HHS Public Access

Author manuscript

J Abnorm Child Psychol. Author manuscript; available in PMC 2020 May 01.

Published in final edited form as:

J Abnorm Child Psychol. 2019 May ; 47(5): 881–894. doi:10.1007/s10802-018-0494-7.

Age Moderates Link between Training Effects and Treatment Response to Attention Bias Modification Treatment for Social Anxiety Disorder

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Abstract

Attention bias modification treatment (ABMT), aims to reduce anxiety symptoms via practice on computerized attention training tasks. Despite evidence of efficacy, clinical effects appear heterogeneous. More research on ABMT mechanisms and moderators of treatment response is needed. Age is one potentially important moderator, as developmental differences in training effects may impact response. We examined developmental links between ABMT training effects and response in social anxiety disorder (SAD). We pooled data from two randomized controlled trials in treatment-seeking youths and adults with SAD (N=99) that used identical ABMT methods. We first characterized learning effects associated with the eight-session ABMT training protocol. We then tested whether learning magnitude predicted the clinical (change in SAD symptoms) and cognitive (change in attention bias) responses to treatment. Finally, we tested whether age moderated the association between ABMT learning and treatment response. Results indicate that ABMT was associated with an incremental learning curve during the protocol, and that learning improved with age. Age further moderated the association between learning gains during the ABMT protocol and subsequent reduction in self-reported SAD symptoms, such that this association was stronger with age. These effects were not evident in bias scores or clinician ratings. Finally, pre-treatment SAD symptoms and bias scores predicted ABMT learning gains. This study highlights the links among age, learning processes, and clinical response to ABMT. These insights may inform attempts to increase the clinical efficacy of ABMT for anxiety.

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All authors declare no conflicts of interests.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study.

Keywords

Anxiety; Development; Attention bias; Treatment; Learning; Children; Age

Introduction

Social anxiety disorder (SAD) involves a severe fear of social settings and is the most prevalent among anxiety disorders (e.g., Stein & Stein, 2008). It commonly emerges in childhood or adolescence and often persists if left untreated (DeWit, Ogborne, Offord, & MacDonald, 1999; Kashdan & Herbert, 2001). SAD is associated with reduced quality of life, and negative outcomes even when compared to other psychiatric disorders (Leigh & Clark, 2018; Stein & Kean, 2000). First-line treatments include pharmacotherapy and cognitive-behavioral therapy; other treatment approaches, such as psychodynamic therapy, relaxation and meditation techniques, and social skills training, administered separately or as combined treatment, also show efficacy (Acarturk, Cuijpers, van Straten, & de Graaf, 2009; Bandelow et al., 2015; Connolly & Bernstein, 2007; Spence, Donovan, & Brechman-Toussaint, 2000; Wang et al., 2017; Weisz et al., 2017). Nevertheless, many patients do not respond or have limited accessibility to extant treatment for reasons such as cost, stigma, or priorities in health care systems (Acarturk et al., 2009; Beesdo, Knappe, & Pine, 2009; Blanco et al., 2003; Ginsburg et al., 2014; Kazdin, 2017; Weisberg, Dyck, Culpepper, & Keller, 2007). These problems are particulary salient among younger patients (Ginsburg et al., 2014; Halldorsson & Creswell, 2017; Kazdin, 2017), creating a need for alternative, more accessible treatment approaches.

Social anxiety symptoms are associated with attention biases to threat-related social information in both youth and adults (Abend et al., 2018; Bar-Haim, Lamy, Pergamin, Bakermans-Kranenburg, & van IJzendoorn, 2007; Pergamin-Hight, Naim, Bakermans-Kranenburg, van IJzendoorn, & Bar-Haim, 2015); however, findings are inconsistent (Bantin, Stevens, Gerlach, & Hermann, 2016; Salum et al., 2013). Biased attention to threats has been targeted by computerized tasks designed to implicitly train participants to shift attention away from threat cues (Bar-Haim, 2010; MacLeod & Mathews, 2012; MacLeod, Mathews, & Tata, 1986). Attention training tasks have been adapted into multi-session attention bias modification treatment (ABMT) protocols, with ABMT randomized controlled trials (RCTs) reporting small-to-medium effect sizes on anxiety (Hallion & Ruscio, 2011; Linetzky, Pergamin-Hight, Pine, & Bar-Haim, 2015; Price et al., 2016). Heterogenous clinical outcomes of ABMT (Cristea, Kok, & Cuijpers, 2015; Mogoase, David, & Koster, 2014; Price et al., 2016) highlight the need to identify ABMT mechanisms and moderators of clinical outcome, such that improved treatment protocols may be implemented and patients most likely to benefit might be identified (Jones & Sharpe, 2017; Konen & Karbach, 2015; MacLeod & Clarke, 2015). To date, however, few studies examine mechanisms or moderators of clinical effects.

ABMT can be conceptualized as a learning paradigm in which an implicit attentional contingency is acquired over repeated training (Bar-Haim, 2010; MacLeod & Clarke, 2015). As such, the successful acquisition of the ABMT contingency may constitute an important

mechanism in this treatment approach. However, learning effects throughout ABMT protocols have yet to be characterized and examined in relation to clinical response. Preliminary experimental work in non-clinical populations suggests that attention training involves gradual and distinct learning effects (Abend et al., 2013; Abend, Pine, Fox, & Bar-Haim, 2014; Lazarov, Abend, Seidner, Pine, & Bar-Haim, 2017). Specifically, such learning is indexed by changes in reaction time, which manifest as gradual decreases in mean reaction time both within and between training sessions. Greater decreases in active ABMT vs. control training suggest learning specifically related to the acquisition of the attentional contingency. However, no research considers whether the magnitude of such learning predicts the magnitude of the clinical response in treatment-seeking anxiety patients (Bar-Haim, 2010; Konen & Karbach, 2015; MacLeod & Clarke, 2015).

