Published in final edited form as:

Contemp Clin Trials. 2018 December ; 75: 59–66. doi:10.1016/j.cct.2018.10.014.

Attentional bias modification treatment for depression: Study protocol for a randomized controlled trial

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Abstract

Theoretical models and empirical research point to negatively biased attention as a maintaining factor in depression. Although preliminary studies suggest experimentally modifying attentional biases (i.e., attentional bias modification; ABM) reduces depression symptoms and depression risk, relatively few rigorous studies with clinical samples have been completed. This clinical trial examines the impact of ABM on a sample of adults ($N = 123$) with elevated depression severity who also exhibit at least modest levels of negatively biased attention prior to treatment. Participants will be randomly assigned to either active ABM, placebo ABM, or an assessment-only control condition. Individuals assigned to ABM will complete 5 trainings per week (2 in-clinic, 3 brief trainings at-home) during a four-week period. Throughout this four-week period, participants will complete weekly assessments of symptom severity and putative treatment mediators measured across different levels of analysis (e.g., eye tracking, behavioral measures, and functional Magnetic Resonance Imaging). This article details the rationale and design of the clinical trial, including methodological issues that required more extensive consideration. Our findings may not only point to an easily-accessible, efficacious treatment for depression but may also provide a meaningful test of whether a theoretically important construct, negatively biased attention, maintains depression.

Keywords

depression; attentional bias; attention bias modification

Introduction

Depression is the leading cause of disability worldwide and is associated with significant physical health problems, interpersonal discord, other mental health challenges, and economic burden [1–6]. Cognitive models of depression posit that negatively biased

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attention has an important role in the maintenance of the disorder [7–11]. These models assert that depressed individuals preferentially attend to negative stimuli and have difficulty disengaging attention from negative stimuli, leading to sustained negative affect and a persistent depressive episode.

Meta-analyses of cross-sectional research have found that depressed individuals exhibit negatively biased attention relative to non-depressed individuals [12,13]. In addition, negatively biased attention is associated with impaired mood recovery [14,15] and prospectively predicts increases in depression symptoms in students [16], dysphoric individuals [17], and soldiers [18]. These findings collectively suggest an association between depression and negatively biased attention.

Building upon these correlational findings, studies that have experimentally modified negatively biased attention (i.e., attention bias modification; ABM) have shown that ABM reduces depression symptoms and depression risk [19–22]. However, there have been null ABM findings as well [23]. Although these preliminary experiments support the hypothesis that negatively biased attention maintains depression, these studies are limited in number and often draw from student samples. Very few rigorous clinical trials of ABM have been completed with depressed adults. Accordingly, additional experimental work is required to determine whether negatively biased attention maintains depressive episodes, as proposed by theoretical models of depression.

This clinical trial seeks to address this question in a sample of adults with elevated depression severity. Moreover, this trial will recruit a homogeneous group of depressed individuals who theoretically are more likely to benefit from ABM – i.e., individuals with elevated symptoms of depression *and* who exhibit at least modest levels of negatively biased attention. Furthermore, to identify putative mediators of ABM and to test theoretical models of depression symptom maintenance, this study adopts an experimental therapeutics approach and examines whether ABM reduces negatively biased attention and functional connectivity within neural circuits thought to support negatively biased attention (e.g., connectivity between lateral prefrontal cortices and the anterior cingulate cortex [19]). More specifically, we will examine whether changes in negatively biased attention and functional connectivity between the lateral prefrontal cortex and anterior cingulate cortex mediate the effect of ABM on depression symptom severity change, as suggested by our prior work.

Methods

Design

This study is a three-armed, double-blinded, randomized controlled trial (RCT) comparing the efficacy and mechanisms of change for active ABM compared to placebo ABM and assessments only in adults with elevated depression symptom severity and negatively biased attention. Participants randomly assigned to the active ABM and placebo ABM will complete interventions in the clinic and at home a total of 5 times per week during a four-week period. Throughout the intervention period, we will also obtain weekly in-clinic assessments of attention bias, general sustained attention, and depression severity for a total of five assessments (pre-ABM, week 1, week 2, week 3, and post-ABM). Functional

Magnetic Resonance Imaging (fMRI) assessments will occur at pre-ABM, week 2, and post-ABM to assess for changes in functional resting state connectivity. The assessment only condition will complete all of the same assessments on the same schedule without receiving any ABM. The protocol has been reviewed and approved by the University of Texas at Austin IRB.

