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Attention Bias Modification training in individuals with depressive symptoms: A randomized controlled trial



experimental psychiatry

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ABSTRACT

Background and objectives: Negative attentional biases are often considered to have a causal role in the onset and maintenance of depressive symptoms. This suggests that reduction of such biases may be a plausible strategy in the treatment of depressive symptoms. The present clinical randomized controlled trial examined long-term effects of a computerized attention bias modification (ABM) procedure on individuals with elevated depressive symptoms.

Methods: In a double-blind study design, 77 individuals with ongoing mild to severe symptoms of depression were randomly assigned to one of three conditions: 1) ABM training (n = 27); 2) placebo (n = 27); 3) assessment-only (n = 23). In both the ABM and placebo conditions, participants completed 8 sessions of 216-trials (1728 in total) during a 2-week period. Assessments were conducted at pre-training and post-training (0, 2, 4, 8-week, 3, 7-month follow-ups). Change in depressive symptoms and restoration of asymptomatic level were the primary outcome measures.

Results: In the ABM, but not the other two conditions, significant reductions in depressive symptoms were found at post-training and maintained during the 3-month follow-up. Importantly, more participants remained asymptomatic in the ABM condition, as compared to the other two conditions, from post-training to 7-month follow-up. ABM also significantly reduced secondary outcome measures including rumination and trait anxiety, and notably, the ABM effect on reducing depressive symptoms was mediated by rumination.

Limitation: Generalization of the findings may be limited because the present sample included only college students.

Conclusions: The ABM effect on reducing depressive symptoms was maintained for at least 3-month duration in individuals with elevated depressive symptoms, and these results suggest that ABM may be a useful tool for the prevention of depressive symptoms. *ClinicalTrials.gov:* NCT01628016.

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According to cognitive theories of depression, negative attentional biases have a primary and causal role in the development and maintenance of depression (Beck, 2008; Disner, Beevers, Haigh, & Beck, 2011). Indeed, a large body of literature has demonstrated that depressed individuals selectively attend to negative information (Gotlib & Joormann, 2010; Mathews & MacLeod, 2005; Peckham, McHugh, & Otto, 2010). Furthermore, recent studies have revealed that currently euthymic individuals with a history of depression (Joormann & Gotlib, 2007) and girls who had never been depressed but were at risk for developing depression because of a depressed mother have also showed negative attention biases (Joormann, Talbo, & Gotlib, 2007). These results suggest that negative attentional biases are associated not just with depressed mood but also with the risk of developing depression. In other words, negative attention biases may be a vulnerability factor for depression rather than simply a marker of mood.

To consider a risk factor as a target for the treatment of depression, an important issue is the causal relationship between this factor and depression. To test the causal role of negative attention biases on depression, a seminal study was conducted by MacLeod and colleagues (MacLeod, Rutherford, Campbell, Ebsworthy, & Holker, 2002). Using a modified probe detection task, they found that undergraduates reacted with higher level of anxiety- and depression-related mood ratings to the experimental

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stressor if they were trained to preferentially attend to negative words than to neutral words. The results indicated that an attention bias toward negative stimuli produced a vulnerability to heightened negative affection in response to stress. This study also demonstrated that selective attention can be modified through attentional bias training.

To our knowledge, there have been three published studies directly manipulating the selective processing of negative information to test the causal relationship and the efficacy of attention training programs on reducing depressive symptoms.

Wells and Beevers (2010) used a modified dot-probe task in which dysphoric scenes and sad faces were presented as negative cues for a long duration (faces: 3 s; scenes: 4.5 s), and attention was repeatedly redirected away from dysphoric information to induce selective processing of neutral (non-sadness) stimuli. Participants with mild to moderate depressive symptoms completed 4 training sessions during a 2-week period. Compared with a placebo condition, participants in the training condition showed significant reduction in attention bias toward dysphoric stimuli and reported significantly less depressive symptoms both at post-training and in a 2-week follow-up. In addition, differences in depressive symptoms between the training and the placebo conditions were found to be mediated by the change in attention bias.

Baert, De Raedt, Schacht, and Koster (2010) used a modified spatial cueing task involving directing attention away from negative words and toward positive words in dysphoric individuals and depressed patients. Participants completed 10 training sessions (of 220 trials each) during a 10 days period. The results showed that only in the mild dysphoric students, some mild improvements of depressive symptoms were observed while in moderate to severe dysphorics and depressed patients no effects were found. Notably, the study failed to show any training effect on the change in attention bias.

In Browning, Holmes, Charles, Cowen, and Harmer (2012), remitted depressed patients completed a training procedure twice per day for 14 days (28 sessions in total, each of 96 trials). Participants in the ABM training condition always redirected attention toward the positive face or word stimuli while participants in the placebo condition directed attention equally toward the positive and negative stimuli. Results showed the ABM condition produced a training effect on post-training attentional bias and 4-week follow-up residual depressive symptoms, although only for face stimuli but not for word stimuli.

Briefly, these studies showed preliminary evidence regarding the causal role of attention bias in the maintenance of depressive symptoms in situations where negative attention bias was successfully modified, suggesting that ABM programs could be a promising tool for treatment of depressive symptoms. However, the mixed results of the effect on alteration of attention bias and depressive symptoms need to be further clarified. Furthermore, the long-term effectiveness of ABM procedure on depressive symptoms was unknown and the mechanism of the ABM effect on depression was uncertain, which calls for more systematic studies.

In the present study, we used a large sample with a multisession attention modification program testing the causal role of negative attention bias on depression and the long-term effectiveness of ABM procedure on depressive symptoms in a randomized, doubleblind, placebo-controlled trial. We then explored the mechanism of the ABM effect on depressive symptoms through mediation analysis based on the follow-up longitudinal data. As no previous study has tested the long-term effect of ABM procedure on depressive symptoms, we have no strong rationale for predicting the duration for the ABM long-term effect.

On the mechanism of the ABM effect on depressive symptoms, it is believed that ABM may be effective as it alters depressive symptoms via an effect on ruminative processes (Koster, De Lissnyder, Derakshan, & De Raedt, 2011). As rumination, a core feature of depression, is closely linked to attention bias and caused by the impaired attentional disengagement from negative selfreferent information (De Raedt & Koster, 2010; Koster et al., 2011), the reduction of negative attention bias by ABM training would improve ruminative processing due to modification of negative attention bias improving impaired attention control from negative information (Browning, Holmes, Murphy, Goodwin, & Harmer, 2010; Clarke, Browning, Hammond, Notebaert, & Macleod, 2014; Eldar & Bar-Haim, 2010). Meanwhile, as rumination is a critical factor in the occurrence and maintenance of depression symptoms due to the repetitive thinking about the causes, consequences and symptoms of one's negative affect exacerbating depressive symptoms (Nolen-Hoeksema, 1991; Nolen-Hoeksema, Wisco, & Lyubomirsky, 2008), the improvement of rumination would in turn reduce depressive symptoms. Therefore, we predicted that the ABM effect on reducing depression is mediated by the reductions of rumination.

