Abstract

The overall goal of this project is to continue development of an attention bias modification (ABM) intervention that targets and reduces negative attention bias among adults with elevated symptoms of depression. Our prior work indicates that attention bias for negative information is associated with the maintenance of depression and that neural circuitry within frontal-parietal brain networks supports biased attention for negative information, thus allowing us to develop specific and targeted interventions that directly alter the neurobiology of negative attention bias. The proposed R33 study builds upon our prior NIMH funded work (R21MH092430), which examined whether ABM reduces negative attention bias and improves symptoms of depression. Findings indicate that compared to placebo ABM, active ABM reduced negative attention bias and increased resting state connectivity within a neural circuit (i.e., middle frontal gyrus and dorsal anterior cingulate cortex) that supports control over emotional information. Further, change in negative attention bias from pre- to post-ABM was significantly correlated with depression symptom change but only in the active training condition. Importantly, a 40% decrease in symptoms was observed in the active training condition; however, similar symptom reduction was also observed in the "placebo ABM" condition. Exploratory analyses indicated that placebo training may have promoted depression improvement by enhancing sustained attention. Although these preliminary findings are encouraging and demonstrate that ABM successfully alters the treatment target (i.e., negative attention bias), our prior work is among the first to document efficacy of ABM among adults with clinically significant depression. We believe it is prudent and necessary to obtain additional efficacy evidence for ABM before moving forward with large-scale clinical trials of ABM for depression. *Aim 1* is to conduct a randomized clinical trial among adults with elevated symptoms of depression and a negative attention bias that compares the efficacy of active ABM to placebo ABM and an assessment-only control condition that does not involve any ABM procedures. *Aim 2* is to examine whether ABM alters negative attention bias and functional connectivity within frontal-parietal neural circuitry that support negative attention bias. *Aim 3* is to identify mechanisms responsible for the putative efficacy of active and placebo ABM. **Study Impact:** The current project proposes to target and reduce negative attention bias with a novel intervention grounded in basic psychopathology research. We believe this experimental medicine approach will lead to the development of a highly specific and targeted intervention, using cutting-edge cognitive neuroscience to inform treatment development, and improve the quality of life of people whose psychopathology is maintained by negative attention bias.

Public Health Narrative

Although negatively biased attention has a central theoretical and empirical role in the maintenance of depression, there are few behavioral treatments that successfully target and improve this deficit. The current proposal builds upon our prior work and aims to further develop an attention bias modification intervention. We propose to develop a highly specific intervention that directly targets negative attention bias and the neurobiology that supports it, using cutting-edge cognitive neuroscience to inform treatment development and improve quality of life of patients whose psychopathology is maintained by negative attention bias.

Work Cited

1. Kessler RC, Avenevoli S, Costello EJ, Georgiades K, Green JC, Gruber MJ, He JP, Koretz D, McLaughlin KA, Petukhova M, Sampson NA, Zaslavsky AM, Merikangas KR. Prevalence, Persistence, and Sociodemographic Correlates of DSM-IV Disorders in the National Comorbidity Survey Replication Adolescent Supplement. *Arch Gen Psychiatry*. December 2011:1-9. PMCID: PMC3445020

2. Wells KB, Burnam MA, Rogers W, Hays R, Camp P. The course of depression in adult outpatients. Results from the Medical Outcomes Study. *Arch Gen Psychiatry*. 1992;49(10):788-794. PMID: 1417431

3. Greenberg PE, Kessler RC, Birnbaum HG, Leong SA, Lowe SW, Berglund PA, Corey-Lisle PK. The economic burden of depression in the United States: how did it change between 1990 and 2000? *J Clin Psychiatry*. 2003;64(12):1465-1475. PMID: 14728109

4. Beck AT, Rush AJ, Rush AJ, Shaw BF, Emery G. *Cognitive Therapy of Depression*. New York, NY: Guilford; 1979.

5. Beck AT. *Depression: Clinical, Experimental, and Theoretical Aspects*. New York: Harper & Row; 1967.

6. Disner SG, Beevers CG, Haigh EAP, Beck AT. Neural mechanisms of the cognitive model of depression. *Nat Rev Neurosci*. 2011;12(8):467-477. PMID: 21731066

7. Peckham A, McHugh R, Otto M. A meta-analysis of the magnitude of biased attention in depression. *Depress Anxiety*. 2010;27(12):1135-1142. PMID: 21049527

8. Beevers CG, Lee H-J, Wells TT, Ellis AJ, Telch MJ. Association of predeployment gaze bias for emotion stimuli with later symptoms of PTSD and depression in soldiers deployed in Iraq. *American Journal of Psychiatry*. 2011;168(7):735-741. PMID: 2145916

9. Beevers CG, Carver CS. Attentional bias and mood persistence as prospective predictors of dysphoria. *Cogn Ther Res*. 2003;27(6):619-637.

10. Disner SG, Shumake J, Beevers CG. Self-referential schemas and attentional bias predict severity and naturalistic course of depression symptoms. *Manuscript under review*.

11. De Raedt R, Koster EHW. Understanding vulnerability for depression from a cognitive neuroscience perspective: A reappraisal of attentional factors and a new conceptual framework. *Cogn Affect Behav Neurosci*. 2010;10(1):50-70. PMID: 20233955

12. Kellough JL, Beevers CG, Ellis AJ, Wells TT. Time course of selective attention in clinically depressed young adults: An eye tracking study. *Behaviour Research and Therapy*. 2008;46(11):1238-1243. PMCID: PMC2584153

13. Clasen PC, Wells TT, Ellis AJ, Beevers CG. Attentional Biases and the Persistence of Sad Mood in Major Depressive Disorder. August 2012. PMCID: PMC3856951

14. Sanchez A, Vazquez C, Marker C, LeMoult J, Joormann J. Attentional disengagement predicts stress recovery in depression: An eye-tracking study. 2013;122(2):303-313. PMID: 23421524

15. Macleod C, Mathews A. Cognitive bias modification approaches to anxiety. *Annu Rev Clin Psychol*. 2012;8(1):189-217. PMID: 22035241

16. Mogoaşe C, David D, Koster EHW. Clinical Efficacy of Attentional Bias Modification Procedures: An Updated Meta-Analysis. *J Clin Psychol*. March 2014:n/a–n/a. PMID: 24652823

17. Hakamata Y, Lissek S, Bar-Haim Y, et al. Attention bias modification treatment: a meta-analysis toward the establishment of novel treatment for anxiety. 2010;68(11):982-990. PMCID: PMC3296778

18. Hallion LS, Ruscio AM. A meta-analysis of the effect of cognitive bias modification on anxiety and depression. *Psychol Bull*. July 2011. PMID: 21728399

19. Beard C, Sawyer AT, Hofmann SG. Efficacy of Attention Bias Modification Using Threat and Appetitive Stimuli: A Meta-Analytic Review. *Behavior Therapy*. 2012;43(4):724-740. PMCID: PMC3494088

20. Cristea IA, Kok RN, Cuijpers P. Efficacy of cognitive bias modification interventions in anxiety and depression: meta-analysis. *Br J Psychiatry*. 2015;206(1):7-16. PMID: 25561486

