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- Mental illness will affect over 150 million people in the U.S. alone but only a small fraction of people suffering from these problems are able to seek and receive treatment [1]. This gulf between need and access to treatment is linked to a range of barriers, such as cost and low accessibility of evidence-based treatments and the stigma associated with mental illness [2].
- Computerized attention-bias modification training (ABMT) is a cost-effective alternative treatment option with the potential to **reduce barriers to accessing empirically-validated treatments for anxiety** [3, 4]
- Little research to date has delineated specific mechanisms underlying ABMT’s effects on anxiety [5], nor identified predictors of treatment response. **Two distinct cognitive processes that may be modified by ABMT:** early threat evaluation, the relatively bottom-up, initial evaluation of stimulus-threat value, which is elevated in anxiety [6]; and cognitive control, the relatively strategic, top-down control of threat processing and reactivity, which appears to be dampened in anxiety [7].
 - Scalp-recorded event-related potentials (ERPs) are sensitive to both types of cognitive processes on the order of milliseconds and can capture changes in bottom-up attentional capture [P1, N1; 8, 9] and top-down cognitive control [N2; 10, 11].
- We have taken the **core components of the gold-standard ABMT protocol to develop a gamified mobile application** currently available for iOS devices. A previous study showed that this more user-friendly and engaging version of ABMT reduced anxiety, stress reactivity and the threat bias [12].
- Clarifying mechanisms underlying ABMT effects will improve our ability to refine the method of administering ABMT and to identify **how ABMT affects positive change and for whom ABMT may be most effective.**
- Furthermore, 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 gamifying mental health intervention tools as well as the plasticity of attentional biases.

Hypothesis 1: The ABMT version of the app will result in decreased threat bias, anxiety and stress reactivity, and attention capture by threat (P1, N170) and greater control of attention to threat (N2).

Hypothesis 2: Changes in ERP measures of threat processing will predict (testing both moderation and mediation) ABMT effects on behavioral bias, state anxiety, and stress reactivity.

Hypothesis 3: Baseline ERP measures of threat processing will predict (testing both moderation and mediation) ABMT effects on threat bias, state anxiety, and stress reactivity.

METHOD

Participants

- Participants were of 43 adults (22 females, 21 males) aged 18 to 38 ($M = 20.65$, $SD = 3.65$) who were prescreened for elevated trait anxiety (scores greater than 49) using the State-Trait Anxiety Inventory [13].
 - There were 20 participants in the ABMT group (12 females, 8 males) and 23 participants in the PT group (10 females, 13 males).
 - Self-reported race/ethnicity was as follows: 16 White, 6 Hispanic, 15 Asian, 1 African American, and 5 self-reported other race/ethnicity.

Threat Bias Assessment

- The baseline and post-app threat bias was measured using the dot probe task. Stimuli were images of angry (threat) and neutral (non-threat) faces from the NimStim Stimulus Set [14]. In this task, participants viewed two images of faces for 500 ms. These faces were either paired threat & non-threat or paired non-threat & non-threat. On each trial, one of the face cues was randomly replaced by an arrow (probe). Participants were asked to identify the direction of the arrow and reaction times were collected.
 - Three bias scores (attentional threat bias, vigilance, and disengagement) were calculated using differences in reaction times between trial types.

Trier Social Stress Test (TSST)

- Following the app training and threat bias assessment, the TSST was administered [16]. The TSST includes both a social-evaluative threat (giving a speech for 3 minutes after 3 minutes of preparation) and a lack of control task (3 minute arithmetic task). Both tasks were video-recorded and completed in front of two researchers.

