Attentional bias modification reduces clinical depression and enhances attention toward happiness

Qin Dai[a,b,*], Lidan Hu[c], Zhengzhi Feng[b]

[a] Department of Nursing Psychology, The Third Military Medical University, Chongqing, 400038, China
[b] Department of Psychology, The Third Military Medical University, Chongqing, 400038, China
[c] Department of Psychiatry, Geleshan Psychiatric Hospital, Chongqing, China

ABSTRACT

Difficulty in clinical antidepressant treatment leads to the pursuit of alternative treatments, such as cognitive-behavior therapy (CBT). CBT combined with regular antidepressants have indicated an optimal therapeutic effect in clinic. Attentional bias is important in the occurrence and remission of depression, however, few studies have explored the effect of attentional bias modification (ABM) on depression, and inconsistent results have been obtained due to the heterogeneity in the targeted populations, training tasks, strategies, and materials. Hence, the current study aimed to explore the therapeutic effect of ABM on depression in clinical depression.

Study I was designed to explore the optimal training methods regarding task (dot-probe vs. cue-target), material (faces vs. self-referent words), and strategy (mixed ABM toward positive and away from negative stimuli vs. positive ABM toward positive stimuli) in unselected undergraduates once daily for 10 days (N = 309). Study II was carried out to observe the effect of 10 days ABM toward positive and away from negative faces (based on Study I) on clinical depression (N = 32). Depression level was assessed via a self-reporting questionnaire and a structured interview, while attentional bias was tested by cue-target task and attention to positive and negative inventory (APNI).

In unselected undergraduates (Study I), two strategies significantly reduced the self-reporting depression scores: mixed ABM toward positive stimuli and away from negative stimuli with emotional faces, and positive ABM toward positive materials only with self-referent words. In patients with major depressive disorder (MDD) (Study II), the mixed ABM with emotional faces resulted in enhanced attentional bias toward happy materials in the cue-target task and APNI, which predicted a delayed depression reduction in clinical depression at the one-month follow-up investigation.

Our finding confirms the literature and broadens the knowledge with the evidence of the optimal therapeutic effect of ABM combined with regular antidepressants in clinical depression. The findings that a quick enhancement in positive attentional bias, predicting a later therapeutic effect on clinical depression reduction, indicate a potential mechanism that could underlie the therapeutic process of ABM in depression. The findings that two training strategies are effective in depression reduction suggest that different strategies should be utilized to treat different types of depression. This study offers a potential way to cure depression and could be further practiced in clinic.

1. Introduction

In clinic, about 1/3 of depressed patients poorly respond to regular antidepressant treatments such as selective serotonin reuptake inhibitor (SSRI) (Aguglia et al., 2014; Trivedi et al., 2006). Thus, to achieve an optimal therapeutic effect, alternative treatments have been pursued by clinical psychiatrists. Among the alternative treatments pursued, cognitive behavioral therapy (CBT) has been the most frequently used

(Sudak, 2012), due to the safety of CBT and the important role of cognitive bias in the occurrence and maintenance of depression. The optional therapeutic effect of CBT combined with antidepressants has been confirmed in the literature (Ironside, O'Shea, Cowen and Harmer, 2016; Thomas et al., 2012). Indeed, it has been suggested that different factors contribute to depression. Among which, cognitive bias, particularly the processing bias (*e.g.,* attentional bias, memory bias, et al.) for negative stimuli, plays an important role in depression's onset,

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* Corresponding author. Department of nursing psychology, the Third Military Medical University, Chongqing, 400038, China.
E-mail address: daiqin101@hotmail.com (Q. Dai).

maintenance, and remission (Mathews and MacLeod, 2005; Taylor and John, 2004). Negative attentional bias, specifically, is critical in the formation of negative cognitive bias (Cavanagh and Geisler, 2006; Joormann and Gotlib, 2007; Koster et al., 2006; Surguladze et al., 2005), which enhances the vulnerability to depression (MacLeod, Rutherford, Campbell, Ebsworthy and Holker, 2002). Moreover, negative attentional bias can be reduced along with the improvement of depression severity. That is, depression improvement would lead to a modification in attentional bias (Leyman et al., 2011). However, whether attentional bias modification (ABM) would result in a reduction in clinical depression was unclear.

Importantly, studies have demonstrated that attentional biases may be modified by computerized attentional bias training tasks (Browning et al., 2010; Hakamata et al., 2010; MacLeod, Koster and Fox, 2009). ABM has recently been introduced into depression studies, however, limited and inconsistent results were obtained (Baert et al., 2010; Beevers et al., 2015; Browning et al., 2012; Hallion and Ruscio, 2011; Mogoaşe et al., 2014). Specifically, meta-analyses (Hallion and Ruscio, 2011; Mogoaşe et al., 2014) and original investigations (de Voogd et al., 2016) with subclinically depressed individuals or a mixed population (combined with clinical depression, subclinical depression, unselected, or healthy) have reported that ABM is not effective in alleviating depressive symptoms. With the cue-target ABM task, Baert and his colleagues confirmed the effect of ABM on persons showing mild depressive symptoms, but not on individuals who suffered from current major depressive disorder (Baert et al., 2010). In contrast, several later experiments indicated an effect of ABM on clinical depression (Beevers et al., 2015; W. Yang, Zhang J.X., Ding and Xiao, 2016) and remitted depression (Browning et al., 2012). The inconsistent results were mainly caused by the differences in targeted populations, materials, training tasks, and training strategies, which did not allow an identical comparison between them, and led to the largely unknown therapeutic effect of ABM on depression.

The dot-probe task and cue-target task are the most popular tasks used in ABM (Cavanagh and Geisler, 2006; Joormann and Gotlib, 2007; Koster et al., 2006; Surguladze et al., 2005), which have different operations on attentional bias. The dot-probe task embodies the attentional direction or maintenance (Joormann and Gotlib, 2007), while the cue-target task mainly reflects the attentional engagement/disengagement or inhibition of return (Dai and Feng, 2009). In Browning's study (Browning et al., 2012), the dot-probe task was adopted. This cognitive task guides attention allocation by displaying a probe after an emotional stimulus pair. To develop a positive bias, the probe must always replace the relatively positive stimulus of emotional pairs (positive-negative, positive-neutral, or neutral-negative). After 14 days (28 sessions) of training, it was found that the face version ABM significantly reduced the residual depressive symptoms of remitted patients and provided a "cognitive vaccine" against the recurrence of depression. In Baert's study (Baert et al., 2010), a word version of the cue-target task was included. In this training task, the attentional engagement/disengagement is modulated by the congruency between the location of the cue and the target. To reduce a negative attentional bias, the target always appears at the opposite location of negative words, while to enhance a positive attentional bias, the targets always replaces the positive words. After 10 days of training, it was found that the therapeutic effect of ABM on depression depended on depression severity, *i.e.,* the training effect was present in mild to moderate depression but absent in clinically depressed patients. In brief, Browning conducted a dot-probe training task (face version) and indicated a vaccination effect in remitted depression, while Baert used the word version cue-target task, and confirmed the training effect only in cases of mild to moderate depression. Thus, no clear conclusion could be determined, *i.e.,* which task is more effective or stable in depression reduction.