Patient age may be an important factor moderating the association between ABMT learning and treatment response (Price et al., 2016). Similar ABMT protocols are typically administered to youth and adult patients; however, it is not clear whether the cognitive skills and capacities that may be required for effective ABMT learning are similarly developed across age. Development from childhood into adulthood entails substantial developmental changes in such capacities, including sensory-motor skills, attentional control, and associative learning (Amso & Scerif, 2015; Casey, Tottenham, Liston, & Durston, 2005; Karbach & Unger, 2014; Luna, Padmanabhan, & O'Hearn, 2010; Shechner, Hong, Britton, Pine, & Fox, 2014), which may lead to heterogenous clinical effects. Indeed, the findings on the effects of age on ABMT efficacy are mixed. Some meta-analyses indicate no effect of age on clinical outcomes (Hakamata et al., 2010; Heeren, Mogoase, Philippot, & McNally, 2015), whereas others suggest age differences in the response to ABMT (Bar-Haim, 2010; Mogoase et al., 2014; Price et al., 2016). This underscores the need for research on mechanisms of change in ABMT as such mechanisms relate to age. Delineating associations among patient age, ABMT learning, and ABMT clinical response may begin to address this need.

Here, we examined the moderating role of patient age in the link between learning during ABMT and clinical reponse in treatment-seeking patients with SAD. We used an eight-session ABMT protocol training patients to attend away from threat-related social cues (disgusted faces). To increase statistical power and facilitate a dimensional approach to anaysis (Arad & Bar-Haim, 2017; Cuthbert & Insel, 2013), we conducted secondary analyses on data aggregated from two published RCTs using identical ABMT methods (N=99), one in youth and the other in adults, both targeting patients with SAD and conducted in our lab between January 2012 and April 2014 (Naim, Kiviti, Bar-Haim, & Huppert, 2018; Pergamin-Hight, Pine, Fox, & Bar-Haim, 2016). Naim et al. (clinical trial identifier: NCT01503151; 2018) found ABMT to be superior to other training conditions (attention control and interpretation bias modification) among adults (age ⩾18 years) in terms of both clinician rating and self-report SAD measures; Pergamin-Hight et al. (clinical trial identifier: NCT01397032; Pergamin-Hight et al., 2016) found among youth (age <18 years) that ABMT was superior to attention control training in older children in terms of self-report SAD measures but not clinician ratings. Within each RCT, attention bias scores did not change as a function of treatment. In the current study, we performed secondary analyses on data combined from the two trials to address two specific hypotheses. First, we

aimed to characterize the learning effects associated with ABMT training, hypothesizing that performance incrementally improves across sessions. Second, we hypothesized that such learning predicts reductions in SAD symptom severity and threat bias, with affects varying based on the age of the patient; however, in light of mixed previous findings, we could not predict the nature of this effect.

Methods

Participants and Assessment

Data from 99 treatment-seeking participants diagnosed with SAD (46% female) were included in this report. The sample from the RCT reported by Pergamin-Hight et al. (2016) included 59 youth patients (ages 6-17 years; ABMT: n=28, control: n=31); the sample from the RCT reported by Naim et al. (2018) included 40 adult patients (ages 18-50; ABMT: n=20, control: n=20). See Table 1, supplementary material, Pergamin-Hight et al. (2016), and Naim at al. (2018) for additional details about the samples. The pooled sample had an age range of 6-50 years (M=20.25 years, SD=11.13); see Fig. S1 for a histogram depicting the age distribution. This work focuses on data from ABMT training sessions which have not been reported previously.

All participants went through an age-appropriate evaluation process that included independent clinician evaluation and diagnosis using structured clinical interviews and self-reported assessment of SAD symptom severity using gold-standard questionnaires (see below). Evaluations were conducted in each study by four experienced clinical psychologists with at least 4 years of experience each, trained to 85% reliability criterion with a senior psychologist. Consistency in diagnoses was ascertained in weekly meetings of the independent evaluators, and diagnosis was determined by consensus. All measures were translated to Hebrew and back-translated by independent bilingual translators for previous studies. Inclusion/exclusion criteria were similar for the two samples. The inclusion criterion for all participants was a primary DSM-IV diagnosis of SAD with primacy defined as SAD being the main complaint and primary source of behavioral and emotional dysfunction. The exclusion criteria for participants were: a) suicidal ideation; b) reported substance abuse or dependence; c) current or past schizophrenia, mood disorder, or obsessive-compulsive disorder; d) concurrent psychotherapy or pharmacological treatments, or psychotherapy in the past six months; or e) score ⩽50 on the Liebowitz Social Anxiety Scale interview (for adults; see below). Written informed consent/assent was obtained from all individual adult/youth participants and parents of youth participants included in the study. This involved a face-to-face meeting with each participant and their parent (when relevant) to review the material describing the study in the written consent form and addressed any questions raised by the parent/youth. The study was approved by the Tel Aviv University Institutional Review Board and conducted in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki).

Diagnosis

Anxiety Disorders Interview Schedule (ADIS).—The ADIS (Albano & Silverman, 1996) is a semi-structured interview assessing anxiety, mood, and externalizing disorders in

children 6-17 years of age according to DSM-IV criteria, and was used to establish a primary SAD diagnosis in youth patients. The ADIS demonstrates excellent interrater reliability (kappa=0.80-1.0 for anxiety as primary diagnosis; Lyneham, Abbott, & Rapee, 2007) and convergent validity (correlates specifically with other SAD measures; Wood, Piacentini, Bergman, McCracken, & Barrios, 2002). In addition to establishing a clinical diagnosis of SAD, the ADIS was used to rate SAD symptom severity in youth patients. Severity was rated on a scale from 0 (no functional interference) to 8 (severe functional interference).

Mini International Neuropsychiatric Interview (M.I.N.I.).—The M.I.N.I. is a structured diagnostic interview, developed to explore 17 psychiatric disorders in adults according to DSM-IV criteria (Sheehan et al., 1998), and was used to confirm a primary diagnosis of SAD in adult patients.

Self-Reported Measures of Social Anxiety Symptoms

Social Phobia and Anxiety Inventory for Children (SPAI-C).—Youth patients completed the SPAI-C, a 26-item self-report questionnaire assessing physical and cognitive characteristics of social anxiety in youth (Beidel, Turner, & Fink, 1996; Beidel, Turner, & Morris, 1995). Responses are indicated using a 3-point Likert scale from 0 *(never or hardly ever)* to 2 *(most of the time or always)*, for a total score range of 0-52. The SPAI-C demonstrates high test-retest reliability (r=0.86) and internal consistency (Cronbach's α=0.95) in anxious youth, as well as convergent validity (associates with diary ratings of social distress) and discriminant validity (dissociates between socially-anxious youth and youth with other or no disorders) (Beidel et al., 1996; Beidel et al., 1995). Internal consistency in the youth sample measured using Cronbach's α was 0.95.