21. Clarke PJ, Notebaert L, Macleod C. Absence of evidence or evidence of absence: reflecting on therapeutic implementations of attentional bias modification. *BMC Psychiatry*. 2014;14(1):8. PMCID: PMC3899426

22. MacLeod C, Clarke PJF. The Attentional Bias Modification Approach to Anxiety Intervention. *Clin Psych Sci*. 2015;3(1):58-78. PMID: 21349242

23. Baert S, De Raedt R, Schacht R, Koster EHW. Attentional bias training in depression: therapeutic effects depend on depression severity. *J Behav Ther Exp Psychiatry*. 2010;41(3):265-274. PMID: 20227062

24. Browning M, Holmes EA, Charles M, Cowen PJ, Harmer CJ. Using attentional bias modification as a cognitive vaccine against depression. 2012;72(7):572-579. PMCID: PMC3504298

25. Yang W, Ding Z, Dai T, Peng F, Zhang JX. Attention Bias Modification training in individuals with depressive symptoms: A randomized controlled trial. *J Behav Ther Exp Psychiatry*. 2015;49(Pt A):101-111. PMCID: in process

26. Wells TT, Beevers CG. Biased attention and dysphoria: Manipulating selective attention reduces subsequent depressive symptoms. *Cogn Emot*. 2010;24(4):719-728. DOI: 10.1080/02699930802652388

27. Beevers CG, Clasen PC, Enock PM, Schnyer DM. Attention bias modification for major depressive disorder: Effects on attention bias, resting state connectivity, and symptom change. 2015;124(3):463-475. PMCID: PMC4573770

28. Mogg K, Bradley BP. Attentional bias in generalized anxiety disorder versus depressive disorder. *Cogn Ther Res*. 2005;29(1):29-45. PMID: 12573928

29. Aron AR, Poldrack RA. The cognitive neuroscience of response inhibition: relevance for genetic research in attention-deficit/hyperactivity disorder. 2005;57(11):1285-1292. PMID: 15950000

30. Nee DE, Wager TD, Jonides J. Interference resolution: insights from a meta-analysis of neuroimaging tasks. *Cogn Affect Behav Neurosci*. 2007;7(1):1-17. PMID: 17598730

31. Helfinstein SM, Schonberg T, Congdon E, Karlsgodt KH, Mumford JA, Sabb FW, Cannon TD, London ED, Bilder RM, Poldrack RA. Predicting risky choices from brain activity patterns. *Proceedings of the National Academy of Sciences*. 2014;111(7):2470-2475. PMCID: PMC3932884

32. Ochsner K, Bunge S, Gross J, Gabrieli J. Rethinking feelings: An fMRI study of the cognitive regulation of emotion. *J Cogn Neurosci*. 2002. PMID: 12495527

33. Ochsner KN, Gross JJ. The cognitive control of emotion. *Trends Cog Sci*. 2005;9(5):242-249. doi:10.1016/j.tics.2005.03.010.

34. Beevers CG, Clasen P, Stice E, Schnyer D. Depression symptoms and cognitive control of emotion cues: a functional magnetic resonance imaging study. *Neurosci*. 2010;167(1):97-103. PMCID: PMC2840066

35. Joormann J, Talbot L, Gotlib IH. Biased processing of emotional information in girls at risk for depression. 2007;116(1):135-143. PMID: 17324024

36. Clasen PC, Beevers CG, Mumford JA, Schnyer DM. Cognitive control network connectivity in adolescent women with and without a parental history of depression. *Dev Cogn Neurosci*. 2014;7:13-22. PMCID: PMC4209722

37. Dinges DF, Powell JW. Microcomputer analyses of performance on a portable, simple visual RT task during sustained operations. *Behavior Research Methods, Instruments, & Computers*. 1985;17(6):652-655. doi:10.3758/BF03200977.

38. Jaeggi SM, Buschkuehl M, Jonides J, Shah P. Short- and long-term benefits of cognitive training. *Proc Natl Acad Sci USA*. 2011;108(25):10081-10086. doi:10.1073/pnas.1103228108.

39. Gotlib IH, Joormann J. Cognition and depression: current status and future directions. *Annu Rev Clin Psychol*. 2010;6:285-312. PMCID: PMC2845726

40. Jaeggi SM, Buschkuehl M, Shah P, Jonides J. The role of individual differences in cognitive training and transfer. *Mem Cognit*. 2014;42(3):464-480. PMID: 24081919

41. Warren MB, Pringle A, Harmer CJ. A neurocognitive model for understanding treatment action in depression. *Philos Trans R Soc Lond, B, Biol Sci*. 2015;370(1677):20140213. PMCID: PMC45288825

42. Shiroma PR, Thuras P, Johns B, Lim KO. Emotion recognition processing as early predictor of response to 8-week citalopram treatment in late-life depression. *Int J Geriatr Psychiatry*. 2014;29(11):PMID: 24706294

43. Harmer CJ, O'Sullivan U, Favaron E, Massey-Chase R, Ayres R, Reinecke A, Goodwin GM, Cowen PJ Effect of acute antidepressant administration on negative affective bias in depressed patients. *American Journal of Psychiatry*. 2009;166(10):1178-1184. PMID: 19755572

44. Wells TT, Clerkin EM, Ellis AJ, Beevers CG. Effect of antidepressant medication use on emotional information processing in major depression. *American Journal of Psychiatry*. 2014;171(2):195-200. doi:10.1176/appi.ajp.2013.12091243. PMCID: PMC3946310

45. Bedi N, Chilvers C, Churchill R, Dewey M, Duggan C, Fielding K, Gretton V, Miller P, Harrison G, Lee A, William I. Assessing effectiveness of treatment of depression in primary care. Partially randomised preference trial. *Br J Psychiatry*. 2000;177:312-318. PMID: 11116771

46. Brody DS, Khaliq AA, Thompson TL. Patients' perspectives on the management of emotional distress in primary care settings. *J Gen Intern Med*. 1997;12(7):403-406. PMCID: PMC1497129

47. Iacoviello BM, Charney DS. Developing cognitive-emotional training exercises as interventions for mood and anxiety disorders. *Eur Psychiatry*. October 2014:1-7. doi:10.1016/j.eurpsy.2014.09.415.