As Wells and Beevers (2010) found that change of attention bias directly mediated the change of depressive symptoms, the mediation analysis in our study would be performed to test these two possibilities. One tested a possibility that ABM training changes the attention bias toward negative stimuli and directly reduces depressive symptoms. Alternatively, a more likely possibility was that the change in attention bias influences the ruminative processing, which consequently reduces depressive symptoms.

As Baert et al. (2010) proposed that therapeutic effects of ABM may be dependent on severity of depression and ABM in anxiety studies showed that pre-training attention bias predicts the training effect (Amir, Taylor, & Donohue, 2011), we also examined whether depression severity and attention bias score at pre-training moderated the ABM effects on reducing depressive symptoms. In addition, an assessment-only control condition was included to tease apart possible placebo effect as noted in Baert et al. Study (2010). To explore the change of rumination, we used word stimuli as opposed to pictorial stimuli in the modified dot-probe task because abstract verbal materials are more susceptible to the rumination process characteristic to depression (Watkins, 2008).

1. Method

1.1. Design

The design was a 3 (condition: ABM, placebo, assessmentonly) \times 7 (time: pre-training, post-training, 2-week, 4-week, 8week, 3-month, and 7-month follow-ups) with repeated measurement on depressive symptoms and secondary outcomes of rumination and trait anxiety. Participants were randomly assigned to the ABM (n = 27), placebo control (n = 27), or assessment-only control (n = 23) conditions. They were assessed using self-report measures at each level of the time factor. Follow-up assessments were conducted approximately 2-, 4-, 8-week, 3- and 7-month after eight sessions of training in order to examine the longevity of any symptom change.

1.2. Participants

Participants were second-year undergraduates (n = 77) with mild to severe symptoms of depression. The first screening was conducted in 499 undergraduates (mean age: 19.57 years [SD = 0.87], range: 18–22 years) who completed Beck Depression Inventory-II (BDI-II; Beck, Steer, & Brown, 1996) for course requirement. The inclusion criterion was a BDI-II score of 14 and above, which is the cut-off criteria for mild depression. The

exclusion criteria included 1) a current episode of major depression disorder (MDD) as important differences between subclinical dysphoric and clinical depression disorder in ABM training effects (Baert et al., 2010), bipolar disorder, schizophrenia or organic mental disorder; 2) any concurrent psychotherapy; and 3) any concurrent psychotropic medication.

Among the 499 undergraduates, 101 met the inclusion criteria; however, 4 participants declined further participation and 2 were unable to be reached. The remaining 95 participants completed an additional BDI-II two weeks later to ensure that the depressive symptoms met threshold prior to the treatment, and an additional 17 participants were excluded (BDI-II < 14). The remaining 78 participants were administered the SCID-IV, and 1 participant was excluded due to a current episode of major depression (Fig. 1). The eligible 77 participants were randomly assigned to receive the ABM, placebo control, or assessment-only control conditions. Factors matched across conditions included age, gender, BDI-II score, traitanxiety score, rumination score, attention bias score, and the percentage of mild, moderate and severe depression (severity measure). The BDI-II score range was 14–35. See Table 1 for demographic and clinical characteristics and Table 2 for attention bias score.

1.3. Measures

Self-reported measures were used to assess depressive symptoms, trait anxiety and rumination. The emotion distress was measured by BDI-II (Beck et al., 1996) and State-Trait Anxiety Inventory-Trait version (STAI-T) (Spielberger, 1983), and rumination was measured by Rumination Response Style (RRS) (Yang, Ling, Xiao, & Yao, 2009). The average Cronbach's alphas in the present sample were 0.85, 0.88 and 0.80 for the BDI-II, STAI-T and RRS, respectively. The primary outcome measures were depressive symptom and the percentage of asymptomatic status of depression measured by a BDI-II score of less than 10. Secondary outcomes were rumination and trait anxiety. Clinical diagnostic status of depression and other psychiatric diagnoses were assessed by clinical interviews which were conducted by two certified clinical psychologists.

1.4. Procedure

Written informed consent was obtained from each participant. To ensure participants were naïve to the purpose of the study, the consent form stated that the study was to "evaluate a new computer-based experimental task," and no information was provided regarding the rational in any condition. Participants completed a baseline assessment including the administered interview, self-report measures and the attention bias assessment task, lasting approximately 1–2 h. MDD and other psychiatric diagnoses were assessed using the Structured Clinical Interview for Diagnostic and Statistical Manual (4th ed.; *DSM–IV*) Axis I Disorders (SCID-IV) (First, Spitzer, Gibbon, & Williams, 2001). All

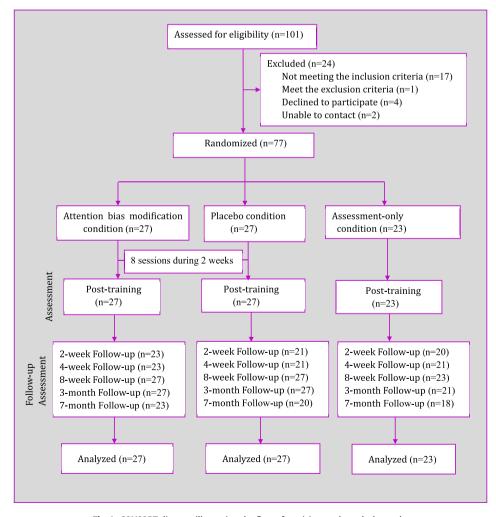


Fig. 1. CONSORT diagram illustrating the flow of participants through the study.

Table 1

Participant demographics and clinical characteristics.

	Condition									
	Attention bias modification ($n = 27$)		Placebo (n =	= 27)	Assessment- $(n = 23)$					
	Mean	SD	Mean	SD	Mean	SD				
Age (years)	19.44	1.58	19.52	0.89	19.57	0.73	0.93 ^a			
Gender							0.46 ^b			
Female	20		17		18					
Male	7		10		5					
Severity of depression (n, %)							0.81 ^b			
Mild (BDI-II ^c score:14–19)	17 (63%)		16 (59%)		15 (65%)					
Moderate (BDI-II score:20-28)	9 (33%)		11 (41%)		7 (31%)					
Severe (BDI-II score > 29)	1 (4%)		0 (0%)		1 (4%)					
Psychopathology scores										
Beck Depression Inventory-II(BDI-II)	17.33	3.81	18.04	4.11	18.13	5.18	0.77 ^a			
State-Trait Anxiety Inventory-Trait	49.44	6.46	50.81	5.20	50.30	7.68	0.74 ^a			
Rumination response style	44.00	4.94	45.85	7.64	46.04	6.51	0.46 ^a			

^a By analysis of variance.

