by three research assistants who were blind to training group assignment. For 12 of the 42 videos, inter-coder reliability ($\alpha = .77$) was calculated using Krippendorff's alpha for ordinal data.

1.3.7.2. Self-report of mood. Self-reported mood was recorded before and after the TSST using the 65-item POMS (McNair et al., 2003). Participants are instructed to indicate on a five-point scale how well each adjective describes their current mood (not at all to extremely). The POMS measures six different mood states [Tension/Anxiety, Depression/Dejection, Anger/Hostility, Vigor/Activity (reverse scored), Fatigue/Inertia, and Confusion/Bewilderment] which are combined to generate a Total Negative Mood score.

2. Results

Participant demographics, baseline anxiety and depression symptoms for both of the training groups (ABMT and PT) are presented in Table 1. Pre- and post-training behavioral attention bias, ERP amplitudes, state anxiety, self-reported mood, and behavioral performance are presented in Table 2. There were no differences between training conditions on any of the measures (all $ps > 0.11$). Inspection of Table 2 shows variability in behavioral attention bias measure at baseline, highlighting the importance of controlling for these baseline differences in subsequent analyses. All statistical analyses were conducted in SPSS (Version 21) using general linear model and hierarchical regressions.

2.1. Correlations among study variables at baseline

We conducted a series of bivariate correlations between self-reported mood, behavioral attention bias, and ERPs at baseline. No significant correlations emerged, suggesting that threat bias measured via the dot probe and ERP responses to threat capture separable aspects of the cognitive response to threat.

2.2. Gender differences at baseline

Given potential gender differences in engaging with mobile technology and games (e.g., Mosa et al., 2012) and in attention biases (e.g., Sass et al., 2010), gender differences were examined for all study variables using independent samples t-tests. As seen in Table 2, several significant gender differences in emerged in baseline ERPs: females compared to males showed reduced P1 amplitudes to threat versus non-threat [$t(40) = -2.03$, $p = .05$] and greater N170 amplitudes to threat versus non-threat [$t(40) = -2.46$, $p = .02$]. There were no gender differences in behavioral attention bias or self-reported mood.

2.3. Effects of training on target outcomes

Next, we tested the hypotheses that ABMT versus PT, even a single session, would reduce subjective state anxiety, self-reported negative mood, observed stress-related behaviors, behavioral attention bias, and ERPs. We also tested the hypothesis that ABMT versus PT would result in larger N2 amplitudes suggesting increased recruitment of cognitive control resources. Given the significant variability at baseline in behavioral attention bias and given gender differences in ERPs, hypotheses were tested using a series of ANCOVAs with Gender and Training Group (ABMT or PT) as

Table 1
Participant demographics and baseline anxiety and depression symptoms.

	ABMT		PT	
	Males ($n = 8$)	Females ($n = 11$)	Males ($n = 13$)	Females ($n = 10$)
Age (years)	23.75 (6.74)	19.00 (0.63)	19.92 (2.02)	20.70 (2.79)
Education (years)	15.38 (2.26)	14.36 (1.29)	15.46 (4.27)	14.35 (1.20)
Ethnicity (frequency)				
Hispanic/Latino	1	2	1	2
Asian	2	2	5	6
Black or African American	0	1	0	0
White	3	5	5	2
More than one race	2	1	2	0
Trait anxiety	49.25 (16.83)	44.55 (6.55)	47.08 (7.69)	45.00 (6.94)
Depression symptoms	16.25 (12.40)	8.36 (5.54)	13.46 (6.59)	16.80 (12.32)

Note. Standard deviations are in parentheses. ABMT = Attention bias modification training.
PT = placebo training.

Table 2
Descriptive statistics for attention bias, ERP amplitudes (μV), state anxiety, self-reported mood, and observed behavioral performance.