Hypotheses

Our primary hypothesis is that active ABM will lead to significantly greater reductions in depression symptoms as compared to the assessment only condition. Our secondary hypothesis is that active ABM will significantly reduce negatively biased attention and improve functional connectivity between the middle frontal gyrus (MFG) and anterior cingulate cortex (ACC), a neural circuit that supports control over negatively biased attention [19]. We hypothesize that improvements in negatively biased attention and functional connectivity between the MFG and ACC will mediate the relationship between intervention condition (i.e., active ABM versus assessment only) and change in depression symptom severity.

In our prior work, we have found mixed results for placebo ABM: our first study found no effect on depression symptom severity change [20] and our second study found it was associated with reductions in depression symptom severity [19]. Thus, we do not have a strong hypothesis about the effects of placebo ABM in the current study. We will explore whether placebo ABM is associated with improvements in depression symptoms and whether any observed changes are mediated through changes in sustained attention, as our prior work pointed to this as a possibility [19].

Eligibility

Inclusion criteria: Participants must be willing and able to provide informed consent, be fluent in English, have a Quick Inventory of Depression Severity – Self Report version (QIDSSR) score of 13 or greater, have at least a moderate attentional bias for negative stimuli relative to neutral stimuli (see next paragraph for more detail), and be between the ages of 18 and 40 years of age (age range was restricted to minimize effects of cognitive aging). A QIDS-SR score of at least 13 indicates depression severity at least in the moderate range and is equivalent to a Hamilton Depression Rating Scale – 17 item (HDRS-17) score of 17 or greater [24].

Determining the criterion to define presence of pre-treatment negatively biased attention was challenging, as the reliability of traditional dot-probe assessments have been found to be somewhat lacking (e.g., [25]). This psychometric issue raises the question of whether the traditional dot-probe scoring method can be used to recruit individuals into a study. Thus, prior to starting this clinical trial, we examined one-week stability of several dot-probe eye-tracking metrics to identify a suitable attention bias criterion. Analyses from 85 adults recruited from the Austin community indicated that number of trials where total fixation time was greater for sad stimuli than neutral stimuli had good one-week stability ($r = 0.67$). Further, a criterion of at least 37.5% of trials (36 out of 96) where total fixation time was greater for sad stimuli than neutral stimuli minimizes spontaneous drift from sufficient to

insufficient bias (or the opposite) across a 1-week period (see Section 1.1 of Supplemental Material for more detail). Thus, in order to be eligible to participate in the current study, participants will have to have at least 36 trials where gaze towards sad stimuli is greater than gaze towards neutral stimuli.

Exclusion criteria: Participants will be excluded if they meet criteria for a current substance use disorder (of mild or greater severity), current or past psychotic disorder, or current or past bipolar disorder as determined by the Mini International Neuropsychiatric Inventory (MINI), have any medical or physical conditions that would preclude participation in an fMRI study (e.g., cardiac pacemaker), are currently receiving psychotherapy or electroconvulsive therapy, have psychiatric or neurological medication changes in the 12 weeks prior to study entry, report current opioid analgesics or systemic corticosteroid use for an acute medical condition or taken as needed, or have had suicidal behaviors or significant suicidal ideation, as indicated by positively endorsing question 4 or 5 on the Columbia-Suicide Severity Rating Scale (C-SSRS), within the last six months.

Recruitment

We plan to enroll a minimum of 123 participants in this study (see Analytic Plan for power analyses). Participants will be recruited from paper flyers around the Austin community, as well as from advertisements placed online on social media platforms (e.g., Reddit, Facebook), and advertising websites (e.g., Craigslist, ResearchMatch). Prospective participants will first complete an online screen, including an informed consent form, conducted through Research Electronic Data Capture (REDCap; [26]).

Research staff will then complete a phone interview to provide further information regarding the study and continue the screening process. During the phone interview, research staff will complete the bipolar, substance use disorder, and psychotic disorder modules from the MINI, as well as conduct a suicide risk evaluation via the C-SSRS. Phone screenings will be audio recorded with participant permission for quality control (e.g., assessment consultation and supervision). Participants who meet eligibility criteria will be scheduled for an in-laboratory (pre-ABM) assessment to confirm presence of negatively biased attention and elevated depression severity. The behavioral assessment will be scheduled to occur within one week of the phone screening.

During the in-person baseline assessment, participants will provide written informed consent electronically via REDCap. Participants will then complete a standard dot-probe task including eye-tracking, which will be used to assess negatively biased attention, as well as the QIDS-SR, to confirm that the QIDS-SR remains at 13 or above. Ineligible participants will be provided with mental health resources, compensated for their time, and dismissed from the study. Eligible participants will complete the remaining baseline assessment measures and confirm their availability for the remainder of their participation in this study. Finally, within 48 hours, participants will complete the baseline imaging assessment, after which the participants will be randomized to one of three treatment conditions.