^b By χ^2 test.

^c BDI-II: Beck Depression Inventory-II.

interviews were audiotaped for reliability assessment, and a randomly selected portion of the interviews (55%) were rated by a second, independent clinician. Inter-rater agreement for MDD diagnosis was excellent (k = 1.00). After the participants completed the pre-training assessment, they were then randomly assigned to one of the three conditions by a computer-generated random assignment. Randomization was stratified by depression severity (i.e. mild, moderate and severe) and gender. Both participants and the experimenters were blind to a participant's condition until all post-training assessments were completed.

After completing 8 sessions in the ABM or placebo control conditions during a 2-week period, all participants including the assessment-only controls completed a post-assessment identical to the pre-assessment except interview as well as 2-, 4-, 8-week, 3- and 7-month follow-up assessments. Participants in the

assessment-only condition only completed the assessments. The post-training assessment and follow-up assessment lasted approximately 0.5 h. Different assessors performed pre-training, post-training and follow-ups assessments (for schema see Fig. 1). All participants received full course credit and ¥40 per hour as compensation for their participation. This protocol was approved by Institutional Review Board in Hunan Normal University. The training sessions were held in Hunan Normal University from September 14 to October 1, 2011. All the training and assessments except 7-month follow-up were conducted in the laboratory during a certain period of time in an individual or a group fashion, while the 7-month follow-up was evaluated individually mainly in student study rooms. No participants started treatment for depression (medication and/or therapy) throughout the study.

Table 2

Dot-probe task performance (in milliseconds) among participants with depressive symptoms randomly assigned to attention bias modification (ABM), placebo, and assessment-only conditions.^a

	Condition									
	Attention bias modification ($n = 27$)		Placebo (n =	27)	Assessment- $(n = 23)$	p ^c value				
	Mean	SD	Mean	SD	Mean	SD				
Pre-training assessment										
Reaction time to sad words	549	71	538	67	543	73				
Reaction time to neutral words	582	74	563	66	571	77				
Attention bias score	33	22	25	17	28	17	0.28			
Post-training assessment old words										
Reaction time to sad words	500	72	472	68	_	_				
Reaction time to neutral words	479	63	498	75	_	_				
Attention bias score	-21	13	26	11	-	-	0.00			
Post-training assessment new words										
Reaction time to sad words	504	81	475	73	-	-				
Reaction time to neutral words	483	69	504	75	-	-				
Attention bias score	-21	14	29	12	_	_	0.00			
Post-training assessment ^b										
Reaction time to sad words	503	75	479	74	501	55				
Reaction time to neutral words	482	64	499	76	525	58				
Attention bias score	-21	24	20	21	24	21	0.00			

Note.

^a The total accuracy for the dot-probe task performance in the ABM, placebo, and assessment-only conditions, respectively, was 98.6% (SD = 1.3), 98.3% (SD = 1.5), and 98.4% (SD = 1.5).

^b As there were a generalization of training for old to new words, the results of attention bias at post-training assessment combined the results of the old and new words. ^c By analysis of variance.

1.5. Experimental stimuli

The visual stimuli included 108 two-character Chinese sadneutral word pairs. Word stimuli were selected from an initial pool of 118 depressive-relevant (i.e. sad) adjective words and 129 neutral concrete adjective words. Some adjectives were utilized in a previous study (Yang, Zhu, Wang, Wu, & Yao, 2011), and other stimuli were selected from a dictionary (Tao, Xiao, Yue, & Zhang, 1995). The 247 candidate words were rated by an independent sample of 53 college students (25 female, mean age: 19.8 [*SD* = 1.00], BDI-II score: 9.04 [*SD* = 7.74], range: 0–42, including 8 dysphoric individuals). The judges rated each item on the dimensions of valence, arousal, imagery, familiarity and relevance to sadness on a 9-point scale (1 = very negative valence, low arousal, imagery, familiarity or relevance to sadness, 5 = neutral, 9 = very positive valence, high arousal, imagery, familiarity or relevance to sadness).

Each pair selected for use contained a sad member and a neutral member, in which the mean ratings of sad and neutral member differed in emotional valence and relevance to sadness (ps < 0.001), but matched in terms of arousal, imagery, familiarity and the number of strokes comprising the words (ps > 0.05) (see Supplemental Table 1). In addition, the difference of the mean valence between the two members of any selected pair was at least 1.45 (Mean: 2.64 [SD = 0.56]). The set of 108 word pairs was divided to create two word pair subsets. To examine the specificity of the training effects, only one subset was used in the attention training trials, but both were used in the attention test trials. The stimulus items assigned to each of the two subsets were matched in average valence, arousal, imagery, familiarity and strokes. Furthermore, the mean difference between the emotional valence ratings of the sad and neutral members of word pairs was the same between the two subsets (2.73 [SD = 0.63] vs. 2.54 [SD = 0.48], F = 3.12, df = 1106, p > 0.05).

1.6. The Attention Bias Modification

1.6.1. Dot-probe task

Each trial began with a 500-msec white fixation cross $(8 \text{ mm} \times 8 \text{ mm})$ located in the center of a black screen. Following termination of the fixation cue, a word pair (song typeface, size 28), one above the fixation and the other below was then presented for 2000-msec. The relatively longer stimulus duration compared to standard dot-probe task (e.g., Bradley, Mogg, & Lee, 1997) was intended to allow participants to have time to more fully process the content of the stimulus, which may allow for more elaborated processing of stimuli congruent with their emotion (Mogg & Bradley, 2005). Each word pair was 50 mm high, with a vertical distance of 30 mm between the two words, subtending less than a 3° visual angle of separation. After 2000-msec duration, the word pair was replaced by a target, which was either one (3 mm in diameter) or two dots (same diameter with a 2 mm center-tocenter distance). Participants discriminated between one or two dots and responded by pressing a left or right button of the computer mouse. Following the response and before the next trial, there was a 100-500 msec random inter-trial interval. The sad word would appear randomly and equally often at the upper or lower position. Both speed and accuracy were emphasized.