Social Phobia Inventory (SPIN).—Adult patients completed the SPIN, a 17-item self-report questionnaire for social anxiety symptoms (Connor et al., 2000), tapping into fears of social interactions, embarrassment, and physical discomfort related to social anxiety. Responses are indicated using a 5-point Likert scale from 0 *(not at all)* to 4 *(extremely)*, for a total score range of 0-68. The SPIN demonstrates high test-retest reliability (r=0.86) and internal consistency (Cronbach's α=0.92-0.95), as well as convergent validity (associates with scores on other measures of social anxiety) and discriminant validity (low correlations with general depression and anxiety scales) (Antony, Coons, McCabe, Ashbaugh, & Swinson, 2006). Internal consistency in the adult sample was α=0.80.

Clinician-Rated Measures of Social Anxiety Symptoms

ADIS.—The ADIS was used to rate SAD symptom severity in youth patients (see above).

Liebowitz Social Anxiety Scale Interview (LSAS).—The LSAS (Liebowitz, 1987), a 24-item clinician-administered scale assessing fear and avoidance (separately) associated with social anxiety, was used to rate SAD symptom severity in the adult sample. Responses are indicated using a 4-point Likert scale from 0 *(no fear/avoidance)* to 3 *(severe fear/usually avoid)*, for a total score range of 0-144. The LSAS demonstrates high internal consistency (Cronbach's α=0.95-0.96) in socially-anxious adults, as well as convergent validity

(associates with diary ratings of social anxiety) and discriminant validity (lesser associations with general depression and anxiety scales) (Fresco et al., 2001; Heimberg et al., 1999).

The Dot-Probe Task

All participants completed the same variant of the dot-probe task (Abend, Pine, & Bar-Haim, 2014) for treatment and bias assessment. The face stimuli were photographs of 20 different individuals (10 female; Tottenham et al., 2009), each individual contributing two photographs depicting angry and neutral expressions. Two sets were constructed. Each participant was assessed pre- and post-treatment with one set of faces, and trained with another set. Each trial in the task (Fig. 1A) started with a fixation cross (500ms), followed by a pair of face stimuli (500ms), and then a target probe appearing in the location vacated by one of the faces (presented until response). Participants were insturcted to identify the probe as quickly as possible without compromising accuracy.

ABMT training.—Participants were randomly assigned into one of two training conditions and completed eight training sessions. Each of the training sessions was composed of 160 trials presented in random order; 120 trials presented pairs composed of neutral and threatening (angry) expressions (NT), and 40 trials presented two neutral expressions (NN). In the ABMT condition, participants were trained to attend away from threat by having the probes repeatedly follow the neutral faces in all NT trials. In the control condition (attention control training; ACT), probes were presented with equal probability at the neutral or angry face location. Of note, the trial by Naim et al. (2018) additionally investigated the efficacy of interpretation bias modification as part of a factorial design of Bias (attention, interpretation) x Group (active, control). Data included here are only from the groups receiving inactive, control interpretation bias training.

Attention bias assessment.—All participants completed an attention bias assessment before and after treatment. Assessment consisted of a 120-trial (80 NT and 40 NN trials) variant of the task, with the probes appearing with equal probability at the location of threat and neutral stimuli (Abend, Pine, & Bar-Haim, 2014).

Procedure

Pre-treatment assessment.—All participants first took part in a pre-treatment assessment (Fig. 1B), during which the ADIS and SPAI-C (youth patients), or M.I.N.I., SPIN and LSAS (adult patients), were administered by a trained clinician. In addition, threat bias was assessed.

Treatment.—Participants were randomly assigned to one of the two training conditions, ABMT or ACT. The eight training sessions were delivered in separate visits to the lab, starting one week after pre-treatment assessment, and spanning four consecutive weeks in total (two visits per week).

Post-treatment assessment.—The post-treatment assessment was identical to the pretreatment assessment, conduced one week following the end of treatment.

The same lab setting was used for all study phases. Participants, experimenters, and clinicians were blind to the assigned training condition throughout the study.

Outcome measures

SAD symptom severity change.—Since the clinical effect of ABMT manifested specifically in self-report SAD measures in both RCTs, we used the SPAI-C and SPIN to assess symptoms severity in the primary analyses. Additional analyses using clinician ratings are presented as well. Pre- and post-treatment scores for the SPAI-C and SPIN appear in Table 1. The difference between pre- and post-treatment scores was used to indicate change in symptom severity. Since these instruments utilize different scales, change scores were Z-transformed for each participant (relative to mean and SD of their age group), to derive a single composite symptom severity change score comparable between all participants (*Δsymptoms*).

Threat bias change.—Bias scores were calculated as the difference in mean RT between NT trials in which the probes replaced the neutral face and NT trials in which the probes replaced the angry face. The difference between pre- and post-treatment threat bias scores was used to indicate change in threat bias following treatment (*Δbias*). Of note, pre-treatment mean threat bias scores did not significantly differ from 0 in the youth, adult, and pooled patient samples (*ps*>0.19), with approximately half of the pooled sample showing a bias score <0 (n=49) and half showing a bias score >0 (n=50).

Learning gains.—Progression of learning over the eight-session ABMT training protocol was assessed using methods similar to those applied in previous studies of learning in threat-related attention training (Abend et al., 2013; Abend, Pine, Fox, et al., 2014; Lazarov et al., 2017). Learning gains in the task were measured by first calculating the mean RT in each of the 8 sessions. Next, for each participant, we fitted these 8 means on the session number using quadratic polynomials (Eberl et al., 2013), constructing individually-fitted learning curves. Finally, similar to prior studies of learning (Abend et al., 2013; Abend, Pine, Fox, et al., 2014; Doyon et al., 2009; Lazarov et al., 2017), we normalized each session's mean RT (across all session trials) relative to the mean RT in Session 1; thus, the RT data were transformed into a curve reflecting learning rate standardized to each participant's performance level (percentage of improvement). This method enabled us to more clearly identify learning capacity by diminishing the influence of individual differences in sensory-motor performance reflected in raw RT measures (Abend, Pine, Fox, et al., 2014). Importantly, the use of standardized learning rates allowed us to directly compare learning trends between different age groups which otherwise are known to be very different in raw RT performance levels (e.g., Burki, Ludwig, Chicherio, & de Ribaupierre, 2014; Thomas et al., 2004). The degree of learning achieved by the end of the protocol (normalized gain in session 8) was used as an index of learning gains (Abend et al., 2013; Eberl et al., 2013; Heeren, Philippot, & Koster, 2015).