Randomization and blinding

Participants will be randomly assigned using a stratified, random-assignment approach, where each participant will be stratified to one of three treatment conditions based on severity of depression symptoms (QIDS-SR 13 – 17, QIDS-SR >17), antidepressant medication usage (yes, no), and gender (male, female, other). The three treatment conditions are active ABM, placebo ABM, and an assessment-only condition. Prior to data analyses, our study biostatistician (JS) will check for the balance of randomization and control for any factors that are imbalanced.

After participants complete their baseline imaging assessment, the study coordinator (KC) will enter the participant ID and their stratification parameters into a web-based application (Shiny app) written by the study statistician (JS) designed to randomize participants by stratification and automatically enter into the study database a unique random alpha-numeric code for each participant. As a failsafe guarding against experimenter error, if a participant already has an alpha-numeric code assigned, it cannot be overwritten by the program. A function that maps these codes to treatment assignments is embedded in the backend of the web-based training program, so the appropriate intervention (i.e., active ABM, placebo ABM, or no intervention) is automatically delivered to the participant. Additionally, the treatment code is stored within the training program after the initial treatment session, such that any accidental changes to treatment codes for participants after they begin treatment have no impact on the version of the training they receive. Only the study coordinator is provided a table in order to determine whether the participant needs to be scheduled for in-lab ABM trainings (and therefore who belongs to the assessment only condition), but even the coordinator remains blind as to whether participants receive the active or placebo ABM. The assessors, who are responsible for post-baseline clinical assessments, remain blind to all treatment assignments, which can only be decoded by running a separate R script.

The study coordinator will not conduct any assessments after treatment randomization and thus the influence of her unblinding to ABM training condition (placebo, active) on post-baseline clinical assessments will be minimized. Hence, all study staff are double-blinded, either to ABM intervention condition (active, placebo) in the case of the study coordinator or whether the intervention is being administered at all in the case of post-baseline assessors. Only the study statistician (JS) and study programmer (SR) have the ability to look up which experimental condition corresponds to a given treatment code, and they will have no interaction with participants.

Interventions

In both ABM conditions, treatment stimuli include pairs of faces, each from a different actor and each expressing sad and neutral emotions, from the Pictures of Facial Affect (POFA; [27]) collection and dysphoric and neutral images from the International Affective Picture System (IAPS; [28]). Each POFA and IAPS scene will be equalized (12.0 cd/m^2) to match mean luminance distribution. Task-related screens will be matched to mean luminance as well. Each trial will begin with the appearance of a central fixation cross (FC) for 1500 msec, followed by an image pair. POFA pairs will be presented for 3000ms and IAPS pairs will be presented for 4500ms. IAPS images will be presented for a longer duration because

they are typically more complex than the POFA faces. Following offset of the images, a small single or double asterisk probe will appear in the location of one of the images and remain on the screen until the participant indicates whether they detected one or two asterisks, with a maximum duration of 10000 msec. Latency and accuracy of each response will be recorded.

In the ABM conditions, we will manipulate the probability that the target probe appears in the location of the neutral stimulus. In active ABM, the probe will appear in the location of the neutral stimulus 80% of the time. Including trials where the probe appeared in the location of the dysphoric stimulus was designed to keep the intent of the study from being transparent given the longer stimulus duration times and to allow us to compute bias scores from the ABM sessions. In placebo ABM, the target will appear in the location of the neutral and dysphoric stimuli with equal probability (50%). The distribution of targets serves as the critical manipulation whereby participants in active ABM are putatively trained to allocate their attention preferentially to the neutral stimuli and away from the dysphoric stimuli.

The treatment protocol for attention training will consist of twice per week in-clinic ABM sessions and three times per week at-home ABM (not including the days when in-clinic ABM occurred) during a one-month training period. The experiment is programmed in HTML5, Javascript, and PHP 5.6, so that participants can easily train both in-lab and on their home computers. Stimulus presentation and data acquisition is controlled by the Javascript library JsPsych [29], while at-home eyetracking data acquisition is controlled by the Javascript library WebGazer [30]. We will measure eye movements for participants who have a webcam and allow access to it; however, those analyses will be considered exploratory and we will primarily examine the behavioral data from the at-home ABM training.