48. Southwick SM, Charney DS. The science of resilience: implications for the prevention and treatment of depression. *Science*. 2012;338(6103):79-82. PMID: 25451246

49. Schnyer DM, Beevers CG, deBettencourt MT, Sherman SM, Cohen JD, Norman KA, Turk-Browne NB. Neurocognitive therapeutics: from concept to application in the treatment of negative attention bias. *Biol Mood Anxiety Disord*. 2015;5(1):1. PMCID: PMC4405858

50. Pacheco J, Beevers CG, Benavides C, McGeary J, Stice E, Schnyer DM. Frontal-limbic white matter

pathway associations with the serotonin transporter gene promoter region (5-HTTLPR) polymorphism. *Journal of Neuroscience*. 2009;29(19):6229-6233. PMCID: PMC2720042

51. Medina JL, Jacquart J, Smits J. Optimizing the Exercise Prescription for Depression: The Search for Biomarkers of Response. *Current Opinion in Psychology*. 2015;4:43-47. PMCID: PMC4545504

52. Telch MJ, Bruchey AK, Rosenfield D, Cobb AR, Smits J, Pahl S, Gonzalez-Lima F. Effects of post-session administration of methylene blue on fear extinction and contextual memory in adults with claustrophobia. *American Journal of Psychiatry*. 2014;171(10):1091-1098. PMCID: PMC4467026

53. Badura-Brack AS, Naim R, Ryan TJ, Levy O, Abend R, Khanna MM, McDermott TJ, Pine DS, Bar-Haim Y. Effect of Attention Training on Attention Bias Variability and PTSD Symptoms: Randomized Controlled Trials in Israeli and U.S. Combat Veterans. *American Journal of Psychiatry*. July 2015:appiajp201514121578. PMID: 26206075

54. Rush AJ, Trivedi MH, Ibrahim HM, Carmody TJ, Arnow B, Klein DN, Markowitz JC, Ninan PT, Kornstein S, Manber R, Thase ME, Kocsis JH, Keller MB. The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. *Biol Psychiatry* 2003;54(5):573-583. PMID: 12946886

55. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, Hergueta T, Baker R, Dunbar GC. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry*. 1998;59 Suppl 20:22-33. PMID: 9881538

56. Posner K, Brown GK, Stanley B, Brent DA, Yershova KV, Oquendo MA, Currier GW, Melvin GA, Greenhill L, Shen S, Mann JJ. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. *American Journal of Psychiatry*. 2011;168(12):1266-1277. PMCID: PMC3893686

57. Ekman P, Friesen WV. Measuring facial movement. *J Nonverbal Behav*. 1976;1(1):56-75. doi:10.1007/BF01115465.

58. Lang PJ, Bradley MM, Cuthbert BN. *International Affective Picture System (IAPS): Affective Ratings of Pictures and Instruction Manual*. Gainsville, FL: University of Florida; 2008.

59. Conway ARA, Getz SJ. Cognitive Ability: Does Working Memory Training Enhance Intelligence? *Current Biology*. 2010;20(8):R362-R364. PMID: 21749957

60. Jaeggi SM, Buschkuehl M, Jonides J, Shah P. Cogmed and working memory training—Current challenges and the search for underlying mechanisms. *Journal of Applied Research in Memory and Cognition*. 2012;1(3):211-213. doi:10.1016/j.jarmac.2012.07.002.

61. Tang Y-Y, Posner MI. Attention training and attention state training. *Trends Cog Sci*. 2009;13(5):222-227. PMID: 19375975

62. Beevers CG, Clasen PC, Enock PM, Schnyer DM. Attention Bias Modification for Major Depressive Disorder: Effects on Attention Bias, Resting State Connectivity, and Symptom Change. *J Abnorm Psychol.* 2015; 124(3):463-75. PMCID: PMC4573770

63. Rush AJ, Bernstein IH, Trivedi MH, Carmody TJ, Wisniewski S, Mundt JC, Shores-Wilson K, Biggs MM, Woo A, Nierenberg AA, Fava M. An evaluation of the quick inventory of depressive symptomatology and the hamilton rating scale for depression: A sequenced treatment alternatives to relieve depression trial report. 2006;59(6):493-501. PMCID: PMC2929841

64. Rush AJ, Carmody TJ, Ibrahim HM, Trivedi MH, Biggs MM, Shores-Wilson K, Crismon ML, Toprac

MG, Kashner TM. Comparison of self-report and clinician ratings on two inventories of depressive symptomatology. *Psychiatr Serv*. 2006;57(6):829-837. PMID: 16754760

65. Posner K, Oquendo M, Gould M, Stanley B, Davies M. Columbia Classification Algorithm of Suicide Assessment (C-CASA): Classification of Suicidal Events in the FDA's Pediatric Suicidal Risk Analysis of Antidepressants. *Am J Psychiatry*. 2007;164(7):1035-1043. PMCID: PMC3804920

66. Chandler GM, Iosifescu DV, Pollack MH, Targum SD, Fava M. Validation of the Massachusetts General Hospital Antidepressant Treatment History Questionnaire (ATRQ). *CNS Neurosci Ther*. 2010;16(5):322-325. PMID: 19769599

67. Beevers CG, Marti CN, Lee H-J, Stote DL, Ferrell RE, Hariri AR, Telch MJ. Associations between serotonin transporter gene promoter region (5-HTTLPR) polymorphism and gaze bias for emotional information. 2011;120(1):187-197. PMID: 21319930

68. Disner SG, Mcgeary JE, Wells TT, Ellis AJ, Beevers CG. 5-HTTLPR, HTR1A, and HTR2A cumulative genetic score interacts with mood reactivity to predict mood-congruent gaze bias. *Cogn Affect Behav Neurosci*. March 2014. PMCID: PMC4169358

69. Price RB, Kuckertz JM, Siegle GJ, Ladouceur CD, Silk JS, Ryan ND, Dahlr RE, Amir N. Empirical Recommendations for Improving the Stability of the Dot-Probe Task in Clinical Research. *Psychol Assess*. November 2014. PMCID: PMC4442069

70. Zvielli A, Bernstein A, Koster E. Temporal dynamics of attentional bias. *Clinical Psychological Science* 2014. doi:10.1177/2167702614551572.

71. Calvo MG, Lundqvist D. Facial expressions of emotion (KDEF): identification under different display-duration conditions. *Behav Res*. 2008;40(1):109-115. PMID: 18411533

72. Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TE, Johansen-Berg H, Bannister PR, De Luca M, Drobnjak I, Fittney DE, Niazy RK, Saunders J, Vickers J, Zhang Y, De Stefano N, Brady JM, Matthews PM. Advances in functional and structural MR image analysis and implementation as FSL. *NeuroImage*. 2004;23 Suppl 1:S208-S219. PMID: 15501092

73. R Core Team. *R: a Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing http://www.R-project.org/.

74. Power JD, Barnes KA, Snyder AZ, Schlaggar BL, Petersen SE. Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. 2012;59(3):2142-2154. PMCID: PMC3254728

75. Smith SM, Miller KL, Salimi-Khorshidi G, Webster M, Beckmann CF, Nichols TE, Ramsey JD, Woolrich MW. Network modelling methods for FMRI. *NeuroImage*. 2011;54(2):875-891. PMID: 20817103

76. Witkowski S, Trujillo LT, Sherman SM, Carter P, Matthews MD, Schnyer DM. An examination of the association between chronic sleep restriction and electrocortical arousal in college students. *Clin Neurophysiol*. 2015;126(3):549-557. PMID: 250439966

77. Wardenaar KJ, van Veen T, Giltay EJ, de Beurs E, Penninx BWJH, Zitman FG. Development and validation of a 30-item short adaptation of the Mood and Anxiety Symptoms Questionnaire (MASQ). *Psychiatry Res*. 2010;179(1):101-106. PMID: 20472297

78. Watson D, Weber K, Assenheimer JS, Clark LA, Strauss ME, McCormick RA. Testing a tripartite model: I. Evaluating the convergent and discriminant validity of anxiety and depression symptom scales. 1995;104(1):3-14. PMID: 7897050

79. Meyer B, Berger T, Caspar F, Beevers CG, Andersson G, Weiss M. Effectiveness of a novel

integrative online treatment for depression (Deprexis): randomized controlled trial. *J Med Internet Res*. 2009;11(2):e15. PMCID: PMC2762808

80. Meyer B, Bierbrodt J, Schröder J, et al. Effects of an Internet intervention (Deprexis) on severe depression symptoms: Randomized controlled trial. *Internet Interventions*. 2015;2(1):48-59. doi:10.1016/j.invent.2014.12.003.