Moreover, emotional faces and words are frequently used in ABM. Emotional faces reflect more interpersonal issues (Joormann and Gotlib, 2007), while emotional words embody more self-relevant

information (Baert et al., 2010; Dai et al., 2015a,b). Importantly, the negative self-referent schema about the self, the world, and the future (cognitive triad) have been considered to be critical in the development of negative bias and the vulnerability to depression (Beck et al., 1996). Specifically, negative bias was found most outstanding for self-relevant materials in depression (Wisco, 2009; J. Yang, Guan, Dedovic, Qi and Zhang, 2012). This phenomenon led to a naturally deducted hypothesis, *i.e.,* ABM with self-referent materials might be more effective in depression reduction. The self-referent materials were expected to be better than general or non self-referent materials because they were inner-oriented and highly relevant to the self-identity (Wisco, 2009). However, no study had tested this hypothesis, which might be important to explore the optimal ABM training strategy in depression.

Furthermore, although Browning's study was different in training task and materials from Baert's study, their training strategies were similar. Both of them used the strategy of guiding attention toward positive materials and away from negative materials (mixed ABM) simultaneously. In fact, based on the rationale of positive psychotherapy (PPT) (Seligman and Csikszentmihalyi, 2000), which guides people's attention to focus on self-referent positive events or positive feelings (happiness, hopefulness) within their bodies at this hour and moment, it could be supposed that the depressed patients might benefit from constant attentional guidance toward happy materials (positive ABM) (Baert et al., 2010; Browning et al., 2012). However, again, no previous study had tested this theory, which might be critical to optimize the ABM training strategy in depression.

Thus, the present study had two aims. Study I was designed to explore the optimal training strategy of ABM on depression in unselected undergraduates, since the results of a non-clinical sample might have potential implications for clinical patients (de Voogd et al., 2016; Ironside et al., 2016). Study II was conducted to test the therapeutic effect of optimized ABM on patients with major depressive disorder (MDD). Our hypotheses were: ① Mixed ABM and positive ABM will show an effect on depression reduction in unselected undergraduates. ② Optimized ABM will show a therapeutic effect on patients with MDD.

2. Methods (study I + study II)

2.1. Study I the training effect of ABM on depression in undergraduates

2.1.1. Participants

In Study I, undergraduate freshmen were recruited to observe the training effect of ABM on depression. Students were invited first. Responders who agreed to participate signed written informed consent to participate in this study, which was approved by the Human Research Ethics Committee of the Third Military Medical University. A total of 309 native Chinese-speaking undergraduate freshmen were randomly assigned into 16 training conditions: two tasks (dot-probe vs. cue-target) * two materials (faces vs. self-referent words) * two strategies (mixed ABM toward positive and away from negative stimuli vs. positive ABM toward positive stimuli only) * two groups (training vs. control). The emotional status of participants was assessed with the patient health questionnaire (PHQ-9), the Beck depression inventory-II (BDI-II), and the Beck anxiety inventory (BAI). Participants were further screened by psychologists to exclude current or previous Axis I psychiatric disorders or alcohol/substance misuse using the Structured Clinical Interview of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV, 4th ed.) (APA, 1994). Participants were excluded if they were taking any psychoactive medication, had any significant neurological condition, or were familiar with any of the tasks used in the study. Students received course credit for their participation. The filter process was shown in Fig. 1.

2.1.2. Materials
2.1.2.1. Emotional faces. To explore the optimal training strategy, emotional faces were included, which were selected from the Chinese
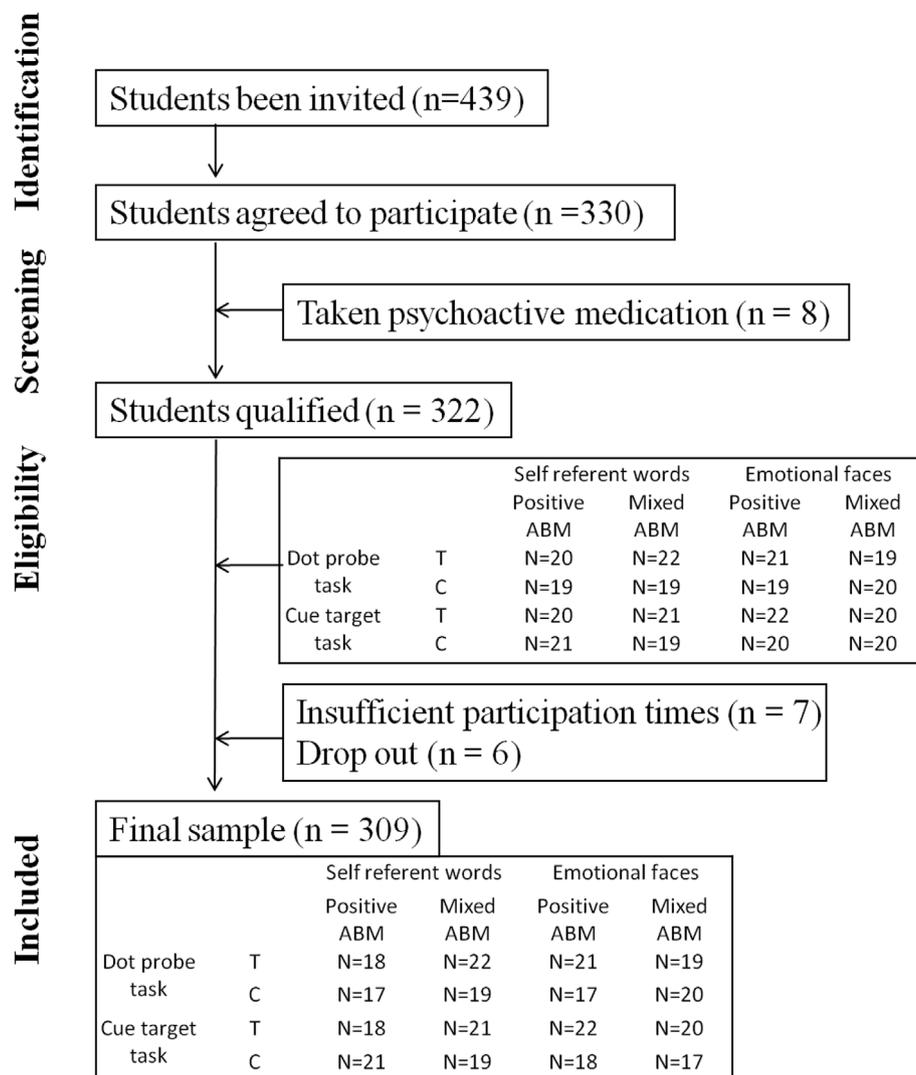
Fig. 1. Flow chart of participant recruitment.

face library that was developed by Wang and Luo of the psychological department of the Chinese academy of sciences (Wang and Luo, 2005). The selection criteria were based on the face category, valence, and arousal, which were depicted in detail in our previous work (Dai and Feng, 2012). Sixty faces in each category (happy, neutral, and sad) were selected. The valence and arousal information of the faces could be found in the Supplemental materials (Table S1).

2.1.2.2. Self-referent words. To observe the influence of self-referent materials on attentional bias modification, self-referent words were generated and included in this study. The words were collected from the Affective Norms for English Words (ANEW) (Bradley and Lang, 1999) and also generated from individual's responses to forty-two self-referent questions (Shestyuk and Deldin, 2010). The translation details of the words and questions could be found in the Supplemental materials. The self-referent words that were used in this study were selected based on the ratings of self-reference (yes or no), valence and arousal (on a 1–9 scale), which were described in details in our previous publication (Dai et al., 2015a,b). Moreover, the frequency of use and length of words were also taken into consideration. However, the number of self-referent words generated from ANEW or self-referent questions varied with participants. Sixty words of each category (positive, neutral, and negative) were used in attentional tasks. The details of the self-referent words could be found in the Supplemental

materials (Table S2).