Data Analysis

Prior to analysis, data were first cleaned following standard procedures (see supplementary material). Due to our focus on associations between learning gains, SAD symptom severity

and threat bias scores, these continuous measures were retained as such throughout analyses. As a consequence, age was treated as a continuous factor when possible, and as a categorical factor when this facilitated interpretation (i.e., decomposition of higher-order interactions). Our first analysis examined learning progression through the ABMT protocol, by entering normalized session mean RTs into a repeated-measures analysis of variance (RM-ANOVA), with Session (1-8) as a within-subject factor, and Condition (ABMT, ACT) and Age Group (youth, adults) as between-subjects factors. Greater learning in the ABMT condition relative to the ACT condition would indicate acquisition of the ABMT attentional contingency, facilitating task performance (Abend et al., 2013; Abend, Pine, Fox, et al., 2014; Lazarov et al., 2017).

Next, we examined whether training condition, learning gains, and age predicted the clinical and cognitive response to ABMT. To assess whether Δsymptoms was predicted by these factors, we constructed a linear regression model using Condition (ABMT, ACT), Gains (continuous), and Age (continuous) as predictors in the first step, and their interaction as the second step in the analysis. Similarly, we constructed a model predicting Δbias by Condition, Gains, and Age (1st step) and their interaction (2nd step). Age was considered continuously in these analyses, and then treated categorically in post-hoc analyses.

Finally, we conducted additional exploratory analyses to examine whether ABMT learning could be predicted at pre-treatment assessment. To that end, we entered SAD symptoms severity and threat bias score, and their interactions with age, into a linear regression model predicting ABMT learning gains.

Analyses in which age was considered as a categorical variable comparing youth and adult patients were additionally followed by auxiliary analyses in which the sample was divided into children (age <13 years, n=30), adolescents (13< age <18 years, n=29), and adults (age ⩾18 years, n=40); children vs. adolescent group assignment was determined by a median split. These analyses enabled us to explore developmental effects with greater sensitivity, but these analyses were considered secondary due to lower power associated with more groups.

All tests were two-tailed with $\alpha \leqslant 0.05$. Significant interactions were followed by lower-order ANOVAs and Fisher's Least Significant Difference tests, or Pearson correlations. Kolmogorov-Smirnov tests indicated that the distribution of learning gains in none of the sessions was significantly different from the normal distribution, permitting the use of parametric statistical tests. As noted, all analyses reported here are secondary, based on data pooled from published work (Naim et al., 2018; Pergamin-Hight et al., 2016).

Results

Learning during the ABMT protocol

A RM-ANOVA on learning gains revealed a significant main effect of Session, $F(7,665)=20.08$, $p<0.001$, $\eta^2=0.17$. Follow-up comparisons revealed incremental learning between successive sessions up to the 4th session of the protocol, $ps<0.01$ (corrected), with maximal gain (6.3%) reached in the 6th session. Trend analysis confirmed a quadratic trend of learning, $F(1,95)=10.91$, $p=0.001$, $\eta^2=0.10$. Effects on performance accuracy are reported

in supplementary material. In addition, a significant Age Group-by-Condition interaction was noted, $F(1,95)=5.16$, $p=0.025$, $\eta^2=0.05$.

These effects were qualified by a significant Age Group-by-Condition-by-Session interaction on learning gains, $F(7,665)=3.72$, $p<0.001$, $\eta^2=0.04$ (Fig. 2), indicating that learning trends varied as function of age and training condition. To explicate this interaction, we next compared learning patterns between the ABMT and ACT conditions (Session-by-Condition interaction) separately within each age group. These analyses revealed a significant Session-by-Condition interaction in adults (Fig 2, right), $F(7,266)=2.94$, $p=0.006$, $\eta^2=0.07$. Follow-up analyses within each training condition yielded a significant main effect of Session in the ABMT condition, $F(7,133)=28.84$, $p<0.001$, $\eta^2=0.60$, indicating incremental learning during the protocol, whereas no main effect of Session was observed in the ACT condition, $F(7,133)=1.49$, $p=0.18$, $\eta^2=0.07$. No significant Session-by-Condition interaction was observed in youth (Fig. 2, left), $F(7,399)=1.52$, $p=0.16$, $\eta^2=0.03$. No other main or interaction effects were observed in the full model.

To explore adolescence-specific developmental effects on learning, the Age Group-by-Condition-by-Session interaction was also decomposed by comparing learning gains during ABMT and ACT separately within the children and adolescent groups. Unlike the significant Condition-by-Session interaction effect in adults (see above), we observed a non-significant interaction in both children, $F(7,196)=1.75$, $p=0.10$, $\eta^2=0.06$, and adolescent, $F(7,189)=0.29$, $p=0.96$, $\eta^2=0.01$, groups. Together with the primary analysis, these results suggest that learning in the ABMT vs. ACT condition improves with age, but that this advantage emerges primarily in adulthood.

In addition, we decomposed the Age Group-by-Condition-by-Session interaction by training condition. We noted a main effect of Session, $F(7,343)=9.93$, $p<0.001$, $\eta^2=0.17$. However, neither the Age Group-by-Session interaction, $F(7,343)=1.59$, $p=0.14$, $\eta^2=0.03$, nor the main effect of Age Group, $F(1,49)=2.46$, $p=0.12$, $\eta^2=0.05$, was significant. In contrast, in the ABMT condition, in addition to a main effect of Session, $F(7,322)=10.12$, $p<0.001$, $\eta^2=0.18$, the Age Group-by-Session interaction was significant, $F(7,322)=2.14$, $p=0.039$, $\eta^2=0.05$, and the main effect of Age Group showed a non-significant trend, $F(1,46)=3.19$, $p=0.081$, $\eta^2=0.07$. These additional results highlight age differences specifically in ABMT learning.

Predicting reduction in anxiety symptoms severity and threat bias

A linear regression model predicting Δsymptoms based on training condition, learning gains, and age (continuous), yielded a non-significant model for the first step, $R^2=0.04$, $F(3,94)=1.19$, $p=0.32$ (see Table 2). In contrast, the model including the interaction between the predictors in the second step was significant, $R^2=0.10$, $F(4,93)=2.54$, $p=0.045$, with the Condition-by-Gains-by-Age interaction term being the sole significant predictor in the model, $\beta=0.36$, $p=0.013$.