1.6.2. ABM condition

In each session, participants completed 216 dot-probe trials. Each of the 54 word pairs was presented 4 times (4×54). Among all trials, 90% of the targets appeared at the neutral word position and 10% at the sad word position. This allowed monitoring attentional bias per session and also obscured the design of the study

from the participants (Wells & Beevers, 2010). Participants received 8 12-min training sessions over a 2-week period (4 sessions a week, roughly one session every other day).

1.6.3. Placebo control condition

In this condition, all were identical to the ABM condition except that the targets appeared with equal probability in the sad (50%) and neutral (50%) word positions.

1.6.4. Assessment of attention bias

The test trials included 108 dot-probe trials at pre- and posttraining to assess attention bias. Each word pair was from the two stimulus subsets and presented once. Half of the trials presented "old" pairs that had been used in training, whereas half presented "new" pairs that had not been used. In all trials, the targets appeared with equal probability in the sad (50%) and neutral (50%) word positions. Attentional bias scores were calculated for each participant using the following equation (Bradley et al., 1997):

Attentional bias score =
$$[(NuPl + NlPu) - (NuPu + NlPl)]/2$$
(1)

where N = Negative (sad) word, P = Probe, u = upper, l = lower.

For example, *NuPl* represents the mean response latency when the negative word was in the upper position and the probe in the lower position. A positive bias value reflects an attention bias toward (i.e., vigilance for) sad words relative to neutral words, while negative values reflect avoidance (Bradley et al., 1997).

1.7. Statistical analyses

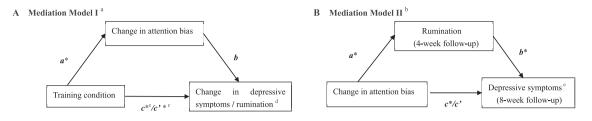
Data were analyzed using SPSS 11.5 (SPSS, Inc., Chicago) and SAS 9.1 (SAS Institute, Cary, N.C.). Statistical significance was set at 2-sided p < 0.05. Based on previous studies (Baert et al., 2010; Wells & Beevers, 2010), an average effect size of 0.8 was estimated on primary dependent measures. With alpha set at 0.05 and power (1-beta) set at 0.80, a minimum sample size of 25 participants per group was obtained for desired effects.

To ensure across-condition match, we conducted tests (chisquares, ANOVAs) at pre-training on all demographic and dependent measures. To examine the change of attention bias for training, attention bias scores were submitted to a 3 (training condition: ABM, placebo, assessment-only) \times 2 (time: pre-training, post-training) \times 2 (pair status: old pairs, new word pairs) ANOVA. To ensure the validity of the attention training procedure and its generalization to new words, attention bias scores for both new and old word pairs were submitted to a one-way ANOVA at posttraining, with training condition (ABM, placebo) as a betweensubjects factor.

An intent-to-treat approach was employed for the follow-up analyses. The primary outcome of BDI-II scores were evaluated at different time points using mixed-models repeated-measures ANOVAS. Condition, assessment point, and their interaction were treated as fixed effects, and participant as a random effect. A compound symmetry structure yielded the best fit among all covariance structures and was used as the covariance structure model for all analyses. The aforementioned mixed-models analyses were used to explore all other secondary outcomes.

Asymptomatic status was examined separately at post-training and each follow-up conducted by chi-square test of cross-tabulate with three conditions and by the Fisher's exact test in the comparisons between conditions.

To understand the mechanism of ABM training on depressive symptoms, two mediation analyses assessing the interrelations



^a Model I: Training condition affects change in depressive symptoms/ rumination from pre-to post-training indirectly through change in attention bias.

^b Model II: Change in attention bias affects depressive symptoms at 8-week follow-up indirectly through rumination at 4-week follow-up.

^c The significant c/c ' path coefficients for change in depressive symptoms

^d 95% confidence interval of the *ab* path overlapped with zero for change in depressive symptoms ([-0.22, 1.00]), but not for change in rumination ([-2.86,

-0.05])suggesting a mediation effect of change in attention bias on rumination, but not on depressive symptoms

⁶95% confidence interval of the *ab* path did not overlap with zero for depressive symptoms at 8-week follow-up ([-0.06, -0.0003]) suggesting a mediation effect of rumination on depressive symptoms

* p < 0.05 for a significant path coefficient.

Fig. 2. Illustration of a mediation design and the main results of mediation effects.

among change of attention bias, rumination and depressive symptoms (Fig. 2) were conducted as in Preacher and Hayes (2004). The first model examined the mediation effect of change of attention bias on depressive symptoms or rumination by testing the product of the coefficients for the effects of 1) *a* path: training condition to change in attention bias; 2) *b* path: change in attention bias to change in depressive symptoms or rumination taking training condition into account; 3) *c* path: training condition to change in depressive symptoms or rumination, not controlling for change in attention bias; and 4) parameter *c*': training condition to change in depressive symptoms or rumination after controlling for change in attention bias; and 5) *ab* path: the product of the *a* path and the *b* path. Critically, if zero was not in the 95% confidence intervals (CI) of *ab* path, it would indicate a significant indirect effect (MacKinnon, Fritz, Williams, & Lockwood, 2007; Preacher & Hayes, 2004). The second analysis was performed using longitudinal data with a temporal order between multiple data points to investigate the mediation effect of rumination on depressive symptoms, in which pre-post change in attention bias as an independent variable, rumination at 4-week follow-up as a mediator, and depressive symptoms at 8-week follow-up as a dependent variable.

To address the moderating effect of depression severity and attention bias score at pre-training on training effects, two moderation analyses examined the moderated effect of the pre-training BDI-II score and attention bias score on the change of depressive symptoms (Supplemental Table 2) using separate, parallel, and hierarchical regression analyses (Frazier, Tix, & Barron, 2004).

2. Results

2.1. Preliminary analyses results

As seen in Table 1, the ABM, placebo and assessment-only conditions did not differ on any demographic and clinical characteristics including BDI-II score, rumination score, trait-anxiety score and the percentage of mild, moderate and severe depression (ps > 0.4).

2.2. Changes in attention bias

Inaccurate trials or trials with response times exceeding 3 standard deviations beyond the mean were excluded (3.41% and 2.28% data removed for the pre- and post-training tests respectively). Table 2 showed the mean response times and attention bias scores. The attention bias scores showed no pre-training differences across different conditions.