81. McKnight PE, McKnight KM, Sidani S, Figueredo AJ. *Missing Data*. Guilford Press; 2007.

82. Hedeker D, Gibbons RD. Application of random-effects pattern-mixture models for missing data in longitudinal studies. *Psychol Methods*. 1997;2(1):64-78.

83. Honaker J, King G, Blackwell M. Amelia II: A program for missing data. *R package version*. 2012. PMCID: PMC3057309

84. Rubin DB. Multiple Imputation for Nonresponse in Surveys. 2009.

85. O'Reilly KC, Shumake J, Bailey SJ, Gonzalez-Lima F, Lane MA. Chronic 13-cis-retinoic acid administration disrupts network interactions between the raphe nuclei and the hippocampal system in young adult mice. *Eur J Pharmacol*. 2009;605(1-3):68-77. PMID: 19168052

86. Bruchey AK, Shumake J, Gonzalez-Lima F. Network model of fear extinction and renewal functional pathways. *Neurosci*. 2007;145(2):423-437. PMCID: PMC1868491

87. MacKinnon DP. *Introduction to Statistical Mediation Analysis*. New York: Taylor & Francis; 2008.

88. Diggle P, Heagerty P, Liang K-Y, Zeger S. *Analysis of Longitudinal Data*. 2nd ed. Oxford, England.: Oxford University Press; 2013.

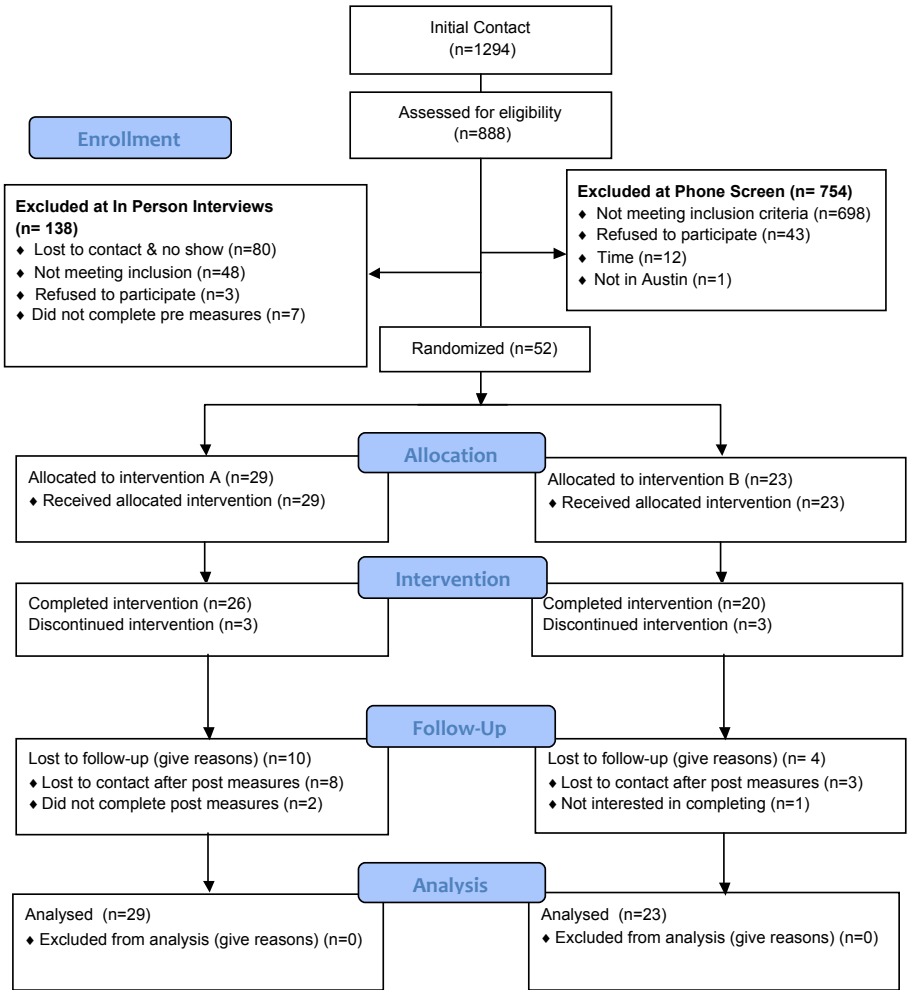
89. González DA, Jenkins SR. Cross-measure equivalence and communicability in the assessment of depression: a focus on factor-based scales. *Assessment*. 2014;21(6):731-741. PMID: 24586091

90. Kraemer HC, Mintz J, Noda A, Tinklenberg J, Yesavage JA. Caution Regarding the Use of Pilot Studies to Guide Power Calculations for Study Proposals. *Arch Gen Psychiatry*. 2006;63(5):484-489. PMID: 16651505

I. Study Participant and Recruitment Description

Recruitment sources and anticipated rate of recruitment. We will use established methods to recruit participants for this current project. Participants will be recruited from local clinics, advertisements placed online, in newspapers, on TV, and social media. The PIs have recruited hundreds of participants in this fashion, so we expect no difficulty recruiting eligible participants for the current project.

To demonstrate our ability to recruit participants, below is a CONSORT diagram from our recent attention bias modification study (R21MH092430) for clinical depression. As can be seen, we received a lot of interest in our study, as we had well over 1000 people contact us regarding the study during a 20-month recruitment period (65 contacts per month). Our advertising was relatively non-specific—it mentioned that the study involved a new computerized treatment for depression, but it did not reveal any of the more subjective inclusion/exclusion criteria, so as to not bias the responding of participants.



Consistent with the current proposal, we had a two-stage screening process. A phone screen interview initially queried individuals about inclusion criteria, which included the presence of a major depressive episode and medical or physical conditions that would preclude participation in an fMRI study. The vast majority of participants were excluded during the phone screen because they did not meet criteria for MDD. That is, most participants who were excluded had elevated depression but did not meet MDD criteria. Notably, this will not be an issue in the current study, as we are recruiting individuals with elevated depression regardless of MDD status (we will still measure the presence/absence of MDD for secondary analyses).

A smaller subset were excluded during the in-person interview, in part because symptom severity changed from the screening interview. The phone and in-person interviews were typically completed within 1 week or less of each other. We will adopt a similar approach for the current study, as we believe it is important to recruit participants who report stable levels of depression severity prior to initiating the clinical trial.