To explicate this interaction, we constructed a model predicting Δsymptoms based on learning gains and age (1st step), and their interaction (2nd step), separately within each training condition. These analyses revealed no significant models in the ACT condition,

R^2s<0.021, *p*s>0.61. However, for the ABMT condition, a significant model emerged for the 2nd step, R^2=0.18, F(3,43)=3,10, p=0.036, with a significant contribution of the Gains-by-Age interaction term, β=0.69, p=0.028. Thus, the association between learning, age, and Δsymptoms was specific to the ABMT condition. We next decomposed this interaction by age, and examined the simple correlations between learning gains and Δsymptoms separately in each age group (Fig. 3). This correlation was significant and positive for adults, r=0.54, p=0.013, and non-significant for youth, r=0.05, p=0.82, indicating that greater ABMT learning gains were associated with greater reduction in SAD severity, but only among adult patients. Correlations computed separately for the children and adolescent groups likewise indicated no significant association between gains and reduction in symptoms in either youth group, *rs*<0.12, *p*s>0.69, in line with the above-reported learning effects.

In a similar manner to the self-reported SAD symptom severity measures, we constructed a linear regression model predicting clinician-rated Δsymptoms based on training condition, learning gains, and age. This analysis yielded a non-significant model for the first step (individual predictors), R^2=0.06, F(3,95)=2.22, p=0.09. The model including the interaction between the predictors in the second step was likewise non-significant, R^2=0.08, F(4,94)=1.93, p=0.11.

A linear regression predicting Δbias based on training condition, learning gains, and age yielded non-significant models for both steps, R^2s<0.03, *p*s>0.47. This indicates that change in attention bias following treatment was not a function of training condition, learning, or age.

What predicts the magnitude of ABMT learning?

To explore whether learning capacity during ABMT training could be predicted at pre-treatment baseline, we conducted a linear regression model with age (continuous) and pre-treatment threat bias score and SAD symptom severity as predictors in step 1, and their individual interactions with age (continuous) in step 2. Step 1 (see Table 3) yielded a significant model, R^2=0.17, F(3,44)=2.92, p=0.044, with symptom severity contributing significantly to the explained variance in learning gains, β=0.32, p=0.027. The addition of step 2 led to a significant increase in explained variance, ΔR^2 =0.15, F(2,42)=4.45,) p=0.018. The regression model for this step was likewise significant, R^2=0.26, F(5,42)=3.81, p=0.006, with significant contribution by age, β=0.28, p=0.038, and the interaction between threat bias score and age, β=0.42, p=0.005 (Fig. 4). To explore this age moderation effect, the correlation between threat bias scores and learning gains was calculated separately within each age group. This analysis revealed a strong positive correlation in adults, r=0.74, p<0.001, and a non-significant correlation in youth, r=−0.27, p=0.16. These correlations were also non-significant when tested separately in the children and adolescent groups, *rs*<0.10, *p*s>0.71.

In a similar manner, we also tested whether learning capacity during ABMT training could be predicted at pre-treatment baseline by clinician-rated SAD measures. To this end, we conducted a linear regression model with pre-ABMT threat bias score and clinician-rated SAD symptom severity as predictors in step 1, and their interactions with age (continuous)

in step 2. Both step 1, R^2=0.01, F(2,45)=0.13, p=0.88, and step 2, R^2=0.09, F(2,43)=1.03, p=0.40, yielded non-significant models.

Discussion

The current study investigated associations among age, learning during ABMT, and treatment response to ABMT for SAD, via secondary analyses on data pooled from two published ABMT RCTs. Three main findings emerged. First, incremental performance improvement occurred across sessions. Second, learning gains in the ABMT condition increased with age. Third, ABMT-induced learning gains predicted the magnitude of reduction in self-reported anxiety symptoms among adults, and were predicted by pre-treatment threat bias scores and symptom severity in this age group. These results demonstrate associations among ABMT-induced learning, treatment response, and patient age.

In terms of ABMT-induced learning, the chronometry of rising learning curves suggests that ABMT induced an incremental learning over training sessions. This suggests that multisession treatment protocols are preferred over single-session schedules (Eberl et al., 2013; Hakamata et al., 2010; Hertel & Mathews, 2011). However, the data also reveal minimal improvement beyond the sixth session, suggesting that additional practice beyond that point may not be necessary. Such inferences demonstrate the utility of tracking learning through multisession protocols, and suggest re-evaluation of the current eight-session ABMT protocol or incorporation of data on individual differences in learning rates.

The current results suggest that age impacts response to ABMT through effects on learning. There is considerable interest in applying computerized paradigms to both pediatric and adult anxiety patients. However, results of ABMT trials in younger participants are inconsistent (Eldar et al., 2012; Lowther & Newman, 2014; Mogoase et al., 2014; White et al., 2017). The present findings suggest that youth may find it harder than adults to acquire the implicit attentional contingency embedded in the ABMT task, as shown in the absence of differential learning. This may lead to a weaker effect on symptoms, and contribute to inconsistent findings in youth.

Why would it be harder for youth to learn the ABMT contingency? Significant age-related improvement occurs in many relevant cognitive and motor abilities (Casey et al., 2005; Huizinga, Dolan, & van der Molen, 2006; Karbach & Unger, 2014; Luna et al., 2010). In the present study, adults exhibited faster RTs and higher accuracy than youth. However, no main effect of age on learning gains was observed, suggesting that basic sensory-motor learning ability in this task did not vary significantly as a function of age.

Age effects in ABMT acquisition may be explained by developmental differences in implicit learning or attentional control capacities, which improve with age (Amso & Scerif, 2015; Maybery, Taylor, & O'Brien-Malone, 1995; Thomas et al., 2004). For example, a core level of neurocognitive maturation may be required for implicitly acquiring the ABMT contingency. Efficiency of ABMT-indcued learning may also depend on the interaction between early, automatic attentional processes and higher-order processes of attentional

control and goal-directed behavior (Corbetta & Shulman, 2002; LeDoux & Pine, 2016; Shechner & Bar-Haim, 2016). Among anxious individuals, threat stimuli in the task may be preferentially processed through automatic processes, while some degree of attentional control is required to sufficiently process the neutral stimuli and effectively learn the embedded contingency. The nature of interaction between these processes may change with age.