	Pre-assessment				Post-assessment			
	ABMT		PT		ABMT		PT	
	Male	Female	Male	Female	Male	Female	Male	Female
Attention bias	15.25 (38.88)	−21.45 (57.40)	1.46 (13.28)	−5.40 (16.09)	8.63 (19.87)	−1.64 (18.54)	1.00 (15.67)	0.80 (9.02)
P1	0.36 (1.05)	−0.62 (0.68)	−0.16 (0.64)	−0.31 (0.93)	0.71 (0.86)	0.23 (0.76)	−0.29 (0.96)	−0.17 (1.29)
N170	0.37 (0.87)	−0.56 (0.73)	0.07 (0.81)	−0.36 (1.07)	0.23 (0.97)	0.16 (0.53)	0.01 (1.03)	0.01 (0.83)
N2	0.12 (1.94)	−0.03 (1.14)	−0.52 (1.52)	−0.23 (1.27)	−0.67 (1.36)	−0.28 (1.07)	0.80 (1.24)	−0.50 (1.30)
State anxiety	37.75 (9.63)	32.91 (9.30)	35.54 (7.28)	32.20 (10.07)	39.13 (11.85)	38.09 (11.90)	37.77 (8.15)	36.90 (11.93)
Negative mood (pre TSST)					68.26 (37.52)	52.87 (17.77)	53.08 (11.71)	52.75 (23.54)
Negative mood (post TSST)					99.00 (43.45)	81.40 (31.06)	79.62 (35.93)	70.20 (25.31)
TSST performance					16.25 (6.50)	18.18 (3.12)	18.08 (3.40)	14.00 (2.75)

Note. Standard deviations presented in parentheses. ABMT = attention bias modification training; PT = placebo training. TSST = Trier Social Stress Test. ERP amplitudes are the difference between the threat-neutral and neutral–neutral conditions. The TSST occurred at post-assessment only.

between-subjects factors[1] and post-training outcomes as the dependent variable, the corresponding pre-training measure as the covariate. This analytic approach may have greater power than a repeated measures ANOVA when assessing treatment effects between randomly assigned groups (Lewis & Stieben, 2004).

The main effect of Training Group did not reach significance for observed behavioral performance, $F(1, 38) = 0.89$, $p = .35$, partial $\eta^2 = 0.02$. However, there was a significant interaction between Training Group and Gender for observed behavioral performance [$F(1, 38) = 5.82$, $p = .02$, partial $\eta^2 = 0.13$; see Fig. 3]. Behavioral performance was better for the ABMT ($M = 18.18$, $SE = 1.20$) versus PT condition ($M = 14.00$, $SE = 1.25$) but only for females ($p = .02$). Additionally, for the PT condition only, males ($M = 18.08$, $SE = 1.10$) had better performance compared to females ($p = .02$).

The interaction between Training Group and Gender was significant for N2 amplitudes to threat versus non-threat [$F(1, 37) = 6.70$, $p = .04$, partial $\eta^2 = 0.11$; see Fig. 4]. As predicted, follow-up comparisons revealed that post-training N2 amplitudes to threat versus non-threat were greater following ABMT ($M = -0.63$, $SE = 0.44$) versus PT ($M = 0.76$, $SE = 0.35$), but only for males ($p = .02$). Additionally, for the PT condition only, post-training N2 amplitudes to threat versus non-threat were greater for females ($M = -0.50$, $SE = 0.39$) versus males ($p = .02$). No other effects reached significance. Although not predicted, there also was a main effect of Training Group emerged for P1 amplitudes [$F(1, 37) = 5.07$, $p = .03$, partial $\eta^2 = 0.12$], such that the ABMT group had *greater* post-training P1 amplitudes to threat versus non-threat ($M = 0.48$, $SE = 0.23$) compared to the PT group ($M = -0.23$, $SE = 0.21$).

[1] Since there was only a post-training measure of observed behavior and TSST performance there was no covariate entered for that analysis.

