Effects of Attentional Bias Modification on Residual Symptoms in depression. A Randomized Controlled Trial.

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Objective: Following treatment, many depressed patients have significant residual symptoms. However, large randomised controlled trials (RCT) in this population are lacking. Attention bias modification training (ABM) can modify biases in emotion processing and may lead to symptom relief. We hypothesized that two weeks of ABM training would reduce clinician rated and self-reported residual symptoms and that change towards more positive attentional biases (AB) would be associated with symptom reduction.

Method: A total of 322 patients with a history of depression were included in a preregistered randomized controlled double-blinded trial. Patients were randomised to an emotional ABM paradigm over fourteen days or a closely matched control condition. Symptoms based on the Hamilton Rating Scale for Depression (HRSD) and Beck Depression Inventory II (BDI-II) were obtained at baseline and after ABM training. The primary outcome was change in HRSD and BDI-II. Participants were assessed for AB before and after the intervention.

Results: ABM training led to significantly greater decrease in clinician rated symptoms of depression as compared to the control condition. No differences between ABM and placebo were found for self-reported symptoms. ABM induced a change of AB towards more positive versus neutral stimuli with a more positive bias being associated with greater symptom reduction.

Conclusion: The current study demonstrates that ABM produces early changes in both AB and residual depressive symptoms. ABM may have practical potential in the treatment of residual depression.

Trial Registration clinicaltrials.gov Identifier: NCT02658682.

A wide range of treatments are available for depression. However, systematic reviews point to limited efficacy in terms of remission, response rates and long- term effects for both pharmacological [1] and psychological treatments [2]. Forty percent of patients do not, or only partially, respond to treatment, and less than one third are completely recovered after treatment [3]. Residual symptoms following treatment are associated with decreased return to function, reduced quality of life and increased risk of recurrence highlighting the need for further intervention [4].

There is an interest in using a mechanistic approach, i.e. using knowledge of the causative processes in mental illness, to guide the development of novel interventions which target those processes [5-7]. Depression is associated with an increased focus on negative interpretations of events and negative biases in attention and memory. Previous studies have reported that clinically depressed subjects orient their attention toward negative faces rather than neutral or positive faces [8]. Biases towards negative faces have also been reported in previously depressed, currently euthymic subjects [9], and in never-depressed individuals with a family history of depression [10]. In a seminal experimental study MacLeod, Rutherford, Campbell, Ebsworthy, Holker [11] demonstrated a causal role for negative attention biases in the expression of depressive and anxious symptoms in healthy individuals. They found higher levels of anxiety and depression related mood ratings in undergraduates, as a reaction to a stressor, after being trained to preferentially attend to negative versus neutral stimuli. Together these results indicate that negative attentional biases may constitute causative, vulnerability and maintenance factors rather than simple markers of lowered mood. This suggests that interventions designed to reduce attentional biases may act to reduce residual symptoms in patients treated for depression.

Computerized Attention Bias Modification procedures (ABM) that aim to shift emotional bias are low on resource requirements and easy to disseminate and might therefore be widely used by patients with residual symptoms or while waiting for more resource intensive interventions like psychotherapy. While some studies have reported an effect of ABM in depression a number of meta-analyses have suggested a small effect size, although definitive conclusions have been limited by small sample size and poor trial methodology employed in many studies [12-14]. In addition, some potential techniques for altering attentional bias have failed to modify attentional biases as part of the treatment programme, which limits their ability to decrease depressive symptoms [15,16]. However, when ABM leads to measurable positive changes in emotional biases, associated changes in clinical symptoms have more often been reported [17-20].

The main objective of our study was to test the early efficacy of ABM in a large group of previously depressed patients, using a preregistered trial design. We hypothesized that two weeks of ABM training would reduce clinically- and self-reported residual symptoms of depression, as compared to a matched control condition.

Given the clear mechanistic role for altered bias in the clinical effects of ABM, we predicted a change towards more positive biases in the ABM group compared to control

and that this change would be associated with decreased residual symptoms within the ABM group.

METHOD

Study design and Procedure

Patients who had previously been identified as suffering from depression, and did not currently meet diagnostic criteria for depression, were randomised to receive two weeks of either positive or control ABM. Participants completed two sessions of ABM daily using laptops provided by the research team. A detailed calendar was used to specify the scheduling of the training sessions for each participant. Symptoms of depression and attentional bias were assessed at baseline and immediately after the intervention.