Stress Reactivity: Anxious Behaviors

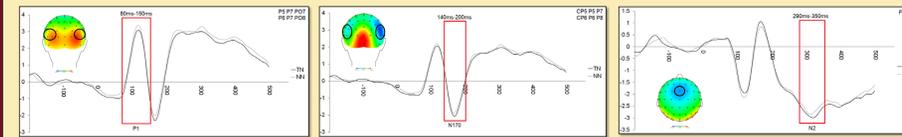
- Behaviors were coded during each of the three-minute social stressor in 10 second epochs. They consisted of flight behaviors: looking down/away from the judge; closing the eyes; drawing the chin in toward the chest; crouching; being still or freezing. Additionally, nervous speech (e.g. “umm” or “hmm”) and expressions of frustration (e.g. “Oh my goodness!” or groaning) were coded. The final score was the sum of all instances (coded yes/no) across all behaviors.

State Trait Anxiety Inventory

- Measures of state anxiety [13] were obtained at baseline, after playing the app, and after the stressor

EEG Recording and Data Reduction

- EEG activity was recorded during the threat bias assessments via BioSemi 64 Ag/AgCl scalp electrodes, sampled at 512 Hz. Eye movements were monitored by electrooculogram (EOG).
- Using Brain Vision Analyzer, data were referenced offline to the average of the entire scalp and filtered with a low-cutoff frequency of .1 Hz and a high-cutoff frequency of 30 Hz.
- Stimulus-locked data were segmented into epochs from 200 ms before stimulus presentation to 2000 ms after stimulus onset, with a 200 ms baseline correction.
- Following ocular correction [15], artifacts were identified using the following criteria and 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. In addition to this semi-automatic identification of artifacts, trials were also visually inspected for any further artifacts.



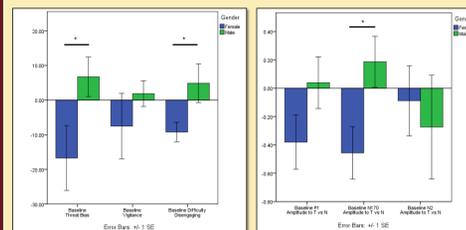
Mobile Application (App)



- Participants were quasi-randomly assigned to either an ABMT version or placebo control version of the app. For every trial, two cartoon characters (sprites), one showing an angry expression and one showing a neutral/positive expression, appeared simultaneously on the screen for 500 ms.
- Both sprites then “burrowed” into the grass field. In the ABMT version, a trail of grass appeared in the location of the non-threat character for every trial, whereas in the placebo version, a trail appears randomly in the location of the angry or neutral sprite. The participant is instructed to follow the grass trail by swiping with their finger as quickly and accurately as possible. Sound effects notify the participant of errors and provide feedback on reaction time.
- Participants completed 16 rounds of the app, for a total of 480 trials (approximately 40 minutes including breaks).

RESULTS

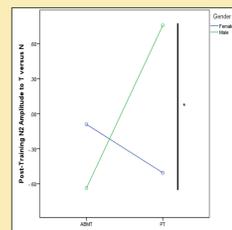
Baseline Gender Differences



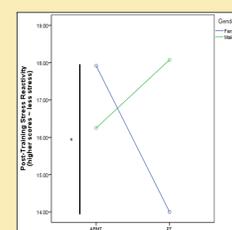
- Females showed a greater attention bias away from threat [$t(41) = 2.11$, $p = .04$] and less difficulty disengaging from threat [$t(41) = 2.29$, $p = .03$] than males.
- Females also showed greater N170 amplitudes to threat versus non-threat [$t(41) = 2.48$, $p = .02$] than males. Follow up one-sample t-tests show that female scores are different from 0 while male scores are not.

Hypothesis 1: The ABMT version of the app will result in decreased threat bias, anxiety and stress reactivity, and attention capture by threat (P1, N170) and greater control of attention to threat (N2).

- This hypothesis was tested with a series of ANCOVAs with post-training as the dependent variable, the corresponding pre-training measure as the covariate, and Training (ABMT or PT) as the between-subjects factor.
- For all participants, the ABMT group had *greater* post-training P1 amplitudes to threat versus non-threat ($M = 0.46$, $SE = 0.23$) compared to the PT group ($M = -0.24$, $SE = 0.21$) [Training: $F(1, 38) = 5.13$, $p = .03$, partial $\eta^2 = .12$].