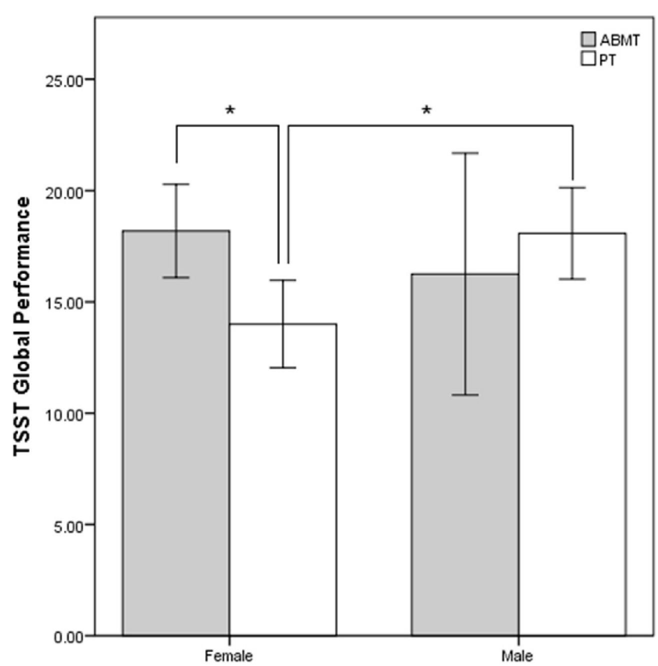

Fig. 3. Observed behavioral performance during the stressor was superior for the ABMT versus PT condition, but only for females.

No other effects (state anxiety, self-reported negative mood, behavioral attention bias, or ERPs) reached significance.

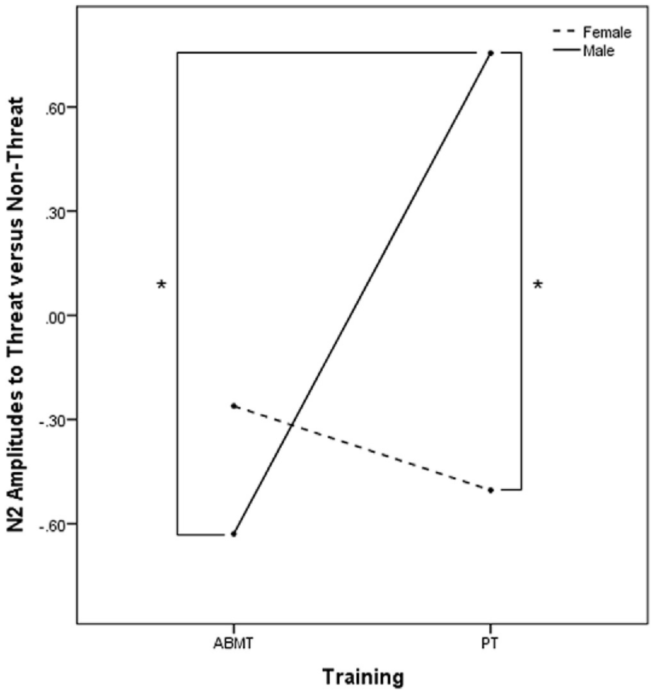

Fig. 4. Post-training N2 amplitudes (in μV) to threat versus non-threat were greater for the ABMT versus PT condition, but only for males.

2.4. Baseline measures as moderators of training effects

Next, we used a series of hierarchical regressions to test the hypothesis that individual differences in ERP responses to threat at baseline would moderate ABMT effects on state anxiety, self-reported negative mood, and observed behavioral performance. Specifically, we predicted that reduced P1 and enhanced N170 and N2 amplitudes would lead to greater reductions in state anxiety, self-reported mood, and observed behavioral performance. We comparatively examined whether baseline behavioral attention bias moderated training effects on these outcomes. Each of the post-training measures were entered separately as the dependent variable with the following variables entered in separate steps: 1) the corresponding pre-training measure; 2) Gender; 3) Training Group; 4) ERP (P1, N170, or N2) or behavioral attention bias; 5) interaction between Training and ERP (e.g., ABMT × N2). There were a total of 12 regressions: three dependent variables (state anxiety, observed behavioral performance, self-reported mood) x four moderators (P1, N170, N2, behavioral attention bias). Given recommendations concerning probing interaction effects (Aiken & West, 1991; Finney, Mitchell, Cronkite, & Moos, 1984), if interaction terms' contributions to R^2 approached significance ($p = .10$), the interactions were followed up with the PROCESS macro for SPSS (Hayes, 2013) by using simple regression equations. The dependent variable on the *y*-axis was plotted against the levels of Training Condition (ABMT and PT). Plotted regression lines represent greater/equal/reduced behavioral attention bias or ERP amplitudes to threat versus neutral cues at baseline. Regression lines were generated as the mean value and ± one standard deviation from the mean. For all steps of the analyses, predictor variables were centered to reduce problems of lack of invariance of regression coefficients and multicollinearity.