For the current proposal, we need to recruit 4.5 participants per month to reach our recruitment goals. Given that our recruitment methods will be highly similar to our prior work, we expect to receive approximately 65 contacts from potential participants per month, which would mean that we would have to convert 7% of these study inquiries each month into eligible participants. Given that our past study required the presence of MDD (which was the most common reason people were excluded from the study) and our current study does not require MDD but instead includes elevated depression symptom severity and a negative attention bias (which we expect to be present in at least 60% of people with elevated depression[10,13,24]), we believe that we should easily be able to reach the recruitment goals.

Monitoring of participants. We have recently invested time and effort into utilizing an electronic system that monitors enrollment and retention of study participants for all of our studies. Study data will be collected and managed using REDCap (Research Electronic Data Capture). REDCap is a secure, web application designed to support data capture for research studies, providing user-friendly web-based case report forms, real-time data entry validation (e.g. for data types and range checks), audit trails and a de-identified data export mechanism to common statistical packages (SPSS, SAS, Stata, R/S-Plus). REDCap also provides a powerful tool for building and managing online surveys. The research team can create and design surveys in a web browser and engage potential respondents using a variety of notification methods. The system was developed by a multi-institutional consortium that includes University of Texas at Austin and was initiated at Vanderbilt University. The database is hosted at the University of Texas. The REDcap server has been cleared for Category-I data by UT's Information Security Office. Importantly, once a participant enters the study, RedCap automatically pre-populates future assessments and determines the dates for when the assessments should occur based on study parameters. We can then generate weekly recruitment reports that clearly indicate how people are proceeding through the study. Further, a second report is automatically generated that produces demographic variables (age, race, ethnicity, gender) so that we can monitor sample composition in real time, as subjects enter the study. Since implementing this system we have found it to be extremely efficient and effective for helping us to accurately monitor participant engagement in our studies.

We will make a concerted and systematic effort to facilitate attendance to all sessions. This task will be accomplished by: (1) scheduling sessions at a time that is convenient for all participants; and (2) making reminder calls/emails 24 hours before each session. We expect that a small number of participants may not complete the full baseline assessment. Participants not completing baseline will be replaced and not included in follow-up assessments. To reduce attrition, participants will be paid up to $250 for completing all assessments. These participant payments are not contingent upon symptom status or intervention session attendance. In addition to monetary compensation for follow-up assessments, we also will use a two-pronged approach to remind participants of their scheduled (follow-up) appointments. First, we will have trained research staff place reminder calls to participants three days prior to each scheduled follow-up session; this approach has been used successfully in past work and we have achieved high retention rates (Hofmann et al., 2013). In this context, we will systematically ask each participant for updated contact information (e.g., phone number, mailing address) at each follow-up assessment to ascertain if phone numbers had changed and adjust our records accordingly. Second, we will send via e-mail a written reminder card for each follow-up assessment approximately 1 week in advance of the scheduled appointment.

Strategies to recruit a diverse sample. The 2010 U.S. Census (most recent available data) indicates that the racial makeup of the U.S. population is 72% White, 12% Black, 5% Asian, and 10% “Other.” Approximately 17% of the population is Hispanic or Latino. Austin is a racially and ethnically diverse city with a population of approximately 1.9 million people (includes the greater Austin-area), which allows us to recruit a sample with this demographic profile. Eligible participants will be enrolled without regard to ethnic background. Our general approach is to monitor recruitment on an on-going basis and if our demographic numbers do not mirror those of the US census, we will utilize a multimedia campaign with the following strategies: public service announcements on local radio stations, announcements in church bulletins, information booths at community functions, community presentations, promotional mailings, and placement of informational materials in retail outlets and organizations known to serve people of color. We have used this approach in numerous studies and have consistently generated a sample that is as ethnically diverse as the general population.

Potential recruitment/enrollment challenges and solutions. Although we expect to be able to recruit the necessary sample for this project, we also have strategies in place to address any recruitment shortfalls. For instance, one possibility is that we may have trouble recruiting enough minority participants for our study. Should this occur, we will contact William Lawson, MD former Chair of Psychiatry at Howard University, who has recently moved to the Dell Medical School at the University of Texas at Austin to manage what will be known as the Sandra Joy Anderson Community Health and Wellness Center at Huston-Tillotson. This clinic will provide mental health resources to historically underserved residents of East Austin and other parts of Travis County. Dr. Lawson is developing a mood disorders comorbidity center promoting state-of-the-art community education and research interventions that target an increasingly diverse community. He has already contacted Drs. Beevers and Schnyer about participating in the development of this research center,

so we could easily build on this existing relationship. Should recruitment fall behind our projections, we also have excellent relations with the mental health reporters at our local newspaper (Austin American Statesman), who are often very interested in reporting about our most recent research findings. We always experience a significant increase in participant inquiries following the publication of a special interest story about our research in the newspaper. Finally, we have utilized the University of Texas's Division of Diversity and Community Engagement, whose mission is in part to develop mutually beneficial community-university partnerships that further the mission of UT. They have been very helpful in the past with connecting us with relevant organizations that are interested in promoting our work and helping with participant recruitment.

Evidence to support feasibility of enrollment from prior research. In addition to the information provided above about our prior attention bias modification clinical trial for depression, we have several other published and on-going projects that support our contention that our team can recruit clinically relevant samples for our research projects. For instance, Dr. Beevers is currently conducting an internet-based depression treatment study (funded by the Brain and Behavior Foundation) where they have recruited more than 300 participants with elevated depression symptoms into his study. For his ongoing NIDA funded project ("Genetic influences on dual processing modes of reward and punishment learning", R01DA032457) the scientific team has screened and recruited over 1000 participants across project studies. Dr. Smits has been PI or Co-I on 8 federal- (e.g., NIMH, NIDA, CIHR) or industry-funded clinical trials. Accordingly, he has screened thousands of potential participants and developed a number of strategies to overcome the challenges to recruitment, enrollment and retention of study participants in clinical trials that we will employ in the proposed study (e.g., social media advertisements, local provider referral networks, strengthening participant incentives for enrolling in studies and providing follow-up data, training of staff regarding importance of data collection regardless of intervention attendance, etc.).

Participant adherence and incentives for participation. We will utilize a number of strategies in effort to promote adherence. Prior to randomization, participants will have completed an extensive screening process. Participants will also be provided a behavioral expectations document informing them of the requirements of their assigned group. To encourage compliance, we have included a mix of in-clinic and at-home training. The in-clinic visits should allow us to troubleshoot any problems the participants are having with the on-line ABM. Our at-home ABM system allows us to monitor compliance in real time and contact participants who miss two or more consecutive training sessions to help them troubleshoot any technical or motivational issues that arise. Further, efficient scheduling of participants to complete imaging assessments can be challenging in some imaging centers, but we are fortunate that we have scheduling flexibility in our imaging center. Conducting timely assessments has not been a problem in the past. The study coordinator will monitor adherence to the assessment schedule. He/she will place reminder calls/emails to participants three days prior to each scheduled follow-up session. Finally, participants will be compensated for $20 for each behavioral assessment and $50 for each imaging assessment. They will not receive payment for completing the ABM procedures.