2.1.3. Instruments

To assess the effect of ABM on emotional status and attentional bias, the BDI-II, BAI, PHQ, and attention to positive and negative inventory (APNI) were surveyed. All questionnaires were self-reported. The BDI-II and PHQ were used to assess depression states. The BDI-II scaled the severity of depression with 21-items (Beck et al., 1996; Liu and Shu, 1999), while the PHQ reflected the frequency of depressive symptoms corresponding to nine diagnostic criteria of MDD (Xu et al., 2007). The BAI examined the anxiety level with 21-items (Beck et al., 1988; Liu and Shu, 1999). The APNI assessed attentional bias toward positive or negative materials (Dai et al., 2015c; Noguchi et al., 2006). This scale contained 22-items, and the Cronbach's α coefficient was 0.83–0.86 for the Chinese APNI (Dai et al., 2015a).

2.1.4. Attentional tasks
2.1.4.1. Dot-probe task. The dot-probe task used in this study was based on Browning's task (Browning et al., 2012). At the beginning of the task, a central fixation appeared on the screen for 1000 ms. After its offset, a stimuli pair (one emotional, one neutral) presented at the upper or lower side of the screen for 1000 ms (Joormann and Gotlib, 2007), about 13 cm apart (measured from their centers) (Koster et al., 2006), followed by a target (●) either on the congruent (defined as trials
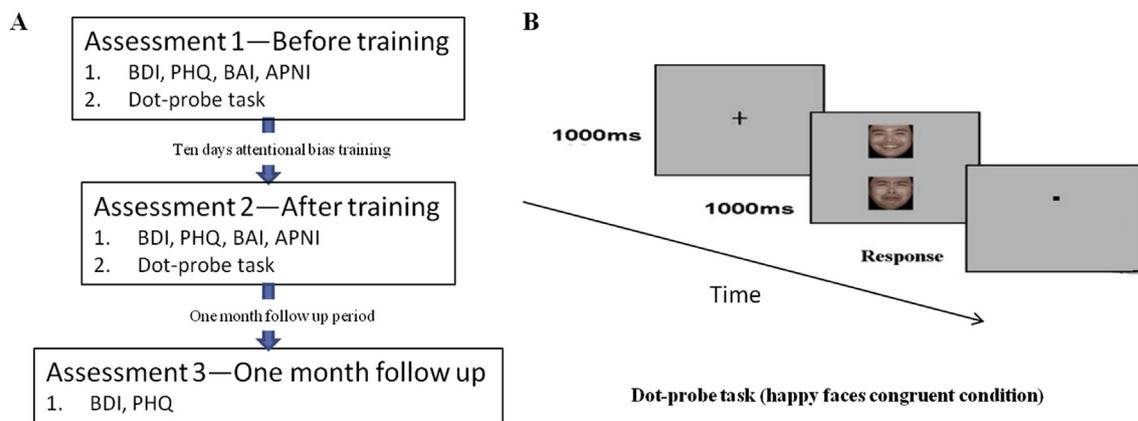
Fig. 2. Study design of the dot-probe training task. (A) Participants were surveyed by questionnaire before and after 10 days training, and at one month follow up. (B) Dot probe task. A stimuli pair (one emotional, one neutral) presented at the upper or lower sides of the screen for 1000 ms, about 13 cm apart (measured from their centers), followed by a target (●) either on the congruent (defined as trials where the targets appeared at the location of the relatively positive materials) or incongruent (trials where the targets appeared on the opposite side of the relatively positive materials) condition, which remained on the screen until the participants made a pressing response.

where the targets appeared at the location of the relatively positive materials) or incongruent condition (trials where the targets appeared on the opposite side of the relatively positive materials), which remained on the screen until the participants made a pressing response. Throughout the whole task, subjects were instructed to gaze at the central fixation cross and make pressing judgments to the location of the target as quickly and accurately as possible. See Fig. 2 for details. Participants started the formal task after they practiced (Joormann and Gotlib, 2007). The locations of the emotional stimuli or dot probe were randomized.

Training task: The training task consisted of 480 trials per day for 10 days. The probability of the dot probe presenting in each position was listed in the Supplemental materials (Table S3). In brief, the probes replaced all relatively positive materials of the stimulus pair in the training group, while the targets only followed half of the relatively positive stimuli in the control group. The difference between the mixed ABM and positive ABM group was that, the negative materials were not included in the positive ABM, which was only composed of positive-neutral pairs.

Test task: Participants who undertook the dot-probe training task completed the dot-probe testing task at pre- and post-testing. The test phase consisted of two blocks of 60 trials. The only difference between the training and the testing task was the possibility of the target location in a congruent or an incongruent location with relatively positive stimuli. In the testing task, the possibility was 50% for both the congruent and incongruent conditions. Half of the stimuli at post test were new.

2.1.4.2. Cue – target task. The cue-target task adopted in this study was based on Baert's task (Baert et al., 2010). First, a central fixation appeared on the screen with two squares at the left or right side (approximately 17 cm apart, measured from their centers) of the screen (Koster et al., 2006) for 500 ms. After that, a stimulus (emotional or neutral) presented at one of the two squares for 1500 ms (Joormann and Gotlib, 2007), followed by a short interval (50 ms). Then a target (●) appeared at either the same location (valid condition) or the opposite side (invalid condition) with the faces/words until a pressing response occurred (Fig. 3).

Training task: The training task consisted of 480 trials per day for 10 days. The probability of the dot probe being presented in each position is listed in the Supplemental materials (Table S4). In brief, probes replaced most (80–90%) positive materials and were at the opposite end from the negative materials in most trials (80–90%) in the training group, while the possibility was 50% for both the positive and negative

stimuli in the control group. The difference between the mixed ABM and the positive ABM groups was that, the negative materials were not included in the positive ABM, which was only composed of positive and neutral stimuli.

Test task: Participants who undertook the cue-target training task completed the cue-target testing task at pre- and post-testing. The test phase consisted of four blocks with 45 trials. The only difference between the training and the testing cue-target task was the possibility of the target location being in the valid or invalid condition. In the testing task, the possibility was 50% for both the valid and invalid conditions.

2.1.5. Procedures

The research protocol was approved by the Human Research Ethics Committee of the Third Military Medical University. The researcher introduced this task to the students in class. After this, students independently applied for participation. Following enrolment in the study, subjects were randomized (with stratification by gender) into one of 16 groups (Figs. 1–3): two tasks (dot-probe vs. cue-target) * two materials (faces vs. self-referent words) * two strategies (mixed ABM toward positive and away from negative stimuli vs. positive ABM toward positive stimuli only) * two groups (training vs. control). Participants who were assigned to the words training task were instructed to complete the self-referent questions and words rating task before pre-test. ABM was completed individually in a separate quiet room once daily over a course of 10 days. Participants were informed that the study examined how "cognitive style varied over time and its influence on emotion". Neither the specific rationale nor group allocation were explained until the follow-up investigation was complete. Self-report questionnaires were conducted in three assessment sessions: before ABM commenced, after the 10 days of ABM, and at 1 month follow-up, while attentional bias was assessed before and after the training. Students were debriefed and given course credit after the follow up investigation.