2.4.1. Baseline ERPs

Two significant interaction effects emerged between Training Condition and ERPs at baseline. First, Training Condition interacted with P1 amplitudes to threat versus non-threat to predict TSST performance: observed behavioral performance was better following ABMT versus PT, but only for participants who showed *smaller* P1 amplitudes to threat versus non-threat at baseline [$t = -2.57$, $p = .01$; full model: $F(4, 37) = 3.62$, $p = .01$, $R^2 = 0.28$; interaction step change statistics: $F(1, 37) = 5.71$, $p = .02$, $R^2 = 0.11$; see Table 3 and left side of Fig. 5]. Second, Training Condition also interacted with N170 amplitudes to threat versus non-threat to predict TSST performance: observed behavioral performance was better following ABMT versus PT, but only for participants who showed *larger* N170 amplitudes to threat versus non-threat at baseline [$t = -2.69$, $p = .01$; full model: $F(4, 37) = 2.78$, $p = .04$, $R^2 = 0.23$; interaction step change statistics: $F(1, 37) = 7.533$, $p = .01$, $R^2 = 0.15$; see Table 4 and right side of Fig. 5].

2.4.2. Baseline behavioral attention bias

No moderation effects using behavioral attention bias reached significance.

3. Discussion

Results of the present study demonstrated that a single session of gamified ABMT improved performance during an anxiety-related stress task among females only, and stress-reduction effects varied with individual differences in the rapid deployment of neurocognitive responses to threat. Findings set the stage for large-scale studies examining neurocognitive mechanisms underlying gamified ABMT in an intervention context and highlight the importance of leveraging measurement of biobehavioral individual differences to more effectively identify target mechanisms that ABMT should engage and subgroups of anxious individuals who are most likely to benefit from ABMT. Gender differences emerged in the effects of ABMT. Training group effects were found among females only, such that females in the ABMT versus PT condition showed improved performance during the social stressor. However, given that performance during the stressor also was significantly reduced among females versus males in the PT condition, it is unclear whether findings are due to the unique effects of ABMT on females, or whether effects are due to the reduced performance of females in the PT condition. In addition, this pattern raises the possibility that the ABMT condition of the app might have served to boost resilience, such that relatively low levels of performance during the stress induction among females overall was ameliorated in the ABMT group.

Gender differences in ERP responses to threat at baseline and due to training further highlight the importance of considering gender differences. Females showed reduced P1 amplitudes and enhanced N170 amplitudes prior to training – the same pattern of ERP responses that predicted greater stress reduction effects of ABMT - and thus might have been more primed to benefit from the app. Moreover, characteristics of the app might have been less suitable for males, thus leading to reduced effects. For example, males may have a preference for games involving competition and

Table 3
Correlations for regression showing training condition × P1 amplitudes predicts TSST performance.

	TSST performance	Gender	Training	P1
TSST performance	1			
Gender	0.14	1		
Training	−0.13	0.14	1	
P1	−0.29*	0.31*	−0.01	1

Note. $N = 42$ for all correlations; **$p < .01$; *$p < .05$, 2-tailed.