II. Project Timeline

Months 1-3. Based on past experience, it will take approximately three months of start-up time prior to data collection. Most of the necessary study personnel are in place, so we do not anticipate a lengthy hiring process. During this initial period, OSP will set up necessary accounts, we will train RAs on the study protocol, order supplies, review and practice study procedures with staff. During this start-up period we will also further refine and test data processing algorithms to efficiently process the self-report, behavioral, eye-tracking, and imaging data as it is collected.

Months 3-30. We will begin data collection. We expect data collection to last 27 months—a recruitment rate of approximately 4.5 participants per month. Given a three month start-up period, annual enrollment milestones will be Y1 = 41, Y2 = 54, and Y3 = 28. Throughout data collection, data will be entered, cleaned, and checked for quality and integrity issues on an ongoing basis. For instance, we have automated data processing scripts for eye tracking and imaging that will clean and process the eye tracking data immediately after it has been collected. We will track how many participants have viable data as it is collected and will recruit additional participants as needed. This will allow us to hit our recruitment targets and begin data analysis almost immediately after obtaining data from our last participant. Our biostatistician, Jason Shumake, Ph.D., has extensive programming experience for managing data intensive studies and he will oversee the

processing of all non-imaging data. Dr. David Schnyer will oversee data processing, checking, and integrity for the imaging data, as in our past collaborations.

Months 30-36. We will then spend the final 6 months with data analysis and writing up our findings for dissemination at conferences and scientific publications. Our biostatistician, Dr. Shumake, will take the lead on data analysis. We expect data analysis for the primary aims to take approximately 3 months. Manuscript writing will then follow, although some of the manuscript writing can start prior to finalizing data analyses. This project will provide a rich database that will likely yield high impact publications. Dr. Shumake will also prepare de-identified data and relevant documentation to facilitate data sharing via the National Database for Clinical Trials related to Mental Illness (see Resource Sharing plan for more detail).

Upon conclusion of this study, we should be in an excellent position to determine whether a follow-up efficacy clinical trial should be completed. If the data suggest a follow-up efficacy clinical trial is warranted, then we will begin to prepare an R01 applicant in the final months of the grant period.

Figure 1. Overview of Project Timeline.

PLANNING AND PREPARATION	ACTIVE TRIAL PHASE	WRAP-UP
Months 1-3	**Months 3-30**	**Months 31-36**
Finalize ABM protocols	Recruit and enroll 123 trial participants and complete treatment	Final analysis of all data
Adapt existing assessment tasks	Meet with project team bi-weekly to discuss findings and trial experience	Present initial findings at conferences
Design and program databases (including participant tracking)	Perform routine data processing on all project data (self-report, behavioral, eye tracking, fMRI)	Write manuscripts and R01 application for efficacy testing
Obtain IRB approval	Monitor treatment fidelity and adherence throughout trial	
Consult feedback on protocols		
Finalize assessment protocols		
Finalize protocols / train staff		
Conduct extensive pre-testing of all technical components		
Begin Recruitment		

Introduction to the Revised Application

We thank the Review Committee for their thoughtful and constructive input on the previous version of this proposal. We appreciated their positive feedback, such as comments about the project's strong investigative team, development of an ABM intervention that alters a novel target, and our use of psychometrically strong methods. We have incorporated the reviewers' suggested changes and believe the proposal is now considerably stronger. Please note that in order to adequately respond to issues raised by the prior review, we have omitted justification for several design decisions that were not questioned in the previous review. Italic text identifies substantive changes in the application. Below is a summary of the changes we made in response to prior reviews.

1. To address concerns about data burden we provide more information about our automated approach to processing imaging data and our use of supercomputing resources at the University of Texas. Note that budgeted effort includes only the proposed imaging analyses—many secondary analysis (DTI, fMRI) will be possible but they will most likely be completed by graduate students or post-docs supervised by Dr. Schnyer in the future. We have also removed a graduate student RA and replaced him/her with a full-time post-doc to specifically assist Dr. Schnyer. Further, we also have automated scripts for all other proposed assessments, which will allow us to process data as it is collected. Our statistician, Dr. Shumake, has substantial experience with managing large, complex, multidimensional data.
2. We now more clearly specify our Go/No-Go criterion for proceeding to a confirmatory efficacy trial for ABM. Importantly, we have a single Go/No-Go criterion and we specify which assessments we will use to evaluate this criterion.
3. We now more clearly indicate that unresolved questions remain regarding whether negative attention bias maintains depression (as noted by the reviewers) and that the proposed study is well positioned to experimentally answer this important question. We also agree that we did not adequately review the ABM and anxiety literature and have now done so to the degree possible within the page constraints.
4. We clarify that we are very interested in the mechanistic specificity of ABM and placebo training and will examine whether similar or divergent mechanisms of change are operating across training conditions (see revisions to mediation analyses).
5. We now provide further detail and justification for our proposed ABM dosage.
6. We also provide an empirical justification for the cut-point used to define negative attention bias as part of the inclusion criteria. Our intent for including this criterion was to recruit a homogenous group of participants who have the cognitive bias that we intend to modify (as recommended in the approach section of the R33 RFA).
7. We now more thoroughly describe our approach to statistical modeling of attention training compliance. In short, we will examine the treatment effect size conditioned on the number of sessions completed (e.g., the effect size given at least 80% adherence, the effect size given at least 90% adherence, etc.) and determine to what degree therapeutic benefit changes as a function of treatment compliance.
8. We will no longer allow people who are receiving psychotherapy to participate in our trial.
9. We will now make ABM available to participants in the assessment only condition at the end of their participation. All participants who do not meet study criteria will receive treatment referrals to local mental health resources, including a clinic located within the IMHR.
10. We are now clearer that we support a pragmatic approach to the development of these cognitive training interventions. If "placebo ABM" is more effective than active ABM, then future efforts should be devoted to developing and understanding placebo ABM. Such a finding could also potentially move the field away from ABM for depression with emotion stimuli and towards non-affective forms of cognitive training. Thus, if either intervention shows promise for reducing depressive symptoms, such an outcome could be quite informative for theoretical models of depression and have a significant impact on future treatment development.
11. We now elaborate on how ABM fulfils an unmet treatment need, as few treatments are currently available that specifically target negative attention bias. Antidepressant medications appear to robustly influence information processing biases for positive stimuli but the effects of antidepressant treatment on negative bias are more mixed.
12. We now exclude people with bipolar disorder, as suggested.
13. Our primary analyses will be intent-to-treat analyses, but, as suggested, we now indicate that secondary analyses will involve completer analyses in the group that completes at least 50% of the assigned intervention.

Specific Aims

Our goal is to further develop an attention bias modification (ABM) intervention designed to target and reduce **negative attention bias,** a key construct of the negative valence system within Research Domain Criteria (RDoC), among adults with elevated symptoms of depression. Our prior work (and work by others) indicates that individual differences in negative attention bias predicts vulnerability to depression and is associated with the maintenance of depression symptoms. We have also demonstrated that neural circuitry within frontal-parietal brain networks supports biased attention for negative information, allowing us to develop a specific and targeted intervention that directly alters the neurobiology that supports negative attention bias.