2.1.6. Analyses

Analysis of the questionnaire scores was performed using ANOVA with the between-subject factors of strategy (positive ABM vs. mixed ABM), materials (self-referent words vs. emotional faces), and group (training vs. control). Time-point (before ABM, after ABM, 1 month follow-up) was included as a within-subject factor (three time-points for BDI and PHQ) ($p < 0.05$ as the significant level, and post hoc tests were two-tailed). For the attentional task, the attentional bias scores were used in the analysis with valence as the within-subject factor. First, scores were obtained by removing error trials (1.77%) or extreme
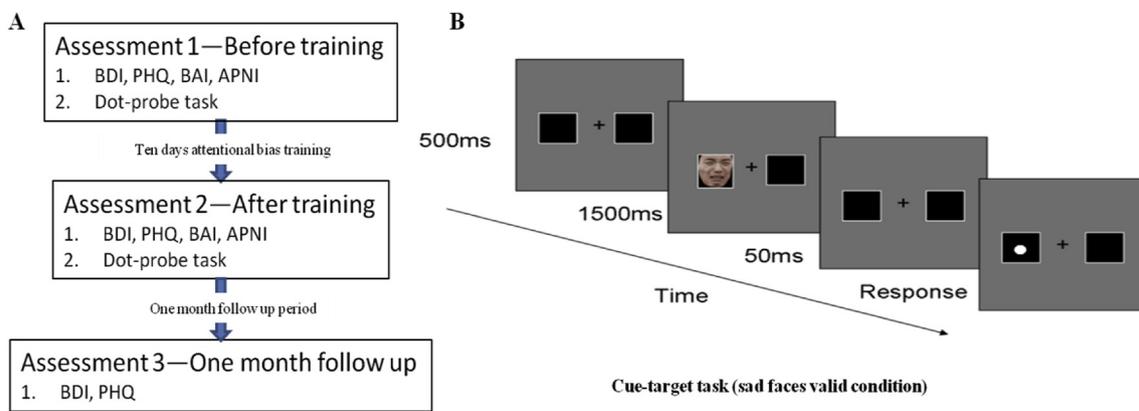
Fig. 3. Study design of the cue-target training task. (A) Participants were surveyed with questionnaire before and after 10 days training, and at one month follow up. (B) Cue-target task. A central fixation appeared on the screen with two squares at the left and right sides (approximately 17 cm apart, measured from their centers) for 500 ms. After its offset, a stimulus (emotional or neutral) presented at one of the two squares for 1500 ms, followed by a short interval (50 ms). Then a target (●) appeared at either the same location with the faces/words (valid condition) or the opposite side (invalid condition) until a pressing responding.

responses (0.94%), those which lay outside 250–1000 ms or were greater than three standard deviations from the group mean. Next, the attentional bias scores were further calculated. For the dot-probe task, the scores were obtained by subtracting reaction times (RTs) of the relatively positive materials from those of the relatively negative stimuli. Positive scores indicated attention toward relatively positive materials, while negative scores indicated attention away from relatively positive materials. Similarly, for the cue-target task, the scores were obtained by subtracting the RTs of the valid condition from those of the invalid condition. Positive scores indicated attention engagement toward the cue, while negative values suggested attention disengagement from the cue. A repeated ANOVA was carried out on the attentional bias, 2 strategies * 2 materials * 2 groups * 2 time-points * 3 valences (happy-neutral, happy-sad, and neutral-sad for the dot-probe task, and positive, neutral, and negative for the cue-target task).

2.2. Study II the therapeutic effect of ABM on depressive symptoms in depressed patients

2.2.1. Participants

In study II, clinical patients were recruited to observe the therapeutic effect of ABM on depressive symptoms. Forty clinically depressed patients were recruited by clinicians, from the inpatient unit of a psychiatric hospital of Chong Qing, China, from June 2013 to January 2015 (expected sample size was achieved). Inclusion criteria were as follows: age between 18 and 65 years old (Avery et al., 2006; Browning et al., 2012; de Graaf et al., 2011; O'Reardon et al., 2007), diagnosed with major depressive disorder (MDD) based on DSM-IV criteria, scored 20 or higher on the Hamilton Depression Rating Scale (HDRS, 24 items), two or more recurrences and adherence to a stable antidepressant for at least 6 weeks during the current episode (Baert et al., 2010). Exclusion criteria were as follows: bipolar disorder, schizophrenia, severe physical disease, learning disability, substance dependence, family history of psychosis, developmental disorders, or personality disorders; infection, trauma, inflammation, or allergy within last 2 weeks; history of alcohol or substance abuse, involvement in current or history of cognitive-behavioral therapy (CBT), or electroconvulsive therapy (ECT) within the past 6 months; or active suicidal ideation. The recruitment process was listed in Fig. 4. Eight patients were dropped or discharged. Thus, 32 MDD patients (the sample size was identical to the literature (Baert et al., 2010; Browning et al., 2012)) were finally involved, all were medicated and remained unchanged until the follow up test of the experiment.

All participants signed a written informed consent to participate in the experiment, which was approved by the Human Research Ethics Committee of the Third Military Medical University. To further assess
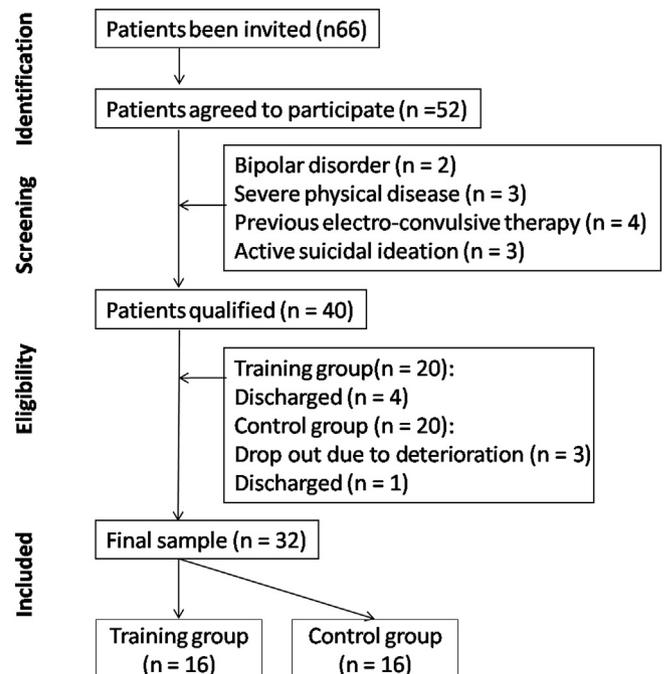

Fig. 4. Flow chart of patient recruitment.

the depressive symptoms, the BDI-II, PHQ-9, BAI were also surveyed. One of the 32 MDD participants had a co-morbid diagnosis of anxiety, and one had a co-morbid diagnosis of post-traumatic stress disorder (PTSD). All participants had normal or rectified eyesight with no color blindness, and all were right-handed. They were in recurrent episodes (mean 4.21 ± S.D. 3.56), the average age of the first onset was 38.71 years old (S.D. 10.97). Patients were randomly grouped into two groups, 16 of them received ABM training, while the other 16 patients experienced sham training. Patients in the two groups were matched in gender, age, and educational level.

2.2.2. Procedures

The research protocol was approved by the Human Research Ethics Committee of the Third Military Medical University. The ABM training procedure was as follows: Patients were grouped into two groups randomly (with randomized number) by clinicians, one group (odd number) was training group, while another group (even number) was control group. Patients and experimenters who participated in the pre- and post-test were bind to the training strategy. Based on the result of

Study I, mixed cue-target ABM toward positive and away from negative stimuli with emotional faces was adopted to ensure a therapeutic effect of ABM. The probes replaced most (80–90%) positive materials and were at the opposite of most negative (80–90%) materials in the training group, while the possibility was 50% for both happy and sad faces in the control group. See the Supplemental materials for details (Table S4, mixed ABM).

The ABM training was completed individually in a separate quiet room of hospital once daily over a course of 10 days. Before and after the ABM training, the attentional bias and depressive status were assessed. At one-month follow-up, the depressive status was investigated again and patients were debriefed. The attentional bias was observed by a cue-target task (same with Study I) and the APNI, while the mood status was assessed by the BDI, BAI, PHQ, and HDRS.