Adolescence involves maturation in executive processing and related cognitive control capacities (Amso & Scerif, 2015; K. Hwang, Velanova, & Luna, 2010; Luna, Velanova, & Geier, 2008). This includes attentional control processes (Blakemore, 2008; Henderson, Pine, & Fox, 2015), particularly as they are deployed in the context of aversive stimuli (Brodeur & Boden, 2000; S. Hwang, White, Nolan, Sinclair, & Blair, 2014). ABMT is thought to induce modulation of attention allocation via top-down, attentional control processes (Browning, Holmes, Murphy, Goodwin, & Harmer, 2010; Clarke, Browning, Hammond, Notebaert, & MacLeod, 2014). Accordingly, reduced capacity in such processes in youth compared to adults could account for the differences observed in the current study. ABMT paradigms that require more explicitly top-down capacities (e.g., visual search), typically find significant changes in attention bias following training alongside generally positive, although inconsistent, clinical effects (de Voogd et al., 2016; De Voogd, Wiers, Prins, & Salemink, 2014; De Voogd, Wiers, & Salemink, 2017; Waters, Pittaway, Mogg, Bradley, & Pine, 2013; Waters et al., 2015). Such findings support a role for attention control processes in the modification of attentional biases, and indicate that top-down conrol processes can be enhanced in youth. Future research could examine whether implementations of ABMT procedures that complement training of bottom-up attention processes with top-down attention training yield stronger clinical effects in youth patients.

More broadly, the results relating ABMT-induced learning to symptom reduction informs ideas on the mechanism underlying ABMT. Findings suggest that symptom reduction relates to the learning of the embedded attentional contingency in the task, i.e., the association between emotional expression and probe location. This learning is believed to rely on implicit associative learning in which the contingency is reinforced by facilitating task performance (Bar-Haim, 2010; Shechner & Bar-Haim, 2016), a rationale which guides the development of ABMT protocols (Bar-Haim, 2010; Mathews & MacLeod, 2002), but has been minimally tested (Price et al., 2016). The current results directly relate the acquisition of the ABMT contingency to its therapeutic effect. Importantly, however, theoretical conceptualizations of ABMT (Bar-Haim, 2010; MacLeod & Clarke, 2015) should account for developmental differences in relevant skills. In addition, it should be noted that while ABMT-induced learning gains related to clinical response, we did not detect such an association with threat bias scores. Inconsistencies in such associations have been previously noted (e.g., Heeren, Reese, McNally, & Philippot, 2012; Shechner, Rimon-Chakir, et al., 2014), along with concerns regarding the dot-probe-derived threat bias score as a reliable index of attention bias (Cisler, Bacon, & Williams, 2009; Price et al., 2015). As such, alternative measures of assessing attention biases may be considered in future research. Such methods may then help elucidate the association between ABMT learning gains and subsequent change in threat bias.

Results may carry practical implications. First, facilitation of learning during ABMT may improve clinical outcome. For example, associating rewards with rapid and accurate probe discrimination may increase learning and reduce symptoms (Abe et al., 2011; Fischer & Born, 2009). A second approach may focus on response accuracy. Both speed and accuracy are critical elements in performance and learning (Vidal, Meckler, & Hasbroucq, 2015). However, the high and constant accuracy rates associated with performance in current dot-probe ABMT tasks (generally >90%) restrict learning indices primarily to the speed domain, while tasks that allow for improvement in accuracy as well may enhance the effective acquisition of the ABMT contingency. Finally, explicitly informing participants of the embedded attentional contingency may improve acquisition by relying on implicit and explicit aspects of the task (Lazarov et al., 2017; MacLeod, Koster, & Fox, 2009).

Second, age-related differences in ABMT response may necessitate adjustments in protocol parameters to enhance acquisition specifically among younger individuals. Prior research finds ABMT to be viewed by adult patients as boring (Beard, Weisberg, & Primack, 2012). Youth participants may likewise find it tedious and difficult to maintain focus for longer periods of time, potentially leading to decreased engagement with the task. Findings ways to increase task engagement may enhance learning as patients may be more attentive to the task and thus more likely to acquire the attentional contingency. One approach may be to deliver shorter training sessions or include breaks within sessions to reduce boredom or fatigue. Offering concrete incentives based on performance may also increase motivation to engage with the task (Dovis, Van der Oord, Wiers, & Prins, 2012). Another approach may involve presenting age-compatible stimuli, such as adolescent actors, which may increase their relevance to youth during the task (Pergamin-Hight et al., 2015). Finally, the “gamification” of training procedures has been suggested to make ABMT procedures more enjoyable and engaging, reduce stigma associated with treatment, and increase compliance, particularly among youth (Dennis & O’Toole, 2014; MacLeod & Clarke, 2015; Rahmani & Boren, 2012). However, it should be noted that such gamification may also lead to decreases in motivation to train (Boendermaker, Sanchez Maceiras, Boffo, & Wiers, 2016). In addition, modifications of length and content of the training sessions may potentially curb learning if the session does not offer enough training trials or fully effective stimuli. As such, continued research is needed to examine how such adjustments may be implemented to enhance learning during the ABMT protocol.

In addition to elucidating the dynamics of learning during ABMT, learning gains may potentially also serve as a marker for ABMT acquisition in individual patients. This learning marker could be applied to dynamically monitor individual ongoing within-session or session-to-session progress and optimize protocol parameters, eventually paving the way for personalized, adaptive treatment (Klingberg, 2010; Konen & Karbach, 2015). For example, task parameters may be modified online according to individual performance rate to enhance learning during the training session (Lovden, Brehmer, Li, & Lindenberger, 2012; Shin, Lee, Yoo, & Chong, 2015). Furthermore, instead of the current practice of administering an identical protocol to all patients, protocol length could vary according to individual learning rates and progress.