The 3 (condition: ABM, placebo, assessment-only) × 2 (time: pre-training, post-training) × 2 (pair status: old, new) ANOVA revealed a condition × time interaction (F(2, 74) = 40.78, p < 0.0001, $\eta^2 = 0.53$). Further contrasts for simple effects of time revealed a reduction in bias scores from pre- to post-training only in the ABM condition (t(26) = 8.63, p < 0.001, Cohen's d = 1.66), but not in the placebo (t(26) = 1.09, p = 0.29, Cohen's d = 0.22) or the assessment-only conditions (t(22) = 0.70, p = 0.49, Cohen's d = 0.14). As shown in Fig. 3, at post-training, the ABM condition showed a significant reduction in bias scores compared to the placebo (t (52) = 6.71, p < 0.001, Cohen's d = 1.83) and the assessment-only conditions (t (48) = 7.14, p < 0.001, Cohen's d = 2.03).

To test for attention training generalization to new words, a oneway ANOVA with training condition as a between-subjects factor for old and new word pairs separately at post-training revealed a significant effect of training condition for both of old word pairs (F(1, 52) = 49.43, p < 0.0001, d = 1.95) and new word pairs (F (1, 52) = 50.67, p < 0.0001, d = 1.97). Furthermore, the further comparison in the ABM condition between old and new word pairs for attention bias scores at post-training revealed no difference (t(26) = 0.19, p = 0.85, Cohen's d = 0.04) between them. These results suggested a generalization of training from old to new word pairs.

2.3. Effects of training on overall condition-by-time effects

All participants in the ABM and placebo conditions completed all 8 training sessions and post-training evaluation. All the assessment-only controls completed the pre- and post-training

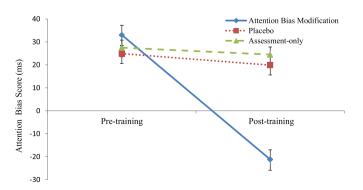


Fig. 3. Attention bias score for sad stimuli at pre- and post-training completed within a two-week time period for attention bias modification (ABM), placebo and assessment-only conditions. Error bars represent the standard error of the mean.

evaluation. Completion rates of the follow-up were 64 (83%), 65 (84%), 77 (100%), 75 (97%), 61 (79%) for the 2-, 4-, 8-week, 3- and 7- month follow-ups assessment, respectively. The non-completed rates did not differ across conditions at each assessment point (χ^2 s < 4.82, *df*s = 2, *ps* > 0.05).

The BDI-II scores showed a significant condition \times time interaction effect (*F* (12,402) = 5.94, *p* < 0.0001, Fig. 4). The effect was also significant on RRS scores (*F* (12,402) = 2.91, *p* = 0.0007) and STAI-T scores (*F* (12,402) = 5.89, *p* < 0.0001).

2.4. Effects of training at post-training

2.4.1. Effects on depressive symptoms

At post-training, the mean BDI-II scores were: (a) ABM: 10.96 (95% CI = 9.14–12.79), (b) Placebo: 16.78 (95% CI = 14.76–18.79), and (c) Assessment-Only: 18.13 (95% CI = 15.39–20.87), and Table 3/Fig. 4 reflects pre- to post-symptom changes as a function of condition. Results reveal a significant condition × time interaction (F(2, 74) = 19.84, p < 0.0001, $\eta^2 = 0.35$). The BDI-II score decreased from pre- to post-training for the ABM condition (t (26) = 7.43, p < 0.0001, Cohen's d = 1.50, 95% CI = 0.90–2.11), but not the placebo (t (26) = 1.92, p = 0.07, Cohen's d = 0.27, 95% CI = -0.27-0.81) or the assessment-only conditions (t (22) = 0, ns).

Further comparisons showed that the score changes were significantly different between the ABM and the placebo conditions (t(52) = 4.39, p < 0.0001, Cohen's d = 1.38, 95% CI = 0.78-1.97) and between the ABM and the assessment-only conditions (t (48) = 4.62, p < 0.0001, Cohen's d = 1.45, 95% CI = 0.83-2.08), but not between the two control conditions (t(48) = 0.84, p = 0.41, Cohen's d = 0.24, 95% CI = -0.32-0.79).

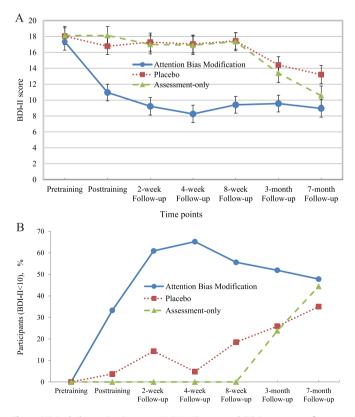


Fig. 4. (A) Beck depression inventory-II (BDI-II) score and (B) Percentages of asymptomatic participants (BDI-II < 10) among attention bias modification (n = 27), placebo (n = 27), and assessment-only conditions (n = 23).

At post-training, 9 (33.3%) participants were no longer symptomatic (BDI-II score <10) in the ABM condition, but only 1 (3.7%) and none were so in the placebo and the assessment-only conditions, respectively ($\chi^2 = 15.38$, df = 2, p < 0.0001) (Fig. 4).

2.4.2. Effects on rumination and trait anxiety

At post-training, mean RRS scores were: (a) ABM: 41.41 (95% CI = 39.26-43.56), (b) Placebo: 45.44 (95% CI = 42.25-48.64), (c) Assessment-Only: 46.78 (95% CI = 44.07-49.49) (Table 3). The corresponding changes of rumination were 2.56, 0.41, -0.74. The mean changes in trait anxiety were 4.70, 0.07, and -1.05 for the three conditions respectively.

For both the RRS and trait anxiety scores, the condition \times time interaction was significant (*Fs* (2, 74) > 5.19, *ps* < 0.008, η^2 s > 0.12). The ABM condition showed a significant decrease in RRS scores from pre- to post-training (t (26) = 4.34, p = 0.015, Cohen's d = 0.49,95% CI = -0.04-1.04). However, as the 95% CI for the effect size of RRS score included zero, the significant statistical effect could not completely rule out the possibility of no clinical training effect on the reduction of RRS score at post-training. The ABM condition also showed a significant decrease in STAI-T scores from pre- to post-training (t (26) = 3.25, p < 0.0001, Cohen's d = 0.88, 95% CI = 0.32–1.44) (Table 3). There was no decrease in the placebo (ts (26) < 0.41, ns), or the assessment-only conditions (ts (26) < 0.41, ns)(22) > -1.85, ns) in RRS and STAI-T scores from pre- to posttraining. Both RRS and STAI-T scores differed between the ABM and the placebo conditions (ts (52) < -3.2, ps < 0.002, Cohen's ds = 0.33 - 0.83), and between the ABM and the assessment-only conditions (ts (48) < -3.25, ps < 0.002, Cohen's ds = 0.92-1.36). but there was no difference between the placebo and the assessment-only conditions (ts (48) < 0.32, ns).