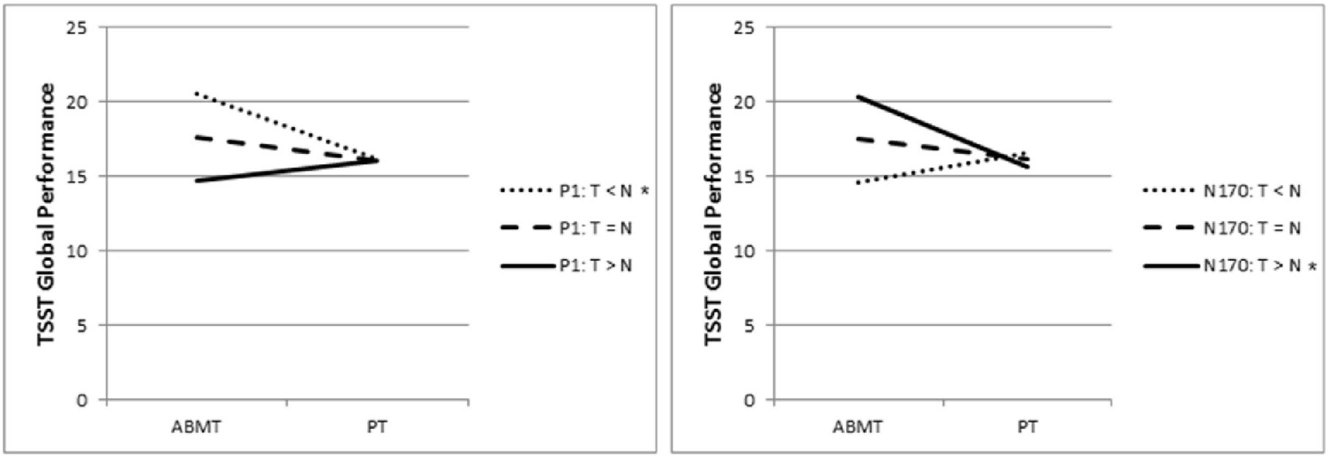

Fig. 5. Observed behavioral performance during the stressor was superior following ABMT versus PT, but only for participants who showed *smaller* P1 amplitudes to threat (T) versus non-threat (N) at baseline (top left) and *larger* N170 amplitudes to threat versus non-threat at baseline (top right).

Table 4
Correlations for regression showing training condition × N170 amplitudes predicts TSST performance.

	TSST performance	Gender	Training	N170
TSST performance	1			
Gender	0.14	1		
Training	−0.13	0.14	1	
N170	−0.12	0.36**	0.03	1

Note. $N = 42$ for all correlations; $^{**}p < .01$; $^{*}p < .05$, 2-tailed.

show greater motivation to play in a social context compared to their female counterparts (Lucas & Sherry, 2004; Veltri et al., 2014; Yoon et al., 2013). The gamified app used in the present study had few competitive aspects and was not explicitly social. Future research is needed to test whether certain game characteristics increase the efficacy of gamified interventions for males versus females.

Two baseline individual differences in ERPs predicted ABMT effects. Those in the ABMT condition who showed *smaller* P1 amplitudes but *larger* N170 amplitudes at baseline showed improved performance under stress – although ABMT versus PT resulted in larger P1 amplitudes to threat after training. One way to interpret this finding is that when the "cost" of rapid attention allocation (P1) is low, but later, evaluative and detection mechanisms (N170) are facilitated, the cognitive flexibility required for attention training is optimized. Upon completed training, attention allocation is sustained (enhanced P1 post-training in ABMT vs. PT). These also interpretations are consistent with research showing that the earliest stages of attention allocation to threat are elevated in anxiety (Mueller et al., 2009; Rossignol, Philippot, Bissot, Rigoulot, & Campanella, 2012) and thus may divert resources away from task-focused processing and learning (Mathews & Mackintosh, 1998; Mogg & Bradley, 1998) such as that happening during attention training. In contrast, research using pupillary oscillations as a measure of task-focused neural engagement shows that greater task-focused cognitive activity promotes cognitive training efficacy (Siegle et al., 2014). Enhanced N170 amplitudes prior to ABMT may specifically reflect increased "gain control" or enhanced cognitive resources devoted to the detection and resolution of the conflict between threat and non-threat cues (angry and neutral faces) (Hillyard & Anllo-Vento, 1998; Luck et al., 2000), with the preferential detection of non-threat being an "active ingredient" in ABMT (Mathews & MacLeod, 2002). Moreover, this combination of efficient attention allocation but enhanced recruitment of detection and discrimination mechanisms may inform how future ABMT protocols are designed. For example, in gamified formats, increasing the number of stimuli competing for attention may boost the recruitment of attention discrimination resources, and thus training efficacy (Cisler & Koster, 2010).