The proposed R33 study builds upon our prior NIMH funded work (R21MH092430) that examined whether ABM reduces negative attention bias and improves symptoms of depression. Findings indicate that compared to placebo ABM, active ABM reduced negative attention bias and increased resting state connectivity within a neural circuit (i.e., middle frontal gyrus and dorsal anterior cingulate cortex) that supports control over emotional information. Further, change in negative attention bias from pre- to post-ABM was significantly correlated with depression symptom change but only in active ABM. Importantly, a 40% decrease in symptoms was observed in active ABM; however, similar symptom reduction was also observed in "placebo ABM." Exploratory analyses indicated that placebo ABM might have promoted depression improvement by increasing sustained attention in general.

Although these preliminary findings are encouraging and demonstrate that ABM successfully alters the treatment target (i.e., negative attention bias), our prior work is among the first to document efficacy of ABM among adults with clinically significant depression. We believe it is prudent and necessary to obtain additional evidence for the efficacy and mechanisms of action of ABM for depression before potentially moving forward with large-scale clinical trials. Building on this preliminary work, we propose the following aims:

1. Conduct a randomized clinical trial among adults with elevated symptoms of depression and negative attention bias that compares the efficacy of active ABM to (1) "placebo ABM" that does not train attention away from negative stimuli and (2) an assessment-only control condition that does not involve any ABM procedures. Our preliminary study found that placebo ABM did not alter negative attention bias (or the neurobiology that supports it) but placebo ABM was associated with significant improvements in depression. An assessment-only comparison condition is needed to clarify whether symptomatic improvement is due to the intervention or to the passage of time.

2. Examine whether ABM alters negative attention bias and functional connectivity within neural circuits that support negative attention bias. More specifically, we hypothesize that active ABM will: (1) decrease negative attention bias measured behaviorally with reliable eye tracking methods; (2) improve functional connectivity between the middle frontal gyrus and anterior cingulate cortex, an important circuit in a network that supports control over negative attention bias; and (3) lead to significant improvement in depression symptoms. **Go/No-Go criterion**: *The effect size of the treatment × time interaction must exceed d >= .5 for negative attention bias (measured with eye tracking) AND change in depression symptoms (measured with QIDS-SR). Thus we have a single and clearly operationalized Go/No-Go criterion.*

3. To identify mechanisms responsible for the putative efficacy of ABM, analyses will determine whether improvement in negative attention bias and connectivity between the middle frontal gyrus and anterior cingulate cortex mediate the association between intervention condition and depression symptom change. Further, we will examine whether improvements in general sustained attention mediate the putative efficacy of placebo ABM. Mediation *analyses will identify the mechanisms responsible for improvement in each form of training and address questions regarding mechanistic specificity by testing whether these mediators are unique or common to each form of ABM.*

Study Impact. Negative attention bias has been implicated theoretically and empirically in the maintenance of depression. However, virtually no treatments are currently available that effectively target and alter this cognitive bias. The current project proposes to target and improve negative attention bias with a novel behavioral intervention grounded in basic cognitive research. We believe this approach can lead to the development of a highly specific intervention, using cutting-edge cognitive neuroscience to inform treatment development and improve quality of life of individuals whose psychopathology is maintained by negative attention bias.

Background and Significance

Depression is a common, recurrent, and impairing condition that predicts future suicide attempts, interpersonal problems, unemployment, substance abuse, and other negative outcomes[1,2]. According to the World Health Organization, depression is one of the leading causes of disability worldwide. The economic cost of depression in the U.S. alone due to medical expenditures, lost productivity, and other costs is substantial, estimated to exceed $200 billion annually[3].

Despite its clear societal importance, the psychological mechanisms that maintain an episode of MDD have not been clearly identified. Cognitive theory[4,5] asserts that negatively biased attention (among other cognitive biases) has an important role in the maintenance of the disorder. That is, depressed individuals selectively attend to negative information and have difficulty disengaging attention from negative stimuli. These attention biases, in turn, reinforce sad mood and contribute to a persistent depressive episode.

A great deal of correlational research supports the idea that depressed individuals' attention is negatively biased[6]. A recent meta-analysis found that depressed participants have a stronger attention bias towards negative stimuli than non-depressed participants, particularly when assessed with a dot-probe task (k =12, n = 937, d = 0.52, p < .001). This effect was not moderated by a number of characteristics, such as age, sex, type of stimuli, or date of publication[7]. We have also shown that negative attention bias prospectively predicts the development of depression[8,9]. Further, among adults with elevated depression, greater negative attention bias was associated with symptom worsening over the subsequent five weeks (r = -.42)[10].

This prior work also indicates that negatively biased attention in depression is rarely observed at stimulus durations of less than 1000ms, but is consistently observed at longer (i.e., > 1000ms) stimuli durations (for a review see[11]). Indeed, our work using eye tracking methodology, which provides a relatively continuous assessment of attention bias, shows that adults with MDD have a sustained attention bias for negative stimuli for up to 30 seconds compared to non-depressed adults[12]. Importantly, using eye tracking assessments, negatively biased attention predicts future increases in depression symptom severity[8,9] and more prolonged mood persistence among people with MDD[13,14].

Attention Bias Modification (ABM) in Anxious and Depressed Samples

Despite this correlational evidence, few experimental studies have convincingly demonstrated that negative attention bias maintains depression and is not simply a byproduct of depressive psychopathology. One way to test this possibility is to conduct a randomized study that experimentally reduces negative attention bias and then determine whether depression symptoms subsequently improve. Broadly speaking, these types of studies are referred to as Attention Bias Modification (ABM).

Numerous ABM studies have been completed with anxious populations[15]. Four published meta-analyses suggest that ABM reduces symptoms of anxiety and negative attention bias[16-19]. However, there have been a number of inconsistent findings in this literature. A recent meta-analysis questioned the efficacy of ABM interventions and concluded that the field is hampered by small low-quality trials, risk of publication bias, and small effect sizes[20]. However, other work has shown that when negative attention biases are successfully modified by ABM, reductions in anxiety do typically follow[21]. Unsuccessful ABM trials tended not to alter the putative mechanism targeted by ABM, thus symptom improvement did not follow. These findings indicate that engaging (and measuring) the ABM treatment target (negative attention bias) is critical for a successful ABM intervention[22]. Importantly, we plan to measure putative treatment mechanisms in the current trial.

Very few rigorous clinical trials of ABM have been completed with depressed adults. Instead, most studies have been relatively short-term examinations of ABM with dysphoric college students.[16] An attention training study that involved a clinically depressed sample utilized an exogenous cueing task with word stimuli to modify negative attention bias. Findings from this study indicated that 10 days of attention training did not significantly reduce symptoms of depression[23]. In a study with a community sample of non-symptomatic adults with recurrent lifetime MDD, active ABM that utilized image stimuli reduced depression risk and lowered cortisol awakening response one month post-training compared to placebo training—notably, attention training with word stimuli in this same study did not produce similar beneficial effects[24]. *Finally, a recent study involving ABM, placebo ABM, and assessment-only reported significant reductions in depression symptoms at post-training and 3-month follow-up only in the ABM condition[25]. Notably, no significant change was observed in the placebo condition where targets appeared with equal probability in the sad (50%) and neutral (50%) word positions. No effects for placebo ABM on depression symptoms are consistent with what we found in our initial ABM study with dysphoric college students[26].*

No additional studies, other than the work we report below, have examined ABM in depressed samples. As such, it remains unclear whether negative attention bias is a critical cognitive mechanism that maintains an episode of depression, as postulated by clinical theories of depression. We believe that the proposed study could shed important light on this fundamental question and, if successful, could spur additional development of interventions designed to alter negative attention bias.