2.5. Effects of training at follow-ups

2.5.1. Effects on depressive symptoms

The significant fixed effects of 2 (time: pre-training, each followup, i.e., 2-, 4-, 8-week, 3-month follow-up) \times 3 (condition) interaction in BDI-II scores (*Fs*(2, 64–74) > 3.98, *ps* < 0.05, $\eta^2 s$ > 0.1) revealed significantly reductions in depressive symptoms for the ABM condition from pre-training to 2-, 4-, 8-week/3-month followup (ts (22-26) > 7.45, ps < 0.0001, Cohen's d = 1.78-2.33) and significantly greater reductions in ABM condition than in the placebo or assessment-only conditions at 2-, 4-, 8-week/3-month follow-up (ts(41-52) > 2.93, ps < 0.005, Cohen's d = 0.80-2.00).From pre-training to 7-month follow-up, the fixed effect of time by condition interaction in BDI-II scores was not significant (F (2, 70) = 1.64, p = 0.20, $\eta^2 = 0.05$). However, an exploratory follow-up contrast between the ABM and placebo conditions revealed a significantly greater reduction of depressive symptoms in the ABM condition compared with the placebo condition (t(41) = -2.1,p = 0.045, Cohen's d = 0.65, 95% CI = 0.04–1.27), despite that the ABM condition was no different from the assessment-only condition (t(39) = -0.85, p = 0.40, Cohen's d = 0.26, 95%CI = -0.36 - 0.88) and there was no difference between the assessment-only condition and the placebo condition (t(36) = 1.06, p = 0.30, Cohen's d = 0.34, 95% CI = -0.30-0.99).

2.5.2. Effects on rumination and trait-anxiety

The significant fixed effect of time (pre-training, 2-week/4-week/8-week) × condition interaction in RRS scores (*Fs*(2, 64–74) > 4.57, *ps* < 0.05, $\eta^2 s = 0.13-0.29$), and STAI-T scores (*Fs*(2, 66–74) > 4.28, *ps* < 0.05, $\eta^2 s = 0.10-0.15$) revealed that from pre-training to 2-, 4-, 8-week follow-ups, significant reductions of RRS scores and STAI-T scores in the ABM condition compared with the placebo and assessment-only conditions. However, from pre-

Table 3

Outcome measures among participants with depressive symptoms randomly assigned to attention bias modification, placebo, and assessment-only conditions.

Outcome	Condition				Analysis					
	Attention bias modification $(n = 27)$		Placebo ($n = 27$)		Assessmen $(n = 23)$	it-only				
	Mean ^b	SD	Mean ^b	SD	Mean ^b	SD	F	df	р	Cohen's d ^c
Primary BDI-II score ^a							5.94	12,402	<0.0001	1.15
Pre-training	17.33	3.81	18.04	4.11	18.13	5.18				
Post-training	10.96	4.62	16.78	5.09	18.13	6.33				
Follow-up 2 w	9.22	4.81	17.29	6.40	17.00	4.60				
4 w	8.26	3.97	17.05	4.78	16.90	4.36				
8 w	9.41	4.56	17.44	4.56	17.35	5.02				
3 month	9.56	4.83	14.41	7.12	13.38	5.97				
7 month	8.95	4.68	13.20	7.95	10.56	7.35				
Secondary										
RRS score ^a							2.91	12,402	0.0007	0.33
Pre-training	44.00	4.94	45.85	7.64	46.04	6.51		,		
Post-training	41.40	5.44	45.44	8.08	46.78	6.27				
Follow-up 2 w	41.22	4.45	45.52	7.78	46.50	6.61				
4 w	38.91	4.16	45.14	7.47	46.33	6.26				
8 w	39.07	5.17	44.29	8.09	45.57	6.51				
3 month	42.96	6.08	44.15	8.11	45.52	7.37				
7 month	43.43	6.75	46.75	8.87	44.22	7.92				
STAI-T score ^a							5.89	12,402	< 0.0001	0.83
Pre-training	49.44	6.46	50.81	5.20	50.30	7.68		,		
Post-training	44.52	4.56	50.74	6.86	51.35	5.46				
Follow-up 2 w	43.82	4.21	50.23	7.48	50.30	5.51				
4 w	44.39	4.28	50.05	6.82	50.05	5.63				
8 w	44.15	4.67	49.19	6.14	50.13	5.74				
3 month	44.74	5.20	47.41	7.42	46.82	7.86				
7 month	47.87	5.31	48.25	6.38	45.94	6.79				

^a BDI-II: Beck Depression Inventory-II; RRS: Rumination Response Style; STAI-T: State-Trait Anxiety Inventory-Trait.

^b Data indicate least squares means.

^c Data were calculated for pre- to post-training between the attention bias modification and placebo conditions (Cohen's *d*).

training to 3-, 7-month follow-up, the time by condition interaction in RRS scores and STAI-T scores was not significant (*Fs* (2, 67-73) < 0.13, *ns*).

2.5.3. From pre-training to each follow-up evaluation on asymptomatic status

As to the percentage of asymptomatic status of depression (i.e. BDI-II score of less than 10), more participants were asymptomatic status in the ABM condition at 2-,4-,8-week and 3-month follow-ups (14, 60.9%; 15, 65.2%; 15, 55.6%; 14,53.8%; respectively) compared with the placebo (3, 14.3%; 1, 6.2%; 5, 18.5%; 7, 26.9%; respectively) and assessment-only conditions (0, 0%; 0, 0%; 0, 0%; 5, 23.8%; respectively), $\chi^2 s > 5.52$, df = 2, ps < 0.05 (Fig. 4). Importantly, more participants continuously maintained asymptomatic status during 7-month follow-up from post-training in the ABM condition (7, 25.9%) compared with the placebo (1, 3.7%) and assessment-only conditions (0, 0%), $\chi^2 = 10.96$, df = 2, p = 0.004. Marginally, more participants maintained asymptomatic at 8-week follow-ups in the placebo condition (5, 18.5%) than the assessment-only condition (0, 0%), Fish exact test $\chi^2 = 4.73$, df = 1, p = 0.054.

2.6. Clinical significance

We followed the procedures outlined by Jacobson and Truax (Jacobson & Truax, 1991) to evaluate clinically significant change on the primary outcome measure of depressive symptoms from preto post-training in ABM and placebo conditions. A participant was classified as meeting criteria for clinically significant change if (a) his or her post-training score fell within the range (mean ± 2 SDs) of the nonclinical population on the basis of BDI-II data (Yang, Wu, &

Peng, 2012), and (b) if they displayed a statistically reliable reduction in scores from pre- to post-assessment according to the reliable change index. The percentage of participants who had achieved clinically significant improvement on the BDI-II score was 52% (14/27) in the ABM condition and 11% (3/27) in the placebo condition, χ^2 (1, N = 54) = 10.39, p = 0.003.