This study is not without limitations. While reflecting the reality of clinical thinking and practice, different measures of SAD symptom severity were used for youth and adults. This practical necessity allowed us to significantly increase our sample size and range of patient age, but might have also introduced noise to the relevant analyses that diminishes the ability to detect the therapeutic signal. This concern is alleviated to some extent by the fact that each of the used measures is considered gold-standard for self-reported SAD symptoms in its age range, and the use of Z-transformed scores to eliminate scale differences. It is also notable that age-related differences in ABMT efficacy only manifested on self-reported, but not clinician-rated, measures of anxiety. Similarly, age-related differences in learning also emerged on self-report measures. While such findings are consistent with previous findings in youth where clinician and self-reported anxiety measures generated different conclusions regarding ABMT (Shechner, Rimon-Chakir, et al., 2014), caution should nevertheless be taken when interpreting the clinical effects reported here. In addition, few common demographic variables were collected in the original RCTs, limiting our ability to examine the effect of other moderators. Standardization of treatment protocols and related data collection may aid future efforts to identify moderators of treatment response. Finally, ABMT learning gains correlated with reduction in SAD symptoms following treatment, but not with change in threat bias scores, as noted above. Poor reliability of the dot-probe-derived threat bias score (Cisler et al., 2009; Price et al., 2015) may explain the absence of measurable pre-treatment threat bias, and may further have limited our capacity to accurately gauge treatment-induced changes in bias. Along these lines, the use of similar task variants to assess, and then train, threat-related attention patterns limits the generalizability of findings. We therefore encourage future studies to assess threat bias both using the methods employed in the current work as well as through multiple, other, complementary methods (e.g., combining eye-tracking and behavioral measures). As such, these studies would augment the procedures employed here such that the transfer of training effects to other tasks could be assessed.

In conclusion, the current findings highlight the importance of studying learning processes during ABMT for SAD. Such data can usefully inform about the processes underlying ABMT as well as be applied to improve the clinical efficacy of ABMT trials for anxiety.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

This research was supported in part by the Intramural Research Program of the National Institute of Mental Health (ZIAMH002781-15, NCT00018057).

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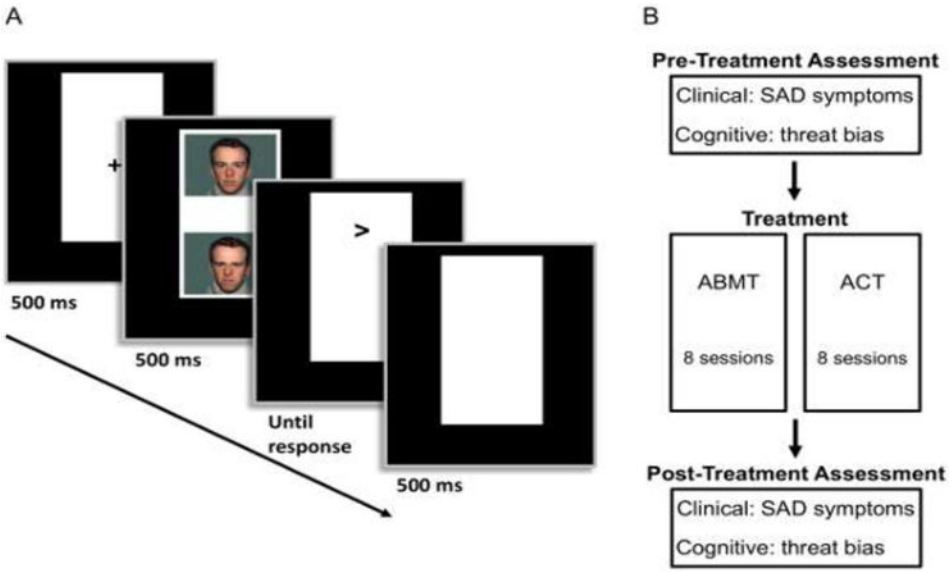

Fig. 1.

(A) Sequence of events in a single ABMT dot-probe trial; (B) Both adult and youth sample utilized the same RCT design: a pre-treatment assessment was followed by an eight-session training protocol (ABMT or ACT), and a post-treatment assessment.

Note: ABMT = attention bias modification treatment, ACT = attention control training.

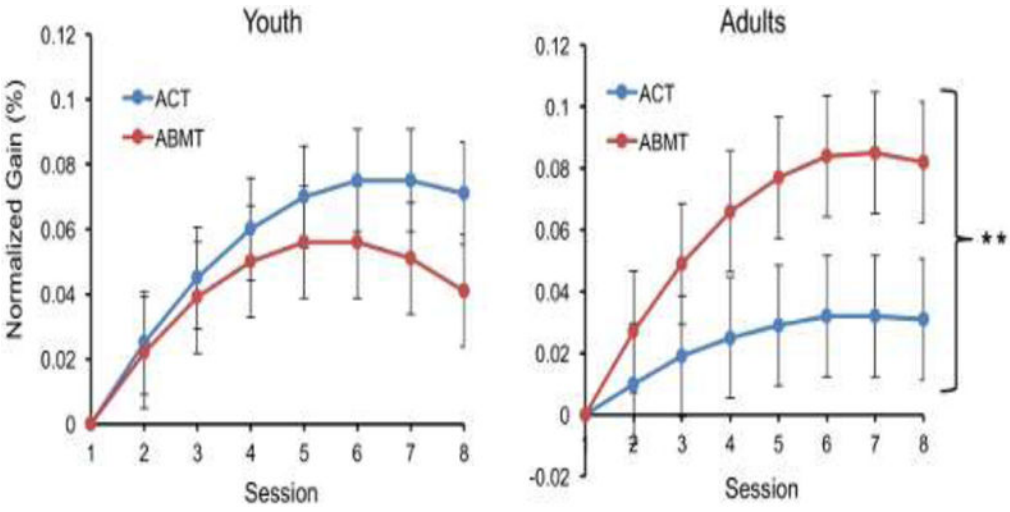

Fig. 2.

Mean normalized gain per session for the ABMT (red) and ACT (blue) conditions for the youth and adult groups. Gains reflect performance improvement relative to Session 1. Error bars signify 95% confidence intervals.

Note: ** $p < 0.01$; ABMT = attention bias modification treatment, ACT = attention control training.