Post-training N2 amplitudes to threat versus non-threat were greater following ABMT ($M = -0.64$, $SE = 0.45$) versus PT ($M = 0.76$, $SE = 0.35$) but only for males ($p = .02$) [Training x Gender: $F(1, 38) = 5.30$, $p = .03$, partial $\eta^2 = .12$].

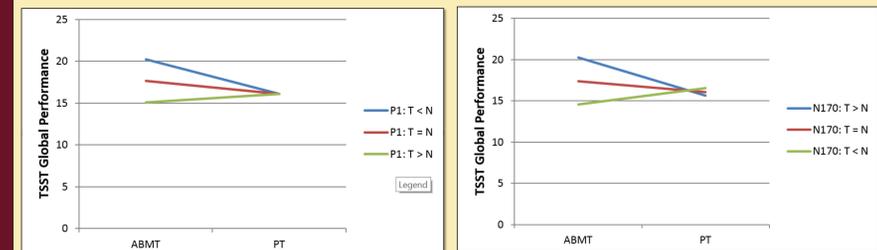


Stress reactivity was reduced (i.e., better global performance) for the ABMT ($M = 17.92$, $SE = 1.14$) versus PT condition ($M = 14.00$, $SE = 1.25$) but only for females ($p = .03$) [Training x Gender: $F(1, 38) = 5.48$, $p = .02$, partial $\eta^2 = .12$].

Hypothesis 2: Change ERP measures of threat processing will predict ABMT effects on threat bias, state anxiety, and stress reactivity. Neither moderation nor mediation analyses reached significance.

Hypothesis 3: Baseline ERP measures of threat processing will predict ABMT effects on threat bias, state anxiety, and stress reactivity.

- 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); 5) interaction between Training and ERP (e.g., ABMT x N2). Significant interactions were followed up with using PROCESS for SPSS [17]



Stress reactivity was reduced (i.e., better global performance) following ABMT versus PT, but only for participants who showed **reduced P1 amplitudes** [$t = -2.42$, $p = .02$; full model: $F(4, 38) = 3.31$, $p = .02$, $R^2 = .26$; interaction step change statistics: $F(1, 38) = 4.57$, $p = .04$, $R^2 = .09$] OR **greater N170 amplitudes** to threat versus non-threat at baseline [$t = -2.69$, $p = .01$; full model: $F(4, 38) = 2.86$, $p = .04$, $R^2 = .23$; interaction step change statistics: $F(1, 38) = 7.50$, $p = .009$, $R^2 = .15$].

DISCUSSION

- Males and females show different patterns of threat bias at baseline: females tend to show behavioral biases away from threat but greater early neural reactivity to threat (N170).
- Following app play, all participants showed greater P1 amplitudes to threat versus non-threat. However, males and females differed in the potentially beneficial effects of ABMT: females showed reductions in stress reactivity while males showed increased controlled attention to threat (N2 amplitudes).
- Moderation analyses suggest that the reduction in stress reactivity for the sample as a whole occurs only for those who evidence a particular pattern of neural reactivity to threat at baseline (reduced P1 amplitudes or greater N170 amplitudes), suggesting that individuals with reduced attention capture by threat at earlier stages of processing but facilitated processing of emotional faces are most amenable to the app.
- This may indicate that – at least in terms of the acute, positive response to ABMT in gamified format – that this pattern of threat processing may reflect relative plasticity of cognitive processes underlying stress reactivity. Future research should explore the plasticity of the threat bias following more extended app play.
- Taken together, the findings suggest that early reactivity is key for females when assessing the effects of the app on anxiety.
- The present study underscores the importance of delineating treatment-relevant individual differences, such as gender, and the benefit of leveraging highly sensitive neurocognitive measures of threat processing when developing computerized and gamified interventions.

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