2.7. Mediator analysis

The mediation analysis of the first model testing the product of the coefficients for the effects of the independent variable (condition: ABM, placebo) to the mediator (pre–post change in attention bias) yielded a $\beta = 49.24$ (*SE* = 7.77) for the *a* path (Table 4). Testing for the effects of the mediator to the dependent variable (pre–post change in depressive symptoms or rumination) when the independent variable was taken into account yielded $\beta s = 0.01$ (*SE* = 0.02) and -0.02 (*SE* = 0.02) for the *b* path for depressive symptoms and rumination, respectively. Results revealed that the 95% confidence interval of the indirect path (*ab*) overlapped with zero for the change in depressive symptoms ([-0.22, 1.00]), but not for the change in rumination ([-2.86, -0.05]) (see Table 4 and Fig. 2).

The analysis of the second model testing product of the coefficients for the effects of the independent variable (pre–post change in attention bias) to the mediator (rumination at 4-week follow-up) yielded a $\beta = -0.06$ (*SE* = 0.02) for the *a* path. Testing for the effect of the mediator to the dependent variable (depressive symptoms at 8-week follow-up) when the independent variable was taken into account yielded a $\beta = 0.38$ (*SE* = 0.16) for the *b* path. Testing the total effect of the independent variable (change in

Table 4
Prediction of change in depressive symptoms after attention bias modification or placebo training. ^a

Outcome	Parameter ^c													
	а			b		с			С'			95% CI of ab		
	β	SE	t	β	SE	t	β	SE	t	β	SE	t	LL ^d	UL ^d
Model I ^b														
Depressive symptoms	49.24	7.77	6.33*	0.01	0.02	0.54	1.08	0.12	-4.73^{*}	4.60	1.45	3.17*	-0.22	1.00
Rumination Model II ^b	49.24	7.77	6.33*	-0.02	0.02	-1.16	-2.18	1.16	-1.87	-1.00	1.55	-0.65	-2.86	-0.05 ^{*e}
Depressive symptoms	-0.06	0.02	-2.22*	0.38	0.16	2.40*	-0.06	0.03	-2.31^{*}	-0.04	0.03	-1.53	-0.06	-0.0003* ^e

*p < 0.05.

^a The path coefficients β (standard errors, *SE*) and *t* values for the separate mediation models are shown.

^b Model I: Training condition (independent variable, *X*) affects depressive symptoms/rumination (dependent variable, *Y*) indirectly through change in attention bias (mediator, *M*). Model II: Change in attention bias (*X*) affects depressive symptoms at 8 -week follow-up (*Y*) indirectly through rumination at 4-week follow-up (*M*). ^c Parameter *a* indicates the effect of *X* on *M*. Parameter *b* indicates the effect of *M* on *Y* controlling for *X*. Parameter *c* indicates the total effect of *X* on *Y*. Parameter *c*' indicates

the direct effect of X on Y after controlling M. Parameter ab indicates the product of a and b or the indirect effect of X on Y.

^d LL indicates the lower limit of the 95% confidence interval (Cl), and UL indicates the upper limit of the 95% CI.

^e As zero is not in the 95%CI, the indirect effect (*ab*) is significantly different from zero at p < 0.05 (two tailed).

attention bias) on the dependent variable (depressive symptoms at 8-week follow-up) yielded a $\beta = -0.06$ (SE = 0.03) for the significant path c (t = -2.31, p = 0.03), while testing for the independent variable (change of attention bias) to the dependent variable (depressive symptoms at 8-week follow-up) after controlling for the mediator of rumination yielded a $\beta = -0.04$ (SE = 0.03) for the insignificant path c' (t = -1.53, p = 0.13). This suggests a complete mediation effect of the rumination on depressive symptoms, which was confirmed by 95% confidence interval of the indirect path (ab) that did not overlap with zero for depressive symptoms ([-0.06, -0.0003]) (see Table 4 and Fig. 2).

2.8. Moderator analysis

The moderation analysis showed that the unstandardized regression coefficient of the condition \times depression severity interaction term at pre-training was 1.04, p = 0.18, *ns* (Supplemental Table 2). The coefficient for the condition \times attention bias score interaction term at pre-training was 0.52, p = 0.37, *ns*. To provide a more detailed data on the relation between the key variables, a full correlation matrix of the key variables at the time points was showed in the Supplemental Table 3.

3. Discussion

The present study was to our knowledge the first randomized, double-blind, placebo-controlled trial exploring the long-term effect of a simple computerized word-based ABM task on reducing depressive symptoms in individuals with elevated depressive symptoms. The results showed significant reductions of both attention biases and depressive symptoms from pre- to posttraining in the ABM condition, but not in the placebo and assessment-only conditions. Follow-up assessments showed continued symptom reduction during 3-month follow-up in the ABM condition. Importantly, significantly more participants in the ABM condition continuously maintained asymptomatic during the 7-month follow-up compared with the placebo condition and the assessment-only condition. Mediation analysis showed that the reduction of depressive symptoms was mediated by the reduction of rumination, but not directly by the change in attention biases while the change in attention biases mediated the reduction of rumination directly. Training effect was unaffected by the severity of depressive symptoms and attention bias scores at pre-training. The placebo control showed a placebo effect as compared to the assessment-only control. These results suggested word-based ABM training was able to modify negative attention bias and had a longterm effect on reducing depressive symptoms, and the effect on reducing depressive symptoms was mediated by rumination. These results indicate that the word-based ABM training may be a useful tool for the prevention of depressive symptoms.

Cognitive models of depression (Beck, 2008; Disner et al., 2011) have suggested that negative attentional biases are causally related to maintain depressive symptoms. The finding that modifying negative attention biases produces change in depressive symptoms here provides further evidence supporting a causal role for these negative biases in depressive symptoms. These results are consistent with previous studies suggesting that modifying biases directly by computerized ABM tasks may be used in the treatment and prevention of depression (Browning et al., 2012; Wells & Beevers, 2010).

Prevention is recognized as the key goal in the long-term management of depression (Cuijpers, Beekman, & Reynolds, 2012; Gladstone, Beardslee, & O'Connor, 2011; Horowitz & Garber, 2006). The present study provides preliminary evidence for a novel method for this aim by reducing the early signs or subclinical symptoms of depression. Application of ABM to reduce subclinical depression may lower risk and help protect against the development of subsequent psychopathology. Ultimately, these results must be confirmed in large-scale trials, in which participants are followed up for a sufficient period of time to assess effects on the rates of clinical onset of episode of major depression.