We will match at-home ABM parameters to the in-clinic training task; hence the stimuli and presentation timing will be the same. However, we chose to shorten the length of at-home training in order to facilitate adherence and completion of training. Specifically, while in-clinic ABM sessions consist of nine blocks of 22 trials [198 trials] lasting approximately 24 minutes, at-home ABM sessions include three blocks of 22 trials [66 trials] lasting approximately 8 minutes. In-clinic ABM sessions include two breaks to reduce participant fatigue, while at-home ABM sessions include no breaks (similar to our recent ABM study [19]).

ABM training begins with an estimate of room luminance by collecting sample images before beginning the task, which are then used to calculate brightness. For participants with a web-cam at home, distance and position along the screen will be controlled using a custom Javascript webcam-based algorithm. Participants will be asked to maintain a position center to the screen at a distance 30–60 cm. If both position and distance are not maintained for a duration window of 10000 msec, this initial calibration attempt will be considered a failure. After two failed attempts or a total duration of 60000 msec, a behavioral version of the same task will instead be employed. The behavioral version of this task will also be used for anyone who does not have a webcam or declines access to it. If initial calibration is successful, a nine-point self-calibration phase used to map eye position to screen

coordinates. To match eye-pixels to gaze locations, the task employs a ridge-regression model that maps gaze to mouse-click locations [30]. During each step, a 200×200 px white-colored ring appears, and participants are required to produce repeated mouse-clicks 20 times before moving to the next step, for a total of 180 calibration samples. This webcam-based approach to eye tracking has been found to be suitably comparable to commercial systems [31] and has already been employed in research on dementia [32] and pupil dilation [33], for example.

Assessment

See Table 1 for the schedule of assessments.

Screening.

Columbia Suicide Severity Rating Scale (C-SSRS; [34]).: The C-SSRS is a clinician-administered interview to systematically assess and track suicidal behavior and ideation. The scale is reliable and well validated in its ability to detect suicide risk [34]. An individual will be deemed ineligible for the study if they report having suicidal ideation with intent (with or without plan) in the last six months.

Mini International Neuropsychiatric Interview (MINI; [35]).: The MINI is a brief, structured, clinician-administered screening interview. The MINI provides accurate diagnoses of a broad variety of mental illnesses for screening of exclusionary/inclusionary criteria. We will use only the sections on psychosis, bipolar disorder, alcohol use, and substance use during the phone screening to determine eligibility. The rest of the MINI will be administered at the baseline visit to help characterize our sample clinically. The MINI has demonstrated acceptable validity and reliability [35].

Primary outcome

Quick Inventory for Depression Symptoms – Self Report (QIDS-SR; [24]).: The primary outcome will be self-reported depression symptom severity, as measured by the Quick Inventory for Depression Symptoms – Self Report (QIDS-SR). The QIDS-SR is a 16-item self-report assessment of depression symptom severity. This brief measure assesses the nine DSM-IV symptom criterion domains for depression and has been shown to be highly reliable, internally consistent, and sensitive to changes in symptom severity [24,36]. The QIDS-SR will be administered on a weekly basis, at every in-lab assessment visit. We will examine the change in QIDS-SR from baseline to end of Week 4 as our primary outcome.

Secondary symptom outcomes—We will utilize two additional symptom severity measures as secondary outcomes, one clinician-administered and one self-report.

Hamilton Depression Rating Scale – 17 item version (HDRS-17; [37]).: This 17-item clinician-administered interview is designed to assess the severity of depressive symptoms. The HDRS-17 has demonstrated acceptable reliability and validity [37,38]. The HDRS-17 will be administered on a weekly basis, at every in-lab assessment. The interview will be administered by trained study staff. Interviews will be audio-recorded with participant permission and a licensed research fellow in clinical psychology will lead weekly

supervision on the administration and scoring of the HDRS-17. Interviewers will also complete weekly fidelity ratings of interviews to track scoring reliability across the team. The research fellow's ratings will serve as a gold standard and reliability will be examined week to week, with any significant deviations in scoring (i.e., more than a 1 point difference from the gold standard) discussed together during supervision. While all clinical staff will conduct baseline HRSD-17 interviews, only clinical staff specifically designated for post-baseline assessments (i.e., not the study coordinator) will conduct subsequent interviews to ensure assessor blinding across all time points.

Mood and Anxiety Symptoms Questionnaire-Short Form (MASQ-SF; [39]).: This 30-item self-report measure examines negative affect that are common to mood and anxiety disorders according to the Tripartite model [39,40]. The measure is well-validated and reliable [39]. It is included as a secondary outcome because it measures depression-related symptoms (e.g., low positive affect, anxious arousal) that are not well represented by the QIDS-SR.