Baseline individual differences in the N2, thought to reflect cognitive control resources, did not impact ABMT effects. This is interesting in light of Eldar and Bar-Haim (2010)'s finding that short-term ABMT resulted in increased N2 responses, which we also detected in males in the ABMT condition. Eldar and Bar-Haim (2010) interpreted this finding to mean that anxious participants gained better control over their attentional resources following ABMT, although changes in the N2 did not predict ABMT effects. Yet, interpretation of this effect is complicated by the fact that it is unclear what greater magnitude N2 amplitudes signify. It may be that enhanced N2 amplitudes indicate recruitment of greater cognitive control resources (Lewis & Stieben, 2004; Nieuwenhuis et al., 2003). Indeed, the finding of the current study that ABMT resulted in selective increases in N2 amplitudes among males in the ABMT condition (relative to both PT males and females) suggests that engagement and recruitment of cognitive control might have been reduced in males prior to training, thus reducing efficacy of ABMT. On the other hand, developmental research documents that N2 amplitudes become increasingly smaller with age, suggesting increased neural efficiency because fewer resources are required to perform the same cognitive operation (Ladouceur, Dahl, & Carter, 2007; Lewis, Lamm, Segalowitz, Stieben, & Zelazo, 2006). Given this lack of direct correspondence between the amplitude of the N2 and whether one has "better" or "worse" cognitive control, future research should examine whether individual differences in this and other ERPs related to executive processes, like the P3 (Eldar & Bar-Haim, 2010; Polich, 2007), predict ABMT efficacy.

Of note was the null finding that baseline behavioral attention bias (measured via the dot probe) did not influence training effects. This is counter to previous clinical findings that ABMT may be most effective for individuals with a greater bias towards or away from threat at baseline (e.g., Kuckertz, Amir, et al., 2014; Kuckertz, Gildebrant, et al., 2014), which may be due in part to the present study's inclusion of a moderately anxious, non-clinical sample. Results from the present study, however, do suggest that ERPs versus the behavioral attention bias measure may capture unique aspects of threat bias that are specifically relevant to training efficacy. Reaction-time based measures of threat bias show low reliability and high context-sensitivity (e.g, Eldar et al., 2012; O'Toole & Dennis, 2012; Shechner, Pelc, Pine, Fox, & Bar-Haim, 2012) and likely reflect a number of performance-related factors beyond attention. That is, these measures assess the endpoint of many processes – including compensatory and regulatory strategies – that intervene between the onset of threat stimuli, allocation of attention, and execution of the response. In contrast, ERPs related to visual processing occur in the absence of response demands and are particularly well suited for delineating fine-grained individual differences in early-emerging neurocognitive responses to threat (Eldar & Bar-Haim, 2010; O'Toole & Dennis, 2012; Smith et al., 2003) that in the present study predicted the magnitude of ABMT stress-reduction effects.

In the present study, ABMT did not result in reductions in untrained measures of threat bias (measured via the dot probe) or in anxiety symptom reduction. This is consistent with a previous study using the app (Dennis & O'Toole, 2014), which required longer exposure (45 min) to reduce threat bias, although 25 min of exposure reduced subjective non-clinical levels of anxiety. This suggests that changes in reaction-time based measures of threat bias are not necessary components of acute ABMT stress-reduction effects. We chose the briefer 25-min exposure for the present study in order to more closely mirror real-world app use. In other words, 45-min of app play is highly unlikely given that mobile games are typically played in shorter bursts (Duggan, 2013). Thus, the 25-min total exposure, with numerous breaks between 1-min blocks of trials, more closely resembled likely patterns of gameplay while being long enough to increase the likelihood of effecting immediate, acute change in target outcomes. Delineating "dosages" of non-traditional ABMT delivery modes is a crucial research goal for the field as a whole.