Participants

The main recruitment base was an outpatient clinic in the Department of Psychiatry, Diakonhjemmet Hospital in Oslo. Participants were also recruited from other clinical sites, by local advertisements, and via social media. Candidates were pre-screened by phone for exclusion criteria before in person formal clinical evaluation and enrollment. Individuals diagnosed with current- or former neurological disorders, psychosis, bipolar spectrum disorders, substance use disorders, attention deficit disorder, and head trauma were excluded.

A total of 377 participants between 18-65 years old were recruited for clinical evaluation. Participants had experienced more than one previous episode of depression as defined using the MINI. A total of 55 subjects were excluded following the clinical evaluation (see flow chart for details).

A total of 322 participants with a history of Major Depressive Episodes (MDE) were randomised to receive positive or control ABM. Thirty-seven participants who fulfilled the M.I.N.I 6.0 criteria for current MDE were enrolled onto the study in error (current MDE was an exclusion criteria). Inclusion of data from these participants did not influence the results (see supplementary analysis).

Written informed consent was obtained before enrollment. The study was approved by The Regional Ethical Committee for Medical and Health Research for Southern Norway (2014/217/REK Sør-Øst D).

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Attention Bias Modification Procedure

The ABM task was a computerized visual dot-probe procedure adopted from [17]. Paired images of faces (the stimuli), were presented followed by one or two dots (a probe), which appeared behind one of the stimuli. Participants were required to press one of two buttons as quickly as possible to indicate the number of dots in the probe. The types of

stimuli used during the ABM task were pictures of emotional faces of three valences; positive (happy), neutral, or negative (angry and fearful). A single session of the task involved 96 trials with equal numbers of the three stimulus pair types. In addition, there were equal numbers of trials in which the stimuli were randomly presented for 500- or 1000 ms before the probe was displayed. In each trial of the task, stimuli from two valences were displayed, in one of the following pairing types: positive-neutral, positive-negative, and negative-neutral. In the ABM condition, probes were located behind positive (valid trials) stimuli in 87 % of the trials, as opposed to 13% with probes located behind the more negative stimuli (invalid trials). Thus, when completing the ABM, participants should learn to deploy their attention toward positive stimuli, and in this way develop a relatively more positive attentional bias. The neutral ABM control (placebo) condition was identical in every respect, other than the location of the probe, which was located behind the positive (valid trials) stimuli in only 50% of the trials. Participants completed two sessions (96 trials) of ABM daily during the course of fourteen days (28 sessions in total) on identical notebook computers that were set up and used exclusively for ABM-training.

Measurement of Attentional Bias

Attention bias was measured at baseline and after two weeks of ABM using a standard visual probe procedure consisting of 96 trials, with the same trial types as used in the ABM procedure. Novel facial stimuli were used in the assessment tasks. Attentional bias was calculated as the difference in reaction between trials in which the probe replaced the relatively more negative face vs. the more positive face. Thus a more positive score reflects a greater bias towards the more positive stimuli.

Randomization and blinding

An independent lab technician (not involved in the day to day collection of data) prepared training computers to deliver either ABM or placebo treatment according to a randomization list in a 1:1 ratio ensuring that allocation was concealed from all researchers involved in screening procedures and all participants. Allocation to intervention is stored in the ABM raw data file (together with reaction times) that was opened and merged with screening data for statistical analyses after the data collection period was finished.

Study outcome

The Hamilton Rating Scale for Depression (HRSD) [21] and Beck Depression Inventory (BDI-II) [22] were administered to assess both rater - and subjective evaluations of symptom severity. Comorbid anxiety symptomatology was screened by the use of The Beck Anxiety Inventory (BAI-II) [23] (Figure 1.).