Putative mediators of ABM—In addition to symptom severity measures, we will also measure putative behavioral and physiological mediators of ABM, including negative attention bias, brain-based resting state connectivity, and sustained attention.

Attentional bias.: We will use an eye tracking dot-probe task to measure negatively biased attention. The dot-probe task utilizes affective stimuli not used during ABM. Positive images are also used to determine whether any observed effects of ABM on attention bias transfer to another stimulus category.

Two images depicting an emotional (sad, happy) or neutral facial expression from the Karolinska Directed Emotional Faces (KDEF; [41]) stimuli collection are presented concurrently on the left and right side of visual field. Each trial consists of a fixation cross for 500ms followed by the stimulus pair for 1000ms. The location of the emotion and neutral stimulus will vary randomly. Following stimuli offset, a target probe will appear on screen (either the letter "O" or "Q") in the same location as one of the images, randomized to appear behind the emotional and neutral image with equal frequency.

The task includes 192 trials (96 trials per block) with 12 pairs of sad and neutral images and 12 pairs of happy and neutral images randomly presented four times each within each block of trials. Stimuli will be matched for actor so that the only difference between stimuli pairs is emotion expression. Eye tracking data will be recorded during this task. The primary outcome will be number of trials toward sad stimuli (i.e., percentage of trials where gaze time for sad stimuli > gaze time for neutral stimuli) [42]. However, if advances in research into the psychometrics of the dot-probe task suggest better indices of attentional bias before publication of our data, we will adopt such recommendations accordingly.

Functional connectivity.: fMRI (functional Magnetic Resonance Imaging) data will be acquired using a whole body 3T Siemens Skyra MRI with a 32-channel head coil. The scanning protocol involves collection of a localizer followed by a high-resolution T1-weighted MPRAGE scans from each participant for anatomical co-registration with other

datasets (TR = 2.3 s, TE = 3.08ms, flip angle = 9 degrees, slice thickness = .9mm, 192 slices, FOV = 22cm and matrix size = 256×256 mm), a field mapping standard double echo GE sequence (TE1/TE2 = 5.19/7.65 ms; TR = 300 ms, 48 axial slices, FOV = 35mm, slice thickness = 3mm) and one resting state scan (described below) of 8 minutes using a multi-band image sequence (TR/TE=1500/30ms, 66 axial slices, MB factor = 3, FOV = 22mm, flip angle = 71 degrees, acquisition voxel size = 2×2×2 mm).

Resting state will be our primary fMRI measure, and we will examine the resting state BOLD signal during periods of task-negative mind wandering [19,43]. Prior to the acquisition of resting-state scans participants will be instructed to remain awake and alert and keep their gaze on a fixation cross (+) presented approximately at the center of their field of view for the 8-minute duration of the scan. The primary resting state fMRI assessment will be connectivity across the frontal parietal cognitive control network but with a specific focus on connectivity between the middle frontal gyrus and the anterior cingulate cortex (c.f., [19]). Exploratory assessments include an fMRI version of the sustained attention to response task (SART) and a multishell (B1K and B3K) 216-direction DTI scan (more detail regarding the exploratory SART and DTI scan is provided in the Supplemental Materials, section 1.2).

Sustained attention. The psychomotor vigilance task (PVT; [44]) will be used to assess sustained attention, which we speculate could serve as a mediator of change for the placebo ABM. The PVT is a high signal-load reaction time test in which participants attend to a small rectangular area at the center of a computer screen. At random intervals, a bright millisecond timer appears in the center of the rectangle (2 to 10 second inter-trial intervals). Participants are instructed to respond via button press as rapidly as possible upon detection of the counter stimulus; participant response stops the counter from updating. The final counter value corresponds to the participant's RT and is displayed on-screen for 1 second, thus providing feedback for that particular trial. Two metrics are particularly sensitive to sustained attention in a neurologically intact population and will be the focus of this investigation – number of lapses and RT for the fastest 10%.

Treatment credibility. For this study, the Credibility/Expectancy Questionnaire (CEQ; [45]) has been adapted to examine how credible participants believed their intervention to be. Example items include “At this point, how logical does the treatment offered to you seem?” and “At this point, how successful do you think this treatment will be in reducing your depressive symptoms?” Given previous research that has suggested credibility is a strong predictor of ABM treatment outcome [46], we want to examine to what extent reduction in depression symptoms was associated with credibility.