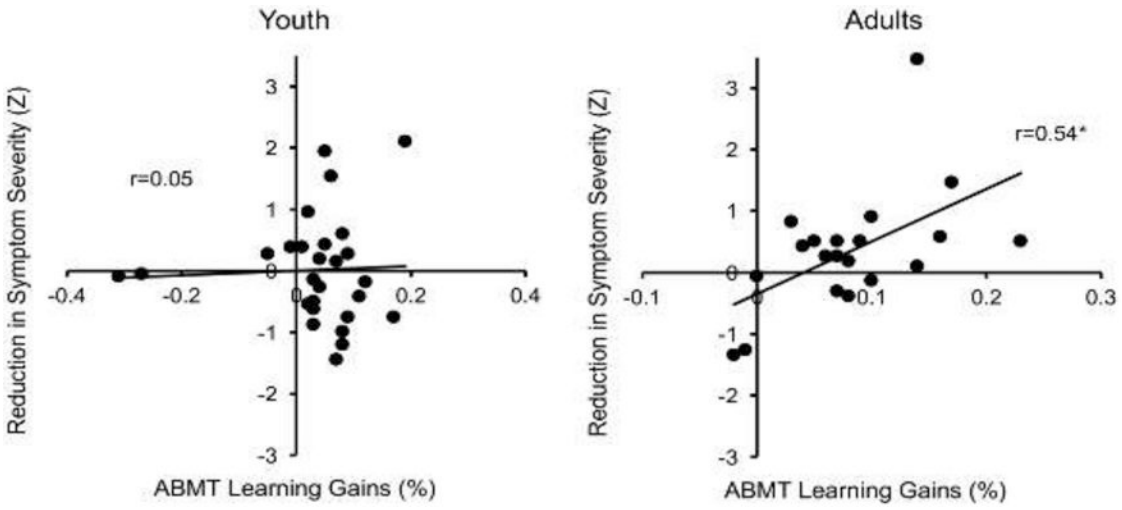

Fig. 3.

Scatterplots depicting the correlations between learning gains in the ABMT condition and reduction in symptom severity (Δsymptoms) for the youth and adult groups.

Note: * $p < 0.05$; ABMT = attention bias modification treatment.

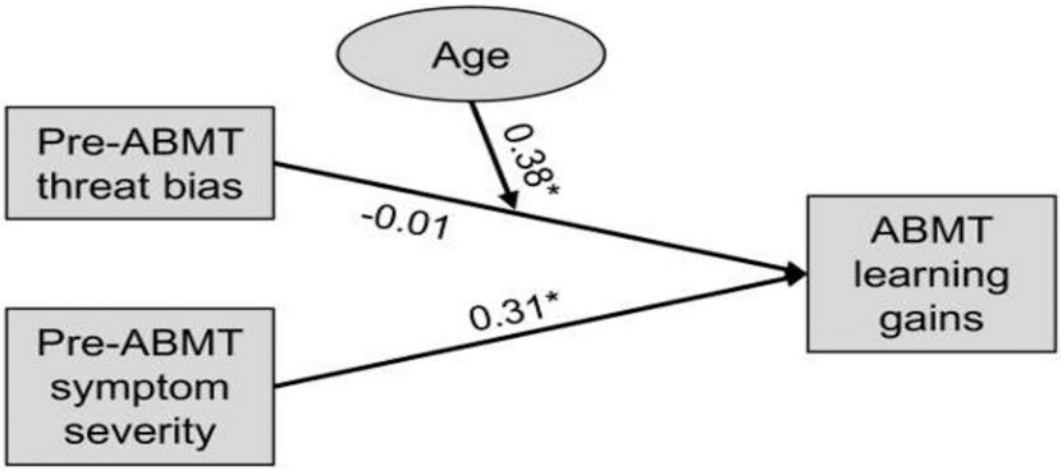

Fig. 4.

Regression analysis predicting ABMT learning gains by pre-treatment threat bias scores and anxiety symptom severity, with age as moderator.

Note: * $p < 0.05$; ABMT = attention bias modification treatment.

Table 1.

Means (and standard deviations) of age (in years), gender distribution (% female), pre- and post-ABMT social anxiety symptom severity and threat bias scores (in ms) for the ACT and ABMT conditions in youth and adult patients. Symptom severity was assessed using the SPAI-C (youth) or the SPIN (adults).

				Pre-ABMT		Post-ABMT	
Group	**n**	**%female**	**Age**	**Symptom severity**	**Threat bias**	**Symptom severity**	**Threat bias**
Youth							
ACT	31	48%	12.2 (3.2)	54.2 (28.2)	−11.8 (43.6)	40.2 (25.8)	8.9 (20.5)
ABMT	28	46%	12.7 (3.2)	61.5 (22.4)	3.3 (39.4)	48.0 (22.1)	10.0 (36.5)
Total	59	47%	12.4 (3.1)	57.6 (25.6)	−4.6 (42.0)	43.8 (24.3)	9.4 (28.9)
Adults							
ACT	20	55%	32.3 (7.4)	43.5 (8.2)	7.8 (37.9)	35.3 (11.0)	1.8 (16.0)
ABMT	20	25%	31.3 (8.9)	48.0 (10.9)	5.2 (22.2)	30.9 (11.4)	2.9 (17.2)
Total	40	40%	31.8 (8.1)	45.8 (9.8)	6.5 (30.7)	33.1 (11.3)	2.3 (16.4)

Note: SAD=Social Anxiety Disorder; ABMT=Attention Bias Modification Treatment; ACT=Attention Control Training; SPAI-C=Social Phobia and Anxiety Inventory for Children; SPIN=Social Phobia Inventory.

Table 2.

Results of a regression analysis predicting Δsymptoms based on age, learning gains, and training condition.

	Statistic	p-value
Model 1	$F(3,94)=1.19$	0.32
Age	ß=0.01	0.90
Learning gains	ß=0.11	0.29
Training condition	ß=0.16	0.13
Model 2	$F(4,93)=2.54$	0.045
	$\Delta R^2=0.06$, $F(1,93)=8.27$	0.013
Age	ß=−0.11	0.33
Learning gains	ß=−0.05	0.69
Training condition	ß=0.00	>0.99
Age×Learning gains×Training condition	ß=0.36	0.013

Table 3.

Results of a regression analysis predicting active ABMT learning gains based on age and pre-treatment threat bias score and social anxiety symptom severity.

	Statistic	p-value
Model 1	$F(3,44)=2.92$	0.044
Age	ß=0.23	0.10
Threat bias	ß=0.00	0.98
Symptom severity	ß=0.32	0.027
Model 2	$F(5,42)=3.81$	0.006
	$\Delta R^2=0.15$, $F(2,42)=4.45$	0.018
Age	ß=0.28	0.038
Threat bias	ß=0.16	0.27
Symptom severity	ß=0.26	0.07
Age×Threat bias	ß=−0.15	0.31
Age×Symptom severity	ß=0.36	0.013

Note: ABMT=Attention Bias Modification Treatment.