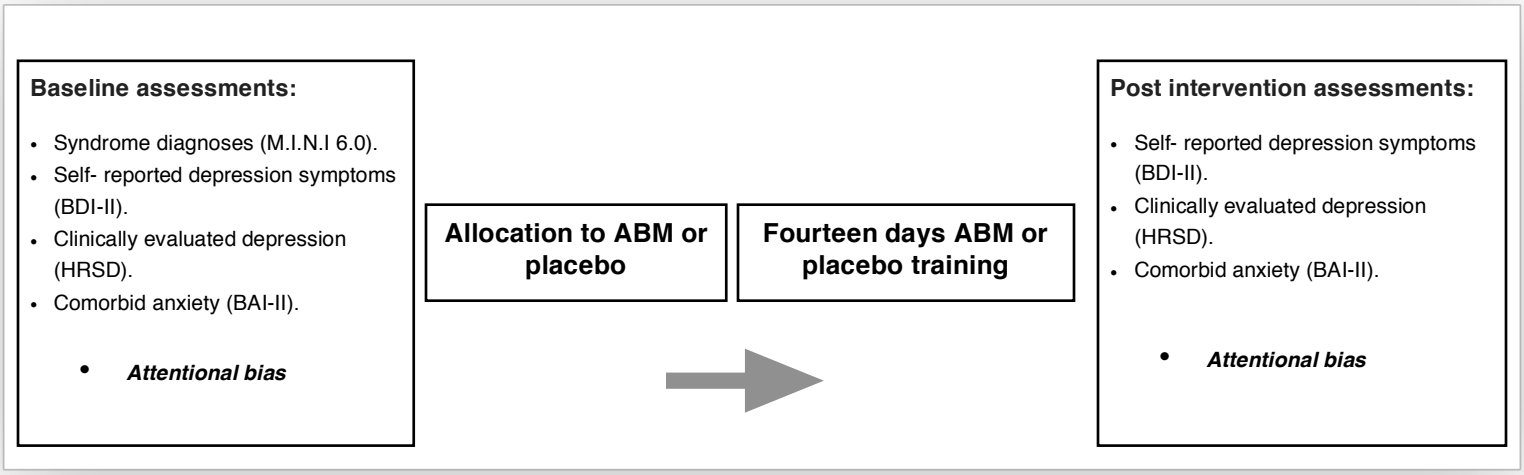

Figure 1 The procedures and primary outcome variables for the clinical trial. Attentional bias is measured at baseline and post intervention based on the dot-probe task.

Statistical analysis

All data were analyzed using PASW 23.0 (IBM). The primary outcomes were analysed using univariate ANOVAs with intervention (ABM versus placebo) as a fixed factor, symptom differences (HRSD or BDI-II) from baseline to follow-up were the dependent variables, and baseline symptom level (using the same measure) was entered as a covariate. As two primary outcome measures were specified, the threshold for statistical significance was set at .025. Analyses per protocol for primary outcomes were provided as supplementary information.

A requirement of the overseeing ethical committee was that study participants could elect to have all data stored on them during the study erased (i.e. including randomisation information) which precludes imputation of missing data. Of the 20 participants who did not complete the study following randomisation, 10 elected to have their data erased and thus data was imputed only for the remaining 10.

Group differences in attentional biases, time (pre-post) and stimulus face pairing or duration were explored using a repeated measure ANOVA. Thereafter, the predicted association between symptom reduction and more positive attention was explored between and within groups with linear regression models. A detailed description of procedures for data reduction, imputation and a post hoc analysis of the potential impact of noncompliance are provided as supplemental information.

RESULTS

Sample characteristics

	Placebo (n=149)	ABM (n=153)	p-value
Age	41.5 (13.6)	40.2 (12.7)	.688
Gender (females)	103	109	.688
Education Level (ISCED)	5.9 (1.2)	6.0 (1.1)	.799
Medication (SSRI)	43	38	.430
Number of previous MDE	4.1 (4.6)	4.1 (4.9)	.922
Symptoms at baseline:			
BDI-II	13.6 (9.8)	15.0 (10.6)	.234
HRSD	8.3 (5.1)	9.2 (6.0)	.121
BAI-II	9.0 (7.4)	9.6 (9.4)	.543

Table 1 Demographic and sample characteristics. MDE=Major Depressive Episodes according to M.I.N.I. SSRI= any current usage of an antidepressant belonging to the Selective Serotonin Reuptake Inhibitors. ISCED= International Standard Classification of Education. P-values from Pearson Chi-Square test are presented for dichotomous variables.