Analytic plan

Sample size estimation. As we expect effect sizes for ABM on proximal targets (attention bias, right medial frontal gyral-dorsal anterior cingulate cortex (rMFG – dACC) resting state functional connectivity, or sustained attention) to be greater than for the more distal target (depression change), we assume the latter to be the limiting constraint. Therefore, we

conducted a power analysis to determine the sample size needed to detect a difference in depression symptom severity change.

To calculate the sample size requirements for linear models of these longitudinal data, we used methods outlined by Diggle et al. [47] and implemented in the R *longpower* package, which contains functions for translating pilot mixed effect model parameters (e.g. random intercept and slope) into marginal model parameters. These methods are specifically tailored for randomized placebo controlled studies in which the primary outcome of interest is the interaction of treatment and time in a linear mixed effects model.

To estimate the time-series correlation and covariance matrices of the assessment-only group, we used the first month of data collected from a previous longitudinal study where depression symptoms were measured on a weekly basis with no intervention [48]. Because this naturalistic study used the CES-D to measure depression symptoms and our prior ABM study used the BDI-II, we first converted the CESD measurements into predicted BDI measurements [49]: $BDI = 1.13 + (.68) * CESD$. Calculations based on the equations provided by Diggle and colleagues [47] employing data from the naturalistic study [48] and our prior ABM study [19] then determined the sample size needed to reject the null hypothesis that the mean rate of improvement for the trained groups will be equal to that of the assessment-only group, given a group difference in slopes of 1 point per week, 5 weekly observations, a variance of random slope equal to 1, a residual variance equal to 13.2, a type-one error rate of $\alpha = 0.05$, and 80% power. This is the equivalent to being able to detect a medium effect, although our pilot data [48] suggests that the effect may be larger. We nevertheless used a medium effect for power analyses ($d = 0.5$), given the difficulties associated with using pilot studies to accurately estimate effect sizes for power analyses [50]. Given these assumptions, to test our hypothesis that the active ABM intervention significantly reduced depressive symptoms compared to the assessment-only group, we will require 37 participants per group for a total of 111. To buffer for an estimated dropout rate of 10%, we plan to enroll 123 participants. If possible, we will recruit additional participants to increase statistical power.

Handling missing data.: In dealing with missing data, we first recognize two kinds of missing data that may arise: 1) intermittent missing values due to an invalid data point or participant non-response and 2) longitudinal missing values due to participant dropout, i.e., all data are missing after a certain time point. In the case of intermittent missing values, since the corresponding participants remain in the study, we should be able to ascertain the reasons for missingness and verify that they are unrelated to the measurement process, in which case the maximum-likelihood-based analyses we have planned (linear mixed effects regression for the primary outcome and longitudinal mediation SEMs) can accommodate missing values and produce valid inferences based on all available data [47,51,52]. Our primary analyses will follow this “ignorable likelihood” approach. In the case of dropouts, however, we may not be able to ascertain the reasons for drop out, and we will follow best-practice recommendations to perform a sensitivity analysis of how departures from the missing-at-random (MAR) assumption might alter our findings [53]. To accomplish this, we will use a version of multiple imputation by chained equations for performing sensitivity analysis as implemented in the R package *SensMice* [54].

Data management.: In order to monitor participant adherence to daily trainings, a training dashboard will be implemented. The dashboard will display whether trainings have been completed across all enrolled study participants. Participants will be contacted by email or phone if they fail to complete two consecutive days of training. Additionally, as a safeguard for any potential data loss, all raw and processed behavioral data will be backed up and stored in a cloud server on a weekly basis.

Primary analyses.: Our primary aim is to examine whether ABM significantly reduces depression symptoms as assessed by the QIDS-SR. The focus of the analysis will be on differences in the rate of change of depression symptoms over the course of the study, which will be analyzed using mixed-effects regression models. We will perform a linear mixed effects analysis using the R package *lme4*. Analyses will test the main effects of time and training condition, as well as how individual time series vary by treatment group (treatment $\times$ time interaction), using random intercept and slope to account for each individual's distinct baseline profile and rate of change.

Secondary analyses.: Our secondary aim is to identify mechanisms responsible for the putative efficacy of active and placebo ABM. For active ABM, we will test whether improvement in negatively biased attention and/or improvement in MFG-ACC resting state connectivity mediates the association between intervention condition (active ABM vs. assessment only) and change in depression symptom severity. Further, we will examine whether improvements in general sustained attention mediates the efficacy of placebo ABM (vs. assessment only) for change in depression symptom severity. Importantly, we will conduct parallel analyses that examine whether the alternative putative mediator is similarly responsible for improvement in the other ABM condition. That is, we will examine whether improvement in sustained attention mediates the effect of active ABM on depression change and whether improvement in negatively biased attention mediates the effect of placebo ABM on depression change. These analyses will address important questions regarding mechanistic specificity for each form of ABM.