Concerning the causal mechanism through which ABM was able to alter depressive symptoms, our results firstly confirmed that rumination plays a crucial role in the ABM effect on reducing depression. The results revealed that ABM training led to alteration of negative attentional bias, and the change in negative attention bias reduced rumination, which in turn led to the reduction of depressive symptoms. These findings provide empirical evidence to support the theoretical hypothesis that rumination is causally associated with negative attention bias and mediates the relation between the impaired attention and depressive symptoms (De Raedt & Koster, 2010), and are consistent with the empirical research that rumination plays a fully mediating role in the relationship between the ability to disengage attention away from emotional stimuli and depressive symptoms (Demeyer, De Lissnyder, Koster, & De Raedt, 2012). These findings also suggest that the reduction in rumination is an effective treatment component of ABM training on depression.

On the word-based ABM procedure, our finding provided the first empirical evidence indicating that the word-based bias modification program was an effective procedure to modify negative attention bias and treat depression. Though in Browning et al. W. Yang et al. / J. Behav. Ther. & Exp. Psychiat. 49 (2015) 101–111

(2012), a word-based ABM task did not show training effects on attention bias and depressive symptoms.

Concerning the probably reason leading to the different efficacy of word-based ABM procedure in different studies, the distinctive training parameters may contribute to the distinctive efficacy such as the content of word stimuli, stimulus duration, number of training trials, training sessions, interval of sessions, and so on. For example, in Browning's study, physically and socially threatening words were used as negative stimuli while in the current study depression-relevant sad words were used. Noteworthy, in the current study the matched pairs selected for training contained a sad adjective word and a neutral concrete adjective word. As several studies have demonstrated that negative attention bias in depression is specific to valence-specific sad stimuli, rather than angry or threating stimuli (Donaldson, Lam, & Mathews, 2007; Gotlib, Krasnoperova, Yue, & Joormann, 2004) and the abstract evaluative thinking characteristic to rumination can be improved by concreteness experience or training (Watkins, 2008). Therefore, the contents of training word pairs in the study may be an indispensable factor leading to the effectiveness in word-based ABM procedure.

In addition, the long stimulus duration (2000 ms), the costefficient number of training trials (218-trail per session), the number of sessions (8 sessions), and intervals of sessions (every other day) may have also had an important role in the training effect in the study. For example, a tentative analysis on a plot of change in attention bias scores in the 8 training sessions in ABM condition showed a developing processing of an adaptive bias by implicit learning of redirecting attention away from sad stimuli and toward neutral stimuli (see Supplemental Table 4 and Supplemental Fig. 1). Admittedly, testing the attention bias scores by the ABM task (90% away vs. 10% toward sadness) led to an underestimation of the attention bias score in the 8 training sessions due to the quickened response time to the neutral word in training task. To clarify the optimal training parameters on the word-based ABM task, further research is needed in clinical trials.

Notably, the present study produced significant larger effect sizes for the reduction of depressive symptoms in ABM training condition (Cohen's d = 1.50, 95% CI = 0.90–2.11 at post-training; Cohen's d = 1.87, 95% CI = 1.22–2.51 at the 2-week follow-up) than in Baert et al. (2010) (Cohen's d = 0.82 at post-training) and Wells and Beevers (2010) (Cohen's d = 0.52 at post-training, Cohen's d = 1.04 at 2-week follow-up). The large effect sizes for the reduction of depressive symptoms may be attributed to the large training effect on the reduction of negative attention bias (Cohen's d = 1.83–2.03) and the optimal training procedure mentioned above. The significantly larger effect sizes in the study would warrant further study as a result of potentially greater clinical significance for ABM on the treatment of depression.

Concerning the moderating effect of pre-training depressive symptoms on the change in depressive symptoms from pre- to post-training, no moderating effect was found. Nor were the pretraining attention bias scores on the change in depressive symptoms. In other words, baseline depressive symptoms and attention bias scores do not predict the size of ABM effects on change in depressive symptoms. On the one hand, the current results showed that baseline level of attention bias was not related to the pre-post change of depressive symptoms (r = 0.05, p = 0.66), and that for participants who maintained asymptomatic (n = 8) during 7month follow-up assessment, baseline attention bias scores were not significantly related to the change in depressive symptoms from pre- to post-training (r = 0.67, p = 0.066). On the other hand, from the mechanisms of ABM effects on depressive symptoms, the modification of negative attention bias through ABM training influences the change in rumination rather than directly influences the change in depressive symptoms. Admittedly, the insignificant findings of pre-training attention bias moderating the ABM effects on depressive symptoms cannot completely exclude the possibility that the baseline attention bias influences the training effects.

On the placebo effect, the results extended previous research on ABM in depression by including an assessment-only control to confirm the placebo effects.

In addition, two controls also exhibited symptom reductions at 3- and 7-month follow-ups as compared with the pre-training. Similar results had been observed for a control group of high-risk adolescents with elevated depressive symptoms at 6-month follow-up (Stice, Burton, Bearman, & Rohde, 2007). Possibly, depressive symptoms in high risk population are instable (Judd, Akiskal, & Paulus, 1997; Stice et al., 2007).

There are limitations to the current study. Our findings on college students with mainly mild to moderated depression may not generalize to other age groups or people with severe depression. Although late adolescents or early adulthood are vulnerable to depression and they are the target population for depression prevention, future research can replicate this study with large-scale community samples and assess the ABM long-term effects on the prevention of clinical onset of major depression episode in high risk population. In addition, as the assessments and training were performed during a certain period of time, some assessment sessions were occurred during exam weeks or before break periods. Therefore, the symptom changes over time may be influenced by the academic schedules despite the fact that the longitudinal symptom changes in the assessment-only controls were similar to that in highrisk adolescents with elevated depressive symptoms (Stice et al., 2007) mentioned above. In the future study, the setting influence on the results should be considered and to maintain the long-term effects of ABM, utilizing booster sessions periodically to reinstate the target patterns of attention training is needed to consider.

Briefly, the present study shows that the translation of basic psychopathology research to reduce depressive symptoms can be useful in the development of new interventions for prevention of depression. Data obtained from such intervention may also help identify the mechanisms involved in the pathogenesis of psychiatric symptoms. Given its short duration (8 12-min sessions in 2 weeks), ease of delivery and the absence of therapist contact, the ABM procedure used here offers a promising intervention for depressive symptoms that is both efficient and accessible.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jbtep.2014.08.005.

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