Primary outcomes

There was a main effect of ABM on baseline corrected changes in HRSD scores. The ABM group showed statistically significant symptom improvement (M=1.08 (5.29)) when compared to the control condition (M= -.48 (4.60)) [$F(1,311) = 5.67$, $\eta^2 = .02$, $p = .02$] (95% CI .2 – 2.3, $p = .02$).

There was no statistically significant difference in self-reported depression as measured by the BDI-II between the ABM (M =3.42 (6.24)) and the control condition (M=2.40 (6.26)) [$F(1,311) = 1.47$, $p = .22$]. However, both ABM and placebo showed statistically significant pre-post (time) improvement based on the BDI-II [$F(1,311) = 67.30$, $\eta^2 = .18$, $p = < .001$].

Symptom changes after ABM

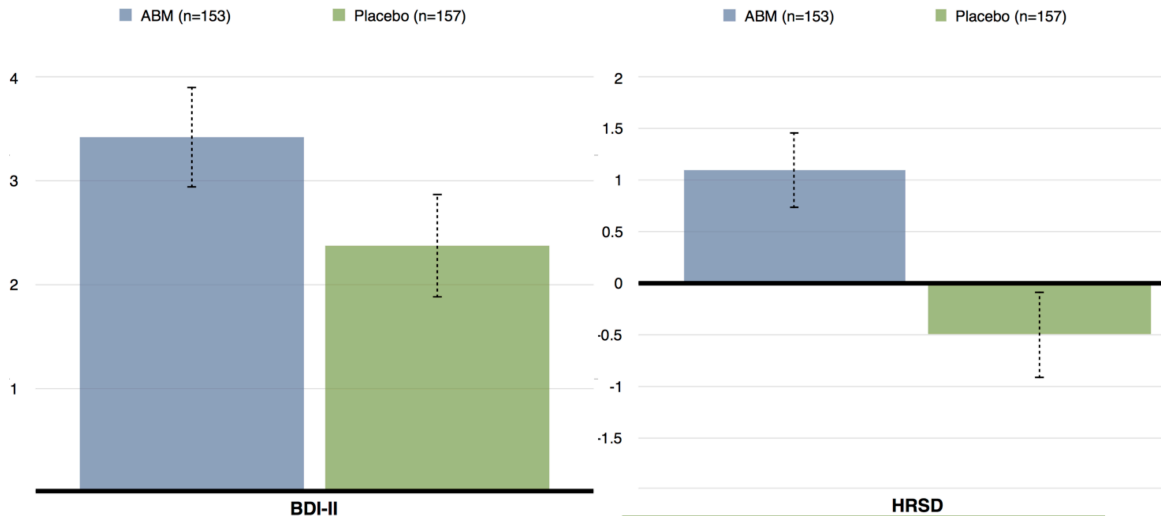

Figure 2 The mean symptom improvement (post- minus baseline) in ABM and placebo after 2 weeks of training for HRSD (left) and BDI-II (right). Whiskers represent +/-1 standard error.

Changes in attentional bias and relationship to clinical symptoms

There was a statistically significant interaction between time x face pairs (positive versus neutral, negative versus neutral, positive versus negative) x intervention (ABM versus placebo) that showed ABM produced a pronounced modification towards more positive versus neutral stimuli [$F(2,300) = 3.278$, $p = .04$]. Follow-up repeated measures ANOVAs of each of the three face pairs revealed a significant effect of ABM for positive versus neutral stimuli [$F(1, 301) = 5.390$, $p = .02$] and was not present for neutral versus negative stimuli [$F(1, 301) = 1.307$, $p = .254$] or in negative versus positive stimuli [$F(1, 301) = .273$, $p = .602$] (Figure 3). Stimulus duration (500- or 1000 ms) did not interact with time and intervention [$F(1, 301) = .386$, $p = .535$].