2.2.3. Statistics

χ^2 test and univariate ANOVA analysis were conducted on the general information of patients. A repeated three-way ANOVA with 2 (group) * 3 (valence) * 2 (time point) was carried out on the attentional bias scores ($p < 0.05$ as the significant level, and the post hoc tests were two-tailed), while a repeated two-way ANOVA with 2 (group) * 3 (time point) was conducted on the scores of the BDI, PHQ, BAI, HDRS, and APNI. The attentional bias scores were calculated by subtracting the RTs of the valid condition from those of the invalid condition after excluding the error trials (1.02%) or extreme responses (0.66%) (shorter than 250 ms or longer than 1000 ms). Independent sample *t*-test was carried out to compare group difference, and paired sample *t*-test was conducted to examine the training effect of ABM.

3. Results (study I + study II)

3.1. Study I the training effect of ABM on depression in undergraduates

3.1.1. Dot-probe task
3.1.1.1. *Group characteristics*. In study I, all participants were Chinese undergraduate freshmen, whose BDI (5.70 ± 5.83) and PHQ (5.47 ± 3.63) scores were relatively low, which indicated that they were emotionally stable. No significant differences existed in the male/female ratio, $\chi^2 < 2.289$, $p > 0.130$, or age, $F < 2.772$, $p > 0.105$, between groups. Groups were also matched in scores of the BDI, PHQ, BAI, or APNI before training, see Table 1 and the Supplementary materials for details.

3.1.1.2. *Influence of the dot-probe training task on depression level (Table 1)*. To explore the training effect of the dot-probe training on depression status, a repeated ANOVA was conducted on the scores of the BDI and PHQ, which indicated a main effect of time on BDI scores, $F (2, 290) = 8.106$, $p < 0.001$, partial-eta$^2 = 0.06$, and the PHQ scores, $F (2, 290) = 20.771$, $p < 0.001$, partial-eta$^2 = 0.13$, with lower scores after training. However, no significant material * strategy * condition * time interaction was found on the BDI scores, $F (2, 290) = 1.347$, $p = 0.262$, partial-eta$^2 = 0.01$, or the PHQ scores, $F (2, 290) = 0.133$, $p = 0.875$, partial-eta$^2 = 0.001$. Hence, no further analysis was conducted.

3.1.1.3. *Influence of the dot-probe training task on attentional bias scores*. To observe the training effect of the dot-probe training on attentional bias, a repeated ANOVA was carried out on the attentional bias scores of the dot-probe task, which indicated a main effect of valence, $F (2, 290) = 7.261$, $p = 0.001$, partial-eta$^2 = 0.048$, with higher attentional bias scores toward neutral stimuli, while no significant material * strategy * condition * time * valence interaction was found, $F (2, 290) = 0.019$, $p = 0.98$, partial-eta$^2 = 0.001$. Hence, no further analysis was carried out. See the Supplemental materials for details (Fig. S1).

3.1.2. Cue-target task
3.1.2.1. *Group characteristics*. All participants were Chinese undergraduate freshmen, whose BDI (5.77 ± 6.36) and PHQ (5.39 ± 4.63) scores were not high, which indicated that they were emotionally stable. There were no significant differences in male/female ratio, $\chi^2 < 1.928$, $p > 0.210$, or age, $F < 1.772$, $p > 0.153$, between groups. Groups were also matched on scores of the BDI, PHQ, BAI, and APNI before training, see Table 2 and the Supplementary materials for details.

3.1.2.2. *Influence of the cue-target training task on depression level (Table 2)*. To explore the training effect of the cue-target training task on depression status, a repeated ANOVA was conducted on the scores of the BDI and PHQ, which indicated a main effect of time on the BDI scores, $F (2, 296) = 19.132$, $p < 0.001$, partial-eta$^2 = 0.12$, and the PHQ scores, $F (2, 296) = 34.864$, $p < 0.001$, partial-eta$^2 = 0.20$, with higher scores before training. As expected, there was a significant material * strategy * condition * time interaction on the BDI scores, $F (2, 296) = 4.156$, $p = 0.017$, partial-eta$^2 = 0.03$, and a marginally significant interaction on the PHQ scores, $F (2, 296) = 2.506$,

Table 1
Group characteristics in the dot-probe training task ($\bar{x} \pm$ SD).

		Word task				Face task			
		Mixed ABM		Positive ABM		Mixed ABM		Positive ABM	
		T (n = 22)	C (n = 19)	T (n = 18)	C (n = 17)	T (n = 19)	C (n = 20)	T (n = 21)	C (n = 17)
Age		18.18 ± 0.80	18.47 ± 0.96	18.72 ± 0.96	18.76 ± 0.75	18.81 ± 0.91	18.30 ± 0.92	18.75 ± 0.72	19.06 ± 0.77
Gender (F/M)		12/10	8/11	12/6	7/10	12/7	9/11	9/12	10/7
BDI	Pre	4.90 ± 5.49	3.79 ± 3.36	5.33 ± 4.23	5.94 ± 10.10	6.16 ± 5.40	5.50 ± 5.87	3.57 ± 2.48	4.69 ± 5.62
	Post	4.10 ± 3.92	4.00 ± 4.32	4.56 ± 4.12	4.63 ± 4.75	5.53 ± 5.16	3.86 ± 4.04	4.05 ± 3.43	3.75 ± 3.84
	Follow	5.10 ± 4.82	4.42 ± 3.66	5.56 ± 5.18	4.06 ± 3.38	5.37 ± 3.58	3.79 ± 2.83	3.90 ± 3.75	3.25 ± 2.65
PHQ	Pre	5.30 ± 3.15	4.84 ± 2.34	5.39 ± 4.05	5.19 ± 5.42	5.58 ± 3.27	5.71 ± 3.10	3.86 ± 2.46	4.38 ± 4.06
	Post	4.85 ± 4.44	4.00 ± 2.49	4.39 ± 4.83	4.44 ± 4.00	4.84 ± 3.72	4.14 ± 2.85	3.48 ± 3.44	3.56 ± 3.56
	Follow	3.95 ± 2.74	3.00 ± 2.03	5.39 ± 4.67	2.75 ± 2.49	4.21 ± 2.49	4.07 ± 3.05	4.76 ± 3.32	2.75 ± 2.59
API	Pre	44.41 ± 6.14	41.53 ± 8.51	42.89 ± 5.39	42.94 ± 5.56	42.63 ± 5.16	43.85 ± 6.84	44.95 ± 6.53	43.35 ± 4.77
	Post	43.18 ± 6.31	42.11 ± 4.40	41.61 ± 6.72	43.00 ± 7.73	40.00 ± 4.92	44.00 ± 6.34	43.24 ± 7.50	43.35 ± 5.42
ANI	Pre	34.09 ± 4.87	33.37 ± 7.18	36.11 ± 5.14	34.24 ± 7.85	33.79 ± 6.32	34.35 ± 5.90	31.67 ± 6.12	33.71 ± 4.66
	Post	34.32 ± 6.36	34.37 ± 5.34	33.72 ± 4.88	34.35 ± 7.39	33.47 ± 6.24	34.00 ± 5.27	33.19 ± 7.12	33.76 ± 4.32
BAI	Pre	3.95 ± 3.08	5.41 ± 5.96	4.06 ± 7.42	3.30 ± 3.36	3.19 ± 4.55	3.23 ± 5.35	3.81 ± 6.59	3.50 ± 4.53
	Post	2.37 ± 2.29	3.27 ± 5.05	3.17 ± 4.34	4.85 ± 5.82	3.90 ± 3.36	3.14 ± 4.24	2.90 ± 4.37	4.05 ± 3.58

Note: API = attention to positive information. ANI = attention to negative information. BAI = Beck Anxiety Inventory. BDI = Beck Depression Inventory. PHQ = patient health questionnaire. Pre = before training. Post = after training. Follow = one month follow up.