To test for mediation, we will use autoregressive models, a longitudinal mediation model that takes advantage of the temporal information from the five waves of repeated assessments (pre-ABM, week 1, week 2, week 3, and post-ABM), to provide more accurate conclusions about mediation. In essence, the mediation hypothesis is strengthened if changes in negatively biased attention and/or general sustained attention temporally precede changes in depression symptoms.

We will first assess mediation based on structural equation modeling (SEM) for the system depicted in Figure 1 which allows for both longitudinal ($a \times b_2$) and contemporaneous ($a \times b_3$) mediation (to simplify the figure, the time points for weeks 1–3 are compressed into a single feature, but in the actual model the same system of equations will repeat between weeks).

In this model, the c' coefficient reflects any effect of training on depression not mediated by attention bias reduction (i.e., through some other mechanism). Each variable depends not only on the a and b paths, but also on autoregressive effects (the s paths), meaning that each

variable is also predicted by the same variable at an earlier wave. Thus, the s_1 and s_2 coefficients reflect the stability of individual differences in attention bias/sustained attention and depression, respectively. This corresponds to a type II autoregressive model as described by MacKinnon [55].

The parameters of this model will be estimated using a covariance structure analysis program (the *OpenMx* package in R). Mediation effects will be considered significant if the 95% confidence interval for the product of the path coefficients a and b does not include 0. Because the $a \times b$ distribution is typically skewed, these confidence intervals are expected to be asymmetric and will be estimated by bootstrap. Assumptions for multi-wave models (stability, stationarity, and equilibrium) will be verified as discussed by MacKinnon [55]. For planned exploratory imaging analyses, see Section 1.3 of Supplementary Materials.

Discussion

This study is the first large-scale randomized clinical trial of attention bias modification for depression in adults. The trial serves to directly test the hypothesis that negatively biased attention maintains depression by targeting this process in a sample that should theoretically be most likely to benefit from this type of intervention: adults with elevated depression symptoms and negatively biased attention. Furthermore, this clinical trial assesses several candidate mechanisms that could mediate the effects of ABM on depression symptoms. Some aspects of the study required extended consideration; we outline our rationale for these aspects of trial design below.

Selecting based on treatment target versus moderator analyses

We considered recruiting a sample of participants simply elevated in depression severity and examining how baseline attentional bias moderated treatment response. However, sample sizes for such studies of moderation are often significantly underpowered, especially when the effect size for interactions may be smaller than main effects¹ [57]. As we are specifically interested in testing the hypothesis that negatively biased attention maintains depression, selectively recruiting individuals with at least a modest attentional bias toward negative stimuli would be a more effective and better powered approach to testing this hypothesis [58]. Future work with larger samples, perhaps with multi-site recruitment, could examine whether baseline negative attention bias moderates the efficacy of ABM for depression.

Intervention design and dosing

In previous studies of ABM for depression, the placebo ABM condition has [19] and has not [20,21] been associated with depression symptom reduction. It is unclear whether the potential therapeutic impact of placebo ABM is due to non-specific effects (e.g., staff interaction, regular clinical assessments, spontaneous remission) or due to improvements in other processes (e.g., sustained attention). It is notable that placebo training has led to symptom improvement in other forms of psychopathology, such as PTSD [59]. Accordingly,

¹Simulations have suggested that if the interaction effect size was half the size of the main effect, detecting this effect at 80% power would require 16 times the sample size compared to the main effect. Even if the effect size for the interaction and the main effect were the same (though this may be unlikely [56]), detecting the interaction would require four times the sample size of the main effect.

we included an assessment only condition to examine potential non-specific effects and also assessed other candidate processes that might underlie improvements in depression symptoms in placebo ABM (see below).

In designing our intervention, we looked to previous research examining aspects of trainings targeting cognitive biases such as negatively biased attention. Prior work in depression has suggested that utilizing negative images, as opposed to negative words, has a stronger training effect for ABM [60]. Accordingly, we employed negative and neutral training stimuli consisting of faces and images. Using both faces and images also allowed us to increase the variety of content participants viewed during the training stimuli. Furthermore, we selected facial stimuli from a different database than the database used for our measurement of attentional bias, in order to reduce potential training effects due to re-exposure of stimuli.