Interaction between ABM and stimulus valence

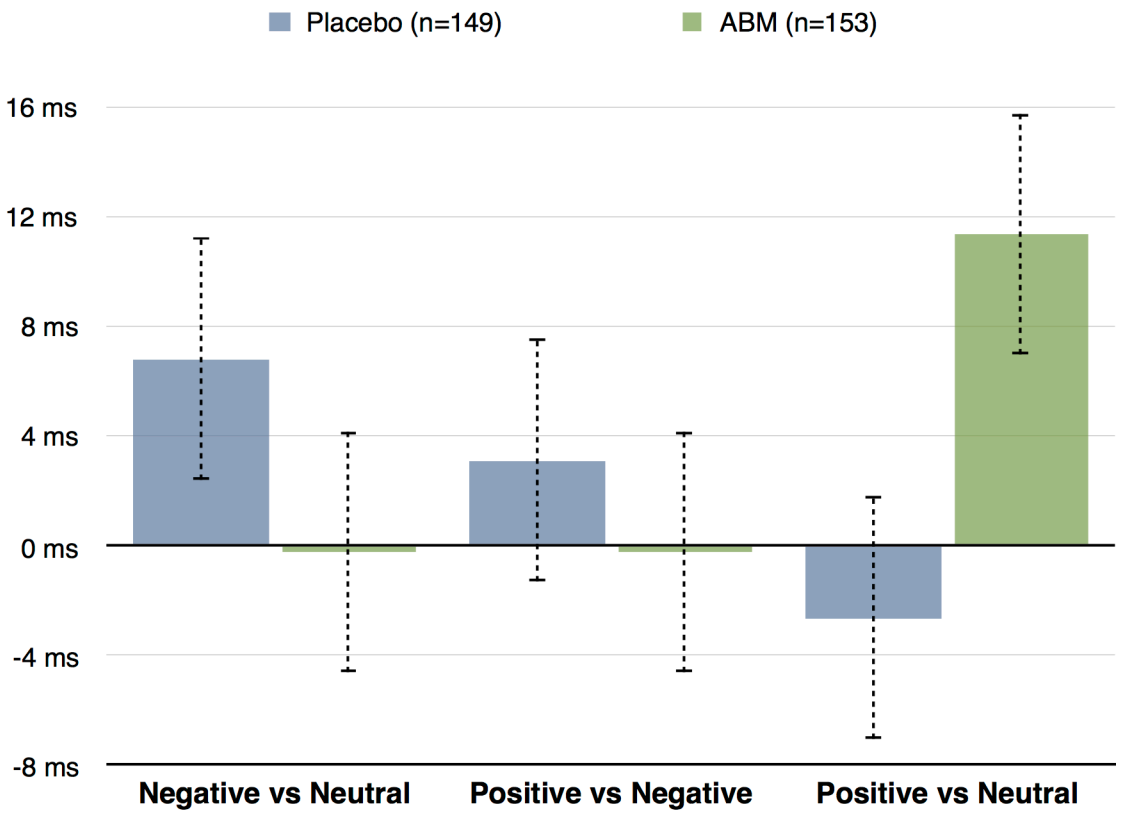

Figure 3 Effect of ABM on attentional bias. Mean of the change in bias scores between baseline and week 2 shown separately for the three face pair types and the two training groups. Time is displayed by pre-post AB difference for illustrative purposes. Whiskers represent +/-1 standard error.

There was a linear relationship between total positive changes in AB and improvement in depression symptoms as measured by the HRSD, meaning that symptom improvement increases with degree of positive modification of negative bias independent of face pairing. The regression model showed that total AB (Beta= .13, p = .01) was a statistically significant predictor for symptom improvement. Adding ABM versus placebo to the model showed that the association between HRSD and AB was uniquely explained only by the intervention (Beta= .12, p <= .02). The interaction between intervention and AB was not associated with symptoms change. The overall model fit was R^2 = .17. However, when considering the within group effects there was a statistically significant positive association between total AB and HRSD in the ABM group (Beta = .17, p = .018) that was not present in the placebo group (Beta= .07, p = .390) A post-hoc exclusion of 2 potential outliers (HRSD change <= 20) did not explain this association found within the ABM group (Beta= .19, p = .015) (Figure 4.).