Table 2
Group characteristics in the cue-target training task ($\bar{x} \pm SD$).

		Word task				Face task			
		Mixed ABM		Positive ABM		Mixed ABM		Positive ABM	
		T (n = 21)	C (n = 19)	T (n = 18)	C (n = 21)	T (n = 20)	C (n = 17)	T (n = 22)	C (n = 18)
Age		18.45 ± 1.28	18.58 ± 0.84	18.33 ± 0.77	18.81 ± 1.03	18.75 ± 0.79	18.69 ± 1.01	18.48 ± 0.81	18.41 ± 0.71
Gnder (F/M)		11/10	10/9	9/9	11/10	9/11	10/7	10/12	10/8
BDI	Pre	4.43 ± 2.56	6.11 ± 10.97	6.93 ± 4.85	5.16 ± 3.11	6.33 ± 8.44	5.65 ± 7.25	5.23 ± 4.41	5.17 ± 6.27
	Post	3.24 ± 2.84	5.63 ± 6.68	3.40 ± 3.81	4.26 ± 3.26	3.33 ± 5.37	5.00 ± 6.26	3.23 ± 3.90	4.56 ± 5.50
	Follow	4.52 ± 3.60	5.00 ± 5.90	3.93 ± 2.84	4.84 ± 3.58	3.56 ± 4.90	4.47 ± 5.11	3.27 ± 3.91	4.67 ± 5.84
PHQ	Pre	5.00 ± 2.97	6.26 ± 6.22	6.53 ± 4.81	4.58 ± 3.40	6.11 ± 5.93	5.71 ± 6.62	4.57 ± 3.30	4.33 ± 3.25
	Post	3.67 ± 2.92	5.95 ± 5.57	3.60 ± 2.29	4.00 ± 3.23	3.39 ± 4.96	4.94 ± 6.57	3.82 ± 4.01	3.61 ± 3.87
	Follow	3.29 ± 2.24	4.47 ± 3.75	3.40 ± 1.68	4.05 ± 2.93	3.28 ± 4.21	4.59 ± 5.15	2.86 ± 2.80	3.00 ± 4.12
API	Pre	43.86 ± 5.21	41.42 ± 6.05	43.17 ± 7.82	44.00 ± 4.75	45.15 ± 5.67	41.65 ± 5.89*	44.91 ± 6.77	42.78 ± 11.98
	Post	42.57 ± 7.28	42.05 ± 6.23	41.78 ± 5.61	44.90 ± 6.50	45.20 ± 6.25	38.94 ± 5.60	42.50 ± 9.54	44.39 ± 6.57
ANI	Pre	33.62 ± 5.31*	34.37 ± 5.53	34.37 ± 5.15	33.14 ± 6.94	32.60 ± 4.98	29.59 ± 5.59	34.70 ± 6.43	33.11 ± 10.01
	Post	31.48 ± 6.27	34.53 ± 6.45	32.61 ± 6.00	33.05 ± 6.84	30.90 ± 4.35	30.59 ± 4.66	33.95 ± 8.33	35.56 ± 6.39
BAI	Pre	4.05 ± 3.58	5.05 ± 4.86	4.21 ± 4.06	4.19 ± 4.43	4.81 ± 6.38	4.30 ± 5.65	5.40 ± 6.64	3.00 ± 2.14*
	Post	3.50 ± 4.53	4.75 ± 6.77	4.47 ± 5.60	4.14 ± 5.32	4.95 ± 5.96	3.74 ± 6.73	4.15 ± 5.19	5.36 ± 5.78

Note: Representatives of abbreviation were same with Table 3. T = training group. C = Control group.

p = 0.083 partial-eta^2 = 0.02.

To observe the influence of different materials on depression status, a repeated ANOVA was carried out, which indicated an expected interaction of strategy * group * time for self-referent words on the BDI scores, F (2, 150) = 3.834, p = 0.024, partial-eta^2 = 0.05, and the PHQ scores, F (2, 150) = 2.995, p = 0.053, partial-eta^2 = 0.04. Follow up analysis on different strategies indicated a group * time interaction for the positive training strategy on the BDI scores, F (2, 74) = 4.36, p = 0.017, partial-eta^2 = 0.12, and the PHQ scores, F (2, 74) = 4.76, p = 0.012, partial-eta^2 = 0.13, with significant lower scores after training and at one month follow-up in the training group.

A repeated ANOVA was also conducted on different strategies, which indicated a material * condition * time interaction in the mixed training strategy on the BDI scores, F (2, 146) = 3.572, p = 0.031, partial-eta^2 = 0.06, and a marginally significant interaction on the PHQ scores, F (2, 146) = 2.639, p = 0.075, partial-eta^2 = 0.04. Further analysis indicated a group * time interaction for emotional faces on the BDI scores, F (2, 70) = 3.52, p = 0.035, partial-eta^2 = 0.10, and the PHQ scores, F (2, 70) = 3.33, p = 0.042, partial-eta^2 = 0.09, with significant lower scores after training and at one month follow-up in the training group. In total, these results suggested a training effect on depressive mood of the two training strategies, *i.e.*, positive ABM with self-referent words as materials, and mixed ABM with emotional faces as stimuli, which offered a reliable suggestion for the training strategy of Study II.

3.1.2.3. Influence of the cue-target training task on attentional bias scores. To observe the training effect of the cue-target training task on attentional bias, a repeated ANOVA was carried out on the attentional bias scores of the cue-target task, which indicated a main effect of time, F (1, 148) = 42.166, p < 0.001, partial-eta^2 = 0.22, and valence, F (2, 296) = 3.041, p = 0.049, partial-eta^2 = 0.02, with higher attentional bias scores after training and for neutral stimuli, while no significant material * strategy * condition * time * valence interaction was found, F (2, 296) = 1.524, p = 0.22, partial-eta^2 = 0.01. See the Supplemental materials for details (Fig. S2).

3.2. Study II the therapeutic effect of ABM on depressive symptoms in depressed patients

3.2.1. Group characteristics

In study II, patients in the training and control groups were matched in male/female ratio ($\chi 2$ = 0.571, df = 1, N = 32, p = 0.476), age (t (30) = 1.094, p = 0.283), educational level (t (30) = −1.287,

p = 0.208), and depression severity before training, with no significant difference between two groups on the PHQ scores (t (30) = 0.683, p = 0.500), BDI scores (t (30) = −0.168, p = 0.868), BAI scores (t (30) = 0.195, p = 0.846), or HDRS scores (t (30) = −0.27, p = 0.79).

3.2.2. Effect of ABM on depressive symptoms (Table 3, Fig. 5)

To observe the therapeutic effect of ABM on depression, a repeated ANOVA was carried out on questionnaire scores, which indicated an expected interaction between group and time on PHQ scores (F (2, 60) = 3.934, p = 0.025, partial-eta^2 = 0.12), BDI scores (F (2, 60) = 5.204, p = 0.008, partial-eta^2 = 0.15), BAI scores (F (2, 60) = 5.052, p = 0.009, partial-eta^2 = 0.14), and HDRS scores (F (2, 60) = 2.453, p = 0.095, partial-eta^2 = 0.08). A between-group independent sample *t*-test showed that compared with the control group, patients in the training group had significantly lower scores at the one month follow-up on BDI scores (t (30) = −5.111, p < 0.001), PHQ scores (t (30) = −2.546, p = 0.017), HDRS scores (t (30) = −3.758, p = 0.001), and BAI scores (t (30) = −2.681, p = 0.013). See Table 3 and Fig. 5 for more details. The results suggested a therapeutic effect of ABM on clinical depression.