In addition to the obvious game element differences (sounds, points, swiping interface, etc.) between this gamified version of ABMT and traditional ABMT, designed in increase engagement with attention retraining task, several elements of the game mechanics should be considered when interpreting results. First, the app used only one threat and one non-threat cartoon character, rather than multiple stimuli (e.g., human faces or words). This design may limit generalizability. Second, in the ABMT condition, there was 100% likelihood that participants would be required to respond to the trail made by the neutral/mildly pleasant sprite. In contrast, in some current ABMT studies, baseline trials (i.e., trials in which only two neutral stimuli are present) are randomly interspersed on up to 20% of trials (e.g., Amir et al., 2009; Heeren, Reese, McNally, & Philippot, 2012), given classic research on reinforcement schedules and the superiority of variable contingencies (Ferster & Skinner, 1957). That is, when the training is presented with a 100% contingency between the neutral stimulus and the target, subsequent threat-cued trials in the post-training assessment may begin to extinguish the training effects. The app was designed to require participants to respond to the mildly pleasant 100% of the time. This design element was chosen assuming that in real-world use, individuals might play the app in unpredictable intervals and durations. Thus, it could be most advantageous to administer only the "active" training condition. Future research must systematically examine this assumption.

Another important difference between the app and traditional versions of ABMT is that the non-threat stimulus, the "friendly" sprite, was mildly positive. It is possible that by directing attention to this positive stimulus, approach motivation was increased rather than threat bias decreased. This is particularly relevant given that the primary effects were in promoting more positive performance during the stress task. Moreover, cognitive bias modification for depression, which often includes positive rather than neutral stimuli, also shows positive stress-reduction effects in clinical and non-clinical samples (Beard et al., 2012; Hallion & Ruscio, 2011). An important focus for future studies is to examine both whether there are differential effects when non-threat stimuli are neutral versus positive, and whether approach-related function, such as reward sensitivity, is altered by such training approaches (Shechner, Britton, et al., 2012).

Taken together, these results provide growing support for the utility and neurocognitive bases of an alternative delivery approach for ABMT. However, several methodological limitations should be considered when interpreting findings. First, the use of the app, chosen in order to optimize engagement with the training, was a unique instantiation of ABMT. While previous research demonstrates that the app shows anxiety- and stress-reduction benefits similar to that of traditional ABMT (Dennis & O'Toole, 2014), whether the current study's findings will generalize to traditional ABMT is an open question. Third, results cannot address whether the app is effective in non-laboratory contexts, such as in the daily life of the individual, in which usage could be less consistent and briefer (e.g., Carlbring et al., 2012; Enock & McNally, 2013). Notably, the single session, experimental therapeutics design of the study may not have been adequate to result in significant reductions in subjective anxiety or symptoms, although floor effects in this non-clinical sample of adults may have reduced our ability to detect such effects.

The present study leveraged the sensitivity and specificity of ERPs to identify treatment-relevant individual differences predicting the magnitude of ABMT stress-reduction effects. Counter to previous research focusing on role of cognitive control in ABMT (Eldar & Bar-Haim, 2010), the present study highlighted the importance of relatively automatic, early-emerging attention allocation versus discrimination processes. Measuring and distinguishing among finely-grained, rapid neurocognitive responses may be crucial for identifying those for whom ABMT will be most effective. Findings have the potential to improve the tailored development of future ABMT interventions, and refine how and for whom ABMT is administered. Findings also add to the growing body of research demonstrating that evidence-based treatment mechanisms can be embedded into highly accessible mobile (Amir & Taylor, 2012; Enock & McNally, 2013; Holmes, Lang, & Shah, 2009) and gamified formats, particularly those that target cognitive biases (Hallion & Ruscio, 2011; Mobini, Reynolds, & Mackintosh, 2013).

Conflicts of interest

No conflicts to report.

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