Symptom reduction and attentional biases

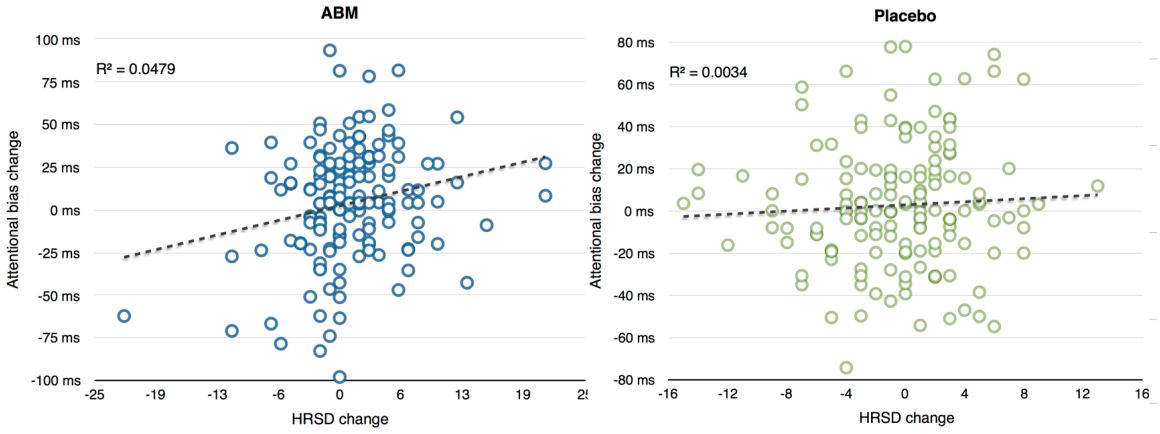

Figure 4 Relationship between change in HRSD and AB (total AB difference pre-post ABM training) across treatment. Data for the placebo group (left) and ABM group (right) are shown separately.

DISCUSSION

Two weeks of ABM training significantly reduced clinically rated (though not subjective) residual symptoms as compared to a control condition in a group of previously depressed patients. There was significant positive change in AB for positive versus neutral stimuli in the ABM group compared to the control condition. Corroborating cognitive models of emotional disorders, the degree of symptom improvement increased with degree of positive bias modification within the ABM group. A larger intervention independent effect was also found for self-reported residual symptoms.

In addition to being among the strongest predictors for recurrence in depressive disorder [4] residual symptoms also cause significant functional impairments, manifested in a variety of domains, including work and leisure activities [24]. The latter is important because one aim of depression treatment is to restore the patients' previous level of functioning. However, residual symptoms in depression have traditionally not been the target of treatment trials. Given the recurrent nature of the illness, we suggest that this should change and that our study provides an example of how this may be done.

A specific effect of the ABM intervention on attentional biases for positive versus neutral faces was seen in the current study. In contrast to the specific effect of ABM on measures of AB, the relationship we observed between change in AB and symptom improvement was found to be general across stimuli valence suggesting patients' symptoms are associated with general rather than specific negative bias.

It is not clear why ABM versus placebo did not differ as measured by the BDI-II self-report scale. Recently, Beevers, Clasen, Enock, Schnyer [25] recruited fifty-two

participants with MDE for ABM training and found a similar significant change in BDI-II in both the ABM- and placebo group. Self- report may be more influenced by placebo or expectation effects. A general pre-post (time) effect of the intervention, as found for self-reported symptoms may also be linked to cognitive training effects present in both the ABM and placebo condition. An assessment only group will help in distinguishing placebo- from ABM in future studies.

Participants completed the training in their homes, which is an advantage as it makes it more feasible as a treatment. Furthermore, compliance was high (see supplemental results) which is important and contrary to the conclusion in a recent review of meta-analyses [14]. These authors conclude that ABM paradigms are most effective when delivered in the laboratory rather than at home. Specifying the scheduling of the training sessions individually might have increased motivation to do and focus on the task.

The results suggest that ABM does indeed exert an immediate, although small, effect on clinician rated symptoms. The finding would be considered clinically non significant in treatment trials. However, it is not clear how to interpret relevance of small HRSD score changes in this group. It is unclear whether the effect of ABM would increase if treatment continued for longer. Although residual symptoms are predictive of risk of relapse, it will be important to test in longer-term prevention studies whether the small observed beneficial effect of ABM could translate into clinical relevance like reduction of relapse.

There is a pressing need to improve treatment and thus clinical trials should focus not only on efficacy, but also on identification of the underlying mechanisms through which treatments operate [26]. We observed a number of people with large changes in AB that go along with symptoms improvement, but also with no change in HRSD or even worsening of HRSD scores. Identification of this individual variability may be useful in evaluations of treatment efficacy and in personalized treatment.