3.2.3. Effect of ABM on attentional bias

3.2.3.1. Cue-target task (Fig. 6). To explore the effect of ABM on attentional bias, a repeated three-way ANOVA was conducted on reaction times (RTs) of the cue-target task, which indicated a main effect of time, F (1, 30) = 4.244, p = 0.048, partial-eta^2 = 0.12, with bigger cue validity after training, and an expected time * valence interaction, F (2, 60) = 4.026, p = 0.023, partial-eta^2 = 0.12. To further explore the group difference, ANOVA was conducted on the two groups independently, which indicated an expected time * valence interaction in the training group, F (2, 30) = 3.556, p = 0.041, partial-eta^2 = 0.19, but not the control group, F (2, 30) = 1.356, p = 0.273, partial-eta^2 = 0.083. A paired sample *t*-test showed that the training group had higher attentional bias scores toward happy faces after training, t (15) = −4.403, p = 0.001. See Fig. 6 for more details. The results indicated that attentional bias toward happy faces was significantly enhanced after ABM which confirmed a therapeutic effect.

3.2.3.2. APNI scores (Table 4). Similarly, a repeated two-way ANOVA was conducted on the scores of the APNI to observe the effect of ABM on attentional bias, which indicated an expected time * group interaction for API scores, F (2, 60) = 3.348, p = 0.042, partial-eta^2 = 0.10, but not for ANI scores, F (2, 60) = 0.974, p = 0.383, partial-eta^2 = 0.03. An independent sample *t*-test showed that the

Table 3
Group characteristics of depressed patients ($\bar{x}$ ± SD).

	Gender (M/F)	Age	Education level	Disease duration	Episodes	PHQ Pre	PHQ Post	PHQ Follow	BDI Pre	BDI Post	BDI Follow	HDRS Pre	HDRS Post	HDRS Follow	BAI Pre	BAI Post	BAI Follow
T	6/10	38.31 ± 11.73	1.94 ± 0.77	20.19 ± 5.82	2.75 ± 1.88	19.63 ± 5.61	13.81 ± 7.08	5.94 ± 4.61	31.69 ± 13.07	22.19 ± 8.84	8.25 ± 3.89	23.13 ± 2.58	11.38 ± 6.04	8.14 ± 3.67	15.75 ± 3.57	10.44 ± 5.39	5.25 ± 4.28
C	8/8	39.00 ± 10.27	2.31 ± 0.87	21.56 ± 7.11	3.06 ± 1.69	17.94 ± 8.14	10.50 ± 5.03	9.75 ± 3.82	32.56 ± 16.25	16.50 ± 7.75	15.38 ± 3.96	22.88 ± 2.66	13.56 ± 5.92	12.00 ± 1.30	16.00 ± 3.67	9.69 ± 3.28	10.25 ± 4.95
t	0.51	−0.176	−1.29	−0.599	−0.494	0.68	1.53	−2.55	−0.19	1.94	−5.13	0.65	1.03	−4.19	−0.20	0.48	−3.06
P	0.48	0.801	0.21	0.554	0.625	0.50	0.14	0.016	0.87	0.06	< 0.001	0.52	0.31	0.001	0.85	0.64	0.005

Note: HDRS = the Hamilton Depression Rating Scale. Education level: 1 = primary school or lower, 2 = middle school, 3 = university, 4 = postgraduates.

training group had higher API scores after training, t (30) = 2.739, p = 0.01, and at one month follow-up, t (30) = 4.064, p < 0.01. See Table 4 for more details. The results indicated that attentional bias toward happy materials was significantly enhanced after ABM, which suggested a therapeutic effect too.

4. Discussions

Our findings confirmed the literature with the evidence of the training effect of ABM on depression in the non-clinical sample. Moreover, this study added to the evidence with the therapeutic effect of ABM on clinical depression. The finding that a quick enhancement in positive attentional bias predicting later therapeutic effect on clinical depression reduction indicated a potential mechanism that could underlie the therapeutic process of ABM in depression. Furthermore, the efficacy of the two training strategies (cue-target training task: positive ABM with self-referent words, mixed ABM with emotional faces) were also indicated in unselected undergraduates.

In the undergraduates, the absence of a training effect in the dot-probe task might have been caused by the competition of cognitive resources during attentional direction, since two stimuli were presented during the cue presentation. Thus, no obvious attentional guidance existed during the cue presentation. Our finding was inconsistent with Browning's study (Browning et al., 2012), which indicated a training effect of the dot-probe task in remitted patients. The differentiation in training population might have led to the difference in the findings, *i.e.,* Browning targeted on remitted patients, while unselected undergraduates were trained in Study I. Moreover, the longer training duration (14 days) and more training sessions (28 sessions) in Browning's study might guarantee the training effect.

In contrast, the training effect was indicated in cue-target ABM, which was consistent with previous reports (De Raedt and Koster, 2010). In the cue-target task, only one emotional stimulus is presented during cue-presentation, which might attract attention automatically, *i.e.,* the attentional engagement is guided implicitly. After that, the disengagement procedure is modulated by training strategy——toward positive stimuli only (positive ABM) or away from negative stimuli simultaneously (mixed ABM) or no modulation at all (control condition). In this study, 80–90% of the positive cues were replaced by a target, while 90% of the negative cues were followed by a contrary located target, thus, subjects learned to follow positive cues (cue validity, faster response for valid condition) and to avoid negative cues (inhibition of return (IOR) effect, faster response to invalid condition). IOR means a slower response to objects appearing at a formerly-attended location, which guides attention away from negative materials effectively and ensures an effective searching strategy in attention (Klein, 2000). Meanwhile, cue validity kept the maintenance of attention on positive materials. Together this led to a reduction in depression.

Furthermore, the training effect of cue-target ABM was only confirmed in two strategies, *i.e.,* positive ABM with self-referent words and mixed ABM with emotional faces. This indicates that with interpersonal cues (emotional faces), it is more effective to guide the attention toward happy faces and away from sad faces simultaneously. Indeed, if people could emphasize on happy cues while ignoring negative information in interpersonal relationships, they might feel more comfortable or optimistic in their interpersonal relationships. With self-referent materials, however, it is more useful to reduce depression by guiding people to focus on self-referent positive feelings only. This is consistent with a rationale of positive psychotherapy (PPT) (Seligman and Csikszentmihalyi, 2000), which proposes that negative emotions emerge with the deficiency in positive feelings. Thus, emphasizing the enhancement of positive feelings is critical to assure a better mood. This offers a potentially important suggestion for clinical cognitive-behavioral therapy (CBT) of depression, *i.e.,* different strategies should be selected for different kinds of depression. For example, to solve self-referent personal issues, focusing on positive events is recommended,

Table 4
Effect of ABM on attentional bias ($\bar{x} \pm$ SD).

	Pre	API Post	Follow	Pre	ANI Post	Follow
T	36.06 ± 7.84	40.69 ± 6.64	44.00 ± 6.72	36.56 ± 4.02	33.38 ± 6.83	35.56 ± 4.02
C	34.00 ± 6.63	35.38 ± 4.01	33.63 ± 7.69	37.31 ± 5.22	35.13 ± 7.45	34.00 ± 7.17
t	0.804	2.739	4.064	−0.455	−0.693	0.76
P	0.428	0.01	< 0.01	0.652	0.494	0.453

while for interpersonal issues, guidance toward positive interpersonal clues and away from negative interpersonal information is optimal.