Another consideration centered on the dosage of training offered to participants. Evidence is accumulating in other cognitive training domains that repeated training is critical for obtaining sustained cognitive improvement ([61,62]; though see [63] for additional discussion of appropriate training dosage). We therefore require participants to come in to the clinic for training a total of twice per week for four weeks, as well as complete briefer trainings at home three times per week (outside of the days the participant is coming into the clinic for training) for four weeks. Our previous research has found that participants were able to maintain good training compliance on a schedule of three times per week (once at home and twice in clinic; [19]). Our training therefore does not represent a substantial increase in burden for participants yet has the potential to produce more robust training effects. We plan to perform sensitivity analyses to determine whether the amount of ABM completed was associated with changes in symptom severity.

Study Risks

For individuals with moderate to severe symptoms of depression, enrolling them into a condition that only provides assessment, and not treatment, may be of potential ethical concern. However, as participants enrolling in our study will not be in therapy currently and, if on antidepressant medication, still express depression symptoms of at least moderate severity despite having been on a stable dose for at least 12 weeks (see Eligibility), weekly assessments by trained study staff likely represents a higher level of clinical “care” than they will be receiving. Our Data Safety Monitoring Board will also oversee the study to ensure the safety of participants in each condition. This committee will meet annually and discuss any human subject concerns (e.g., breaches of confidentiality, adverse events). They will also review changes in symptom severity across conditions with the study statistician (JS) to review whether any conditions result in a significant worsening of symptoms and merit removal of that condition. Beyond these larger, study-wide considerations of risk, this clinical trial includes a number of measures to minimize individual risk.

To minimize risk for each participant, during the consent process we will highlight the potential risks associated with this study (e.g., emotional discomfort and scanning risks) and how this study addresses these potential risks. In addition, we note that participation is voluntary and that they may choose to seek clinical services in lieu of participating. In such

cases, we provide individuals with a list of local mental health resources. If patients drop out, we will assess why and if these reasons include worsening of clinical symptoms, provide resources. At the end of the study, regardless of condition, if a participant has not improved or has endorsed needing additional clinical resources we will provide help with clinical referrals. Finally, all participants are regularly assessed with clinical interviews by trained research assessors that can detect and respond to clinical crises (e.g., suicidal behavior). If participants endorse imminent risk to harm themselves or others, we will implement a standardized risk protocol, withdraw them from our study, and ensure they receive immediate, appropriate attention.

Selection of additional potential treatment mechanisms

Although altering negatively biased attention is the putative mechanism underlying efficacious ABM, exploratory analyses with an efficacious placebo ABM condition in our previous work has also suggested that improvements in non-valenced aspects of attention may underlie the treatment response observed in placebo ABM. In particular, for individuals receiving placebo ABM, improved connectivity between the right middle frontal gyrus and precuneus (associated with spatial shifting of attention; [64,65]) and between bilateral regions of the orbital frontal cortex (associated with sustained attention; [66]) predicted symptom reduction. These associations were not observed in the active ABM condition. Consequently, we included a behavioral measure of sustained attention to also examine the possibility that altering sustained attention may be a mechanism underlying efficacious placebo ABM.

Conclusion

Despite cognitive models of depression positing that negatively biased attention maintains episodes of depression, few studies have directly tested this hypothesis, much less in a randomized clinical trial in adults. This clinical trial examines whether ABM is efficacious for adults with elevated depression severity exhibiting at least a modest attentional bias for negative stimuli. This trial also assesses factors that may underlie treatment response, including reductions in negatively biased attention, non-specific effects due to enrollment in a clinical trial, and strengthening of non-valenced attentional processes. Identifying and refining efficacious treatments for depression is critical for addressing this public health problem. Importantly, many depressed patients prefer non-pharmacologic treatments but often have difficulty accessing such treatment [67]; the findings from this clinical trial may point to an efficacious, nonpharmacological treatment that is highly accessible to the public and provide a critical test of whether a theoretically important construct, negatively biased attention, maintains symptoms of depression.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Funding acknowledgement

This study is funded by NIMH grant MH109600. The funding source has no involvement in the study design, analysis and interpretation of the data, writing of the report, or the decision to submit the article for publication.

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Figure 1. Mediation model that examines longitudinal and contemporaneous mediation of ABM on depression symptom change.

Table 1.

Schedule of Assessments

Visit	Screen	Baseline	Week 1	Week 2	Week 3	Week 4 (End of Treatment)
Day	-7 to -1	0	7	14	21	28
Informed consent	X	X				
Attention bias (eye tracking)		X	X	X	X	X
fMRI/DTI		X		X		X
HAMD, QIDS-SR, MASQ		X	X	X	X	X
C-SSRS		X				X
PVT		X	X	X	X	X
Treatment credibility		X				