The study has several limitations that should be mentioned. Sparse research on this population impede calculations of sample sizes from prior studies but would further increase the stringency of the study design in accordance with CONSORT guidelines [27]. Inclusion of 37 patients that also fulfilled the formal criteria for current depression represents a deviation from the pre-registered protocol. However, including current depression did not explain the results and increases the generalizability of the reported findings. Previous studies have reported a mixture of positive and negative findings [17,18,28,29] leading to a degree of scepticism about the impact of ABM on symptoms of depression [12]. The current study gives a broader and more transparent picture of the true advantage of ABM in depression. Our study is by far the largest randomized controlled clinical trial of Attention Bias Modification in a depressed population. Analysis of the data from the current study followed a pre-specified protocol and used an intention-to-treat framework further increasing confidence in the results.

In conclusion, two weeks of ABM training reduced clinically-, but not self-, reported residual symptoms of depression. The results verify the proof of principle and suggest that ABM may have practical potential in the treatment of residual depression.

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Conflicts of interest: CJH has received consultancy fees form Johnson and Johnson Inc, P1 vital an Lundbeck. MB is employed part time by P1 vital Ltd and owns shares in P1 vital products Ltd. He has received travel expenses from Lundbeck for attending conferences. NIL has received consultancy fees and travel expenses from Lundbeck.

Supplemental information

Data reduction and compliance rates

Bias scores were calculated based on median reaction times. We choose to clean data for reaction times below 200- and 2000ms in accordance with recent literature that have aimed to grasp temporal stability in AB [30]. The mean total trials included after applying the filter was 97.25% (,04%) in the placebo group and 97.23% (.02%) in the ABM group and did not differ between the groups [F (1,301) = .003, p = .958]. A second filter was used to exclude incorrect responses. The filter affected the placebo group by leaving 99.45% (.007%) and also 99.45% (.008%) in ABM group for further analyse and did not differ between ABM and placebo [F (1,301) = .002, p = .962]. A total of 13 participants lacked either pre- or post ABM data that form the basis for the calculation of bias scores. The series mean was used as imputation method for missing data.

Optimal ABM compliance was ensured using a calendar system describing the ABM training that was scheduled individually before the intervention. Compliance rates for the primary outcome measures per protocol (BDI-II and HRSD) were 100%.

Compliance rates (percentage of max 2688 trials) did not differ between ABM (M=83.5 (14.8)) and placebo (M=80.0 (21.2)) [F (1,301 = 2.731, p = .099]. A post hoc analysis restricted to participants with compliance above 50% (ABM n=147, placebo n=133) did not affect the association between HRSD and ABM (M=85.4 (11.5)) versus placebo (M=86.4 (10.4)) [F (1,301) = 6.265, η^2= .02, p = .013].

Symptom specificity and depression status

No statistically significant differences in baseline corrected self reported anxiety as measured by the BAI-II was found between ABM (M =2.19 (6.44)) and placebo (M=1.31 (5.97)) [F (1,301) = 1.273, p = .260].

Current MDD was equally distributed between ABM (n=21) and placebo (n=16) [X (1) = .33, *p* = .377]. Adding depression status to the model (current- and former MDE) increased the unique effect of the intervention [F (1,301) = 8.189, p = .005], and showed no main effect from depression status [F (1,301) = 1.157, p = .283], and no interaction effect between the intervention and depression status [F (1,301) = 3.247 p = .073] that would have indicated that individuals with MDE history plus current MDE would have had more positive effect of the intervention at average than individuals with only a MDE history based on the M.I.N.I 6.0.

Primary outcome per protocol

As in the ITT analyses, there was a main effect of ABM on baseline corrected changes in HRSD scores. The ABM group showed statistically significant symptom improvement (M=1.09 (5.33)) when compared to the placebo (M= - .31 (5.07)) [F (1,301) = 5.47, η^2= .02, p = .02]. Self reported depression as measured by the BDI-II did not differ between ABM (M =3.50 (6.30)) and placebo (M=2.46 (6.33)) [F (1,301) = 1.27, p = .26].

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