Study II further indicated the therapeutic effect of mixed ABM on clinical depression, with the evidence of enhanced attentional bias toward happy materials (in the cue-target task and APNI) after ABM, and significant lower depressive scores at one-month follow-up. The results suggested that the enhancement in positive attentional bias right after ABM would not lead to improvement in clinical depression immediately, instead, it predicted later depression reduction (one-month later). Compared with previous ineffective results of ABM (Baert et al., 2010; de Voogd et al., 2016), the therapeutic effect in this study might be the result of the vivid emotional pictures combined with the cue-target task. The findings that the influence of ABM on attentional bias predicting later therapeutic effect on MDD was consistent with a previous finding (Browning et al., 2010), which confirmed the reduced residual depressive symptoms in remitted depression one-month after ABM. Indeed, the effect of ABM on depression is a long-term process that could be recognized as a secondary prevention of depression (Excellence, 2009). Thus, the influence of ABM on depression reduction is rather slow than quick.

Although parts of previous studies with non-clinical population failed to observe the effect of ABM on depression reduction (de Voogd et al., 2016; Hallion and Ruscio, 2011; Leyman et al., 2011), the current study reported here confirmed a preventive effect of ABM on the occurrence of depression in the undiagnosed undergraduates in Study I. In our study, 16 training conditions with different tasks (cue-target and dot-probe), materials (faces and self-referent words), training strategies (mixed ABM toward positive and away from negative stimuli and positive ABM toward positive stimuli only) have raised the potential possibility of the effectiveness of ABM. Furthermore, our findings added to the evidence of the therapeutic effect of ABM on clinical depression in Study II, which was consistent with previous conclusions of the optimal therapeutic effect of CBT combined with antidepressants in clinic (Beevers et al., 2015; J. Yang et al., 2012). The differences were that Yang targeted adolescents with MDD, while Beevers allocated 8
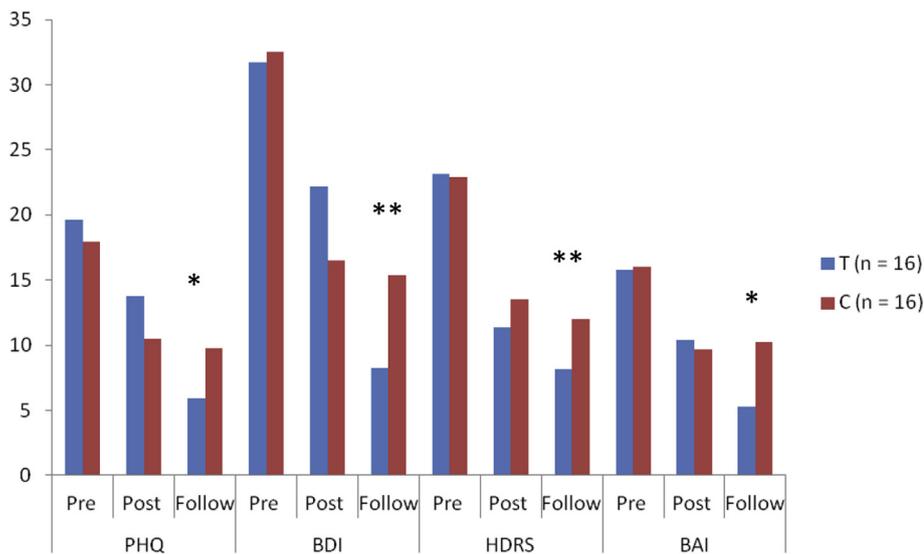

Fig. 6. Attentional bias scores of MDD before and after cue-target ABM. **Note:** **p < 0.01. Paired sample *t*-test showed that training group had higher attentional bias scores toward happy faces after training, t (15) = −4.403, p = 0.001, which indicated a therapeutic effect of ABM.

sessions separately in one-month with sad-neutral pair materials only. Our improvements were to complete the ABM training on adults with MDD daily for 10 consecutive days, and we included happy, neutral, and sad faces as well. Browning's study (Browning et al., 2012) suggested a preventive effect of ABM on the recurrence of depression with remitted depression, while Baert's study (Baert et al., 2010) confirmed a preventive effect of ABM on the occurrence of depression with depressed undergraduates. The current study broadened the knowledge with the optimal therapeutic effect of ABM combined with antidepressants in adult patients with MDD.

Limitations: *First*, the sample size in the current study was relatively small (in both undergraduates and MDD patients), only around 20 individuals in each group, which caused the relatively low effect size in results. *Second*, no obvious attentional bias was observed at the pre-testing stage, which might discount the training effect of ABM. However, literature confirmed a strong training effect even without the

Fig. 5. Effect of ABM on depressive symptoms. **Note:** **p < 0.01, *p < 0.05. Independent sample *t*-test showed that training group had lower scores at one month follow up on BDI scores (t (30) = −5.111, p < 0.001), PHQ scores (t (30) = −2.546, p = 0.017), and HDRS scores (t (30) = −3.758, p = 0.001), as well as BAI scores (t (30) = −2.681, p = 0.013), which suggested a therapeutic effect of ABM on clinical depression.
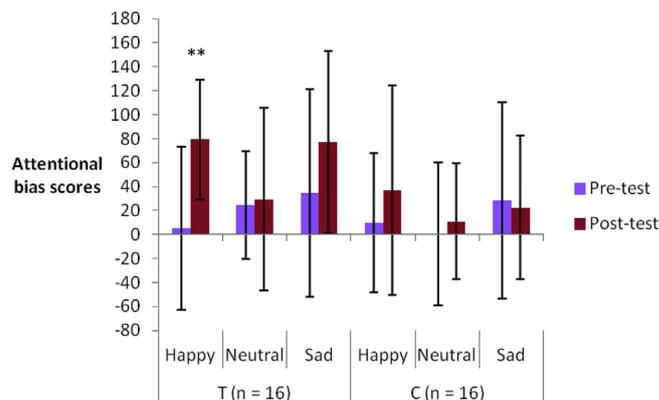
presence of attentional bias before training (Amir et al., 2009). *Third*, the diagnosis of MDD patients was not based on the objective method (*e.g.,* SCID). *Fourth*, the ABM with self-referent words was not tested in clinical MDD patients, due to the educational level of the patients, *i.e.,* some patients were poorly educated, which led to a difficulty in generating self-relevant words. *Finally*, all patients in the current study were medicated, which might influence the behavioral responses of the patients. However, previous research indicated that no significant influence of medication on behavior was observed (Baert et al., 2010; Hernández-Ribas et al., 2013). Importantly, in this study, all patients adhered to stable antidepressants for at least 6 weeks before the experiment and remained unchanged throughout the entire experiment. Thus, we argued here that if any effect of medication on behavior was present, this effect was already present at the beginning of the experiment, and remained unchanged during the task. Most importantly, the inclusion of a control group with medication allowed us to further confirm that the change in depressive symptoms and attentional bias that was observed in the training group of Study II was caused by ABM instead of medicine. Despite these limitations, the present study shed light on the effect of ABM on clinical depression, with attentional biomarkers during this process.

In conclusion, our findings confirm the literature with the evidence of the training effect of ABM on depression reduction in a non-clinical sample. Moreover, this study adds to the evidence of the therapeutic effect of ABM on clinical depression. The findings that quick enhancement in positive attentional bias predicting later therapeutic effect on clinical depression reduction indicate a potential mechanism that could underlie the therapeutic process of ABM in depression. The findings that two training strategies are effective in depression reduction suggest that different strategies should be selected for different types of depression. Hence, the value of this study is to offer a potential way to cure depression and could be further practiced in clinic.

Conflicts of interest

Funding and disclosure

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Appendix A. Supplementary data

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