Attention Bias Modification for Depression – R21MH092430

We recently published the results of a rigorous clinical trial of ABM for negative attention bias among adults with clinical depression. This pilot clinical trial, funded by the NIMH with an R21, represents important preliminary data for the current proposal. A notable feature of this study that differentiates it from many other studies is that we assessed the effects of ABM on attention bias and the neurobiology that supports it. We briefly review our findings, but the reader is referred to our recent publication for more extensive detail[27].

A community sample of treatment-seeking, clinically depressed, adults (*N* = 52, mean age = 28.5 years, 30 female, all met criteria for MDD) was recruited for this study. We utilized ABM procedures identical to those in our prior work[26] (more detail is provided in the Approach section below). In short, ABM utilized a dot-probe task that presented pairs of faces and scenes that were dysphoric or neutral in content. Stimuli were presented for relatively long durations (3000ms – 4500ms) because longer stimulus duration times allow for more elaborated processing and greater activation of relevant cognition[28]. Following offset of images, a single or double white asterisk was presented in the location of one of the previously presented stimuli. Participants' task was to identify probe type (1 or 2 asterisks) as quickly as possible.

The key ABM manipulation was the placement of the target probe. In the placebo ABM condition, the probe appeared in the location of the neutral and dysphoric stimuli with equal probability. In the active ABM condition, the probe appeared in location of the neutral stimulus 80% of the time. The distribution of targets served as the critical manipulation whereby participants in the active training condition were putatively trained to allocate their attention preferentially towards neutral stimuli and away from dysphoric stimuli.

ABM consisted of 8 training sessions (i.e., twice a week for four weeks) and once per week at-home training sessions. Although we recommended a minimum of weekly at-home training, participants were free to complete additional at-home training sessions at their discretion. The at-home training task was implemented on a website using JavaScript and HTML programming, with a MySQL database, that matched in-clinic training where possible. Compliance was very good, as study participants completed an average of 7.36 in-clinic ABM sessions (i.e., 92% adherence) with no differences between active and placebo conditions, $t(50) = 0.11$, p = .90. Similarly, participants completed an average of 8.35 at-home training sessions, which also did not differ between training conditions ($t(50) = 1.13$, $p = .26$).

Does ABM alter negative attention bias? We observed a significant time (pre-ABM, post-ABM) x ABM condition (active, placebo) interaction for negative attention bias, b = -31.58, *SE* = 12.27, z = -2.57, $p = .01$. There was a significant and large reduction of negative attention bias from pre- to post-ABM in the active training condition ($z = -3.62$, $p < .001$, effect size $d = 1.01$), but not the control condition ($z = 0.20$, $p = .84$, effect size $d = .04$). ABM successfully altered the primary treatment target. *Based on the anxiety literature, change in attention bias is critical for observing symptomatic change*[22].

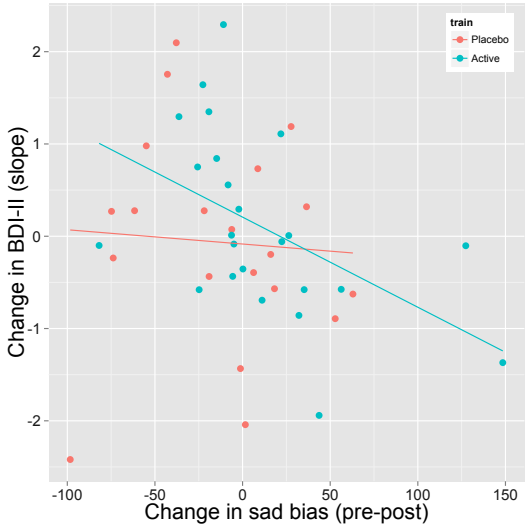


Figure 1. Change in attention bias for sad stimuli is associated with depression symptom change in active ABM (blue) but not in placebo (red) ABM.

Is change in negative attention bias correlated with depression symptom change? To examine whether change in attention bias was associated with symptom change, intercepts and slopes for depression change from pre- to post-ABM for each participant were estimated. Change in attention bias was then correlated with change in depression symptoms, controlling for the intercept (i.e., initial BDI-II severity). The partial correlation indicated that greater change in negative attention bias was strongly associated with reductions in symptoms for active ABM ($r_p = -.42$, p = .04) but not placebo ABM ($r_p = -.05$, p = .83), although the difference between these correlations fell short of statistical significance

(z = -1.34, p = .18; Fig 1). These results indicate that reductions in the primary treatment target (negative attention bias) were correlated with improvements in depression symptoms in active ABM.

Does ABM alter depression symptoms? *Given that we observed relatively little change in negative attention bias in placebo ABM, one might expect to observe little depression symptom change in placebo ABM. However, this was not the case.* Depression symptoms (measured with the BDI-II) decreased by 12.80 points from pre- to post-ABM, a decrease of approximately 40% in depression symptoms (i.e., $(19.068_{post}-31.865_{pre})/31.865_{pre}*100$). However, to our surprise, there were no ABM condition effects. That is, depression symptom change was similar across "placebo" and active ABM conditions (see Fig 2).

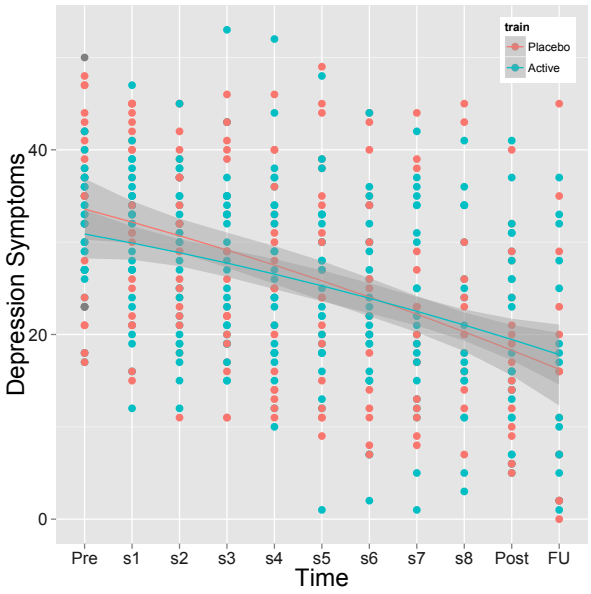


Figure 2. Change in depression symptoms for active (blue) and placebo (red) ABM was similar, suggesting different mechanisms were responsible for symptom change.

We observed significant symptom reduction in both active and placebo ABM, suggesting that the mechanisms of change may have differed across ABM conditions (recall that we did not see any change in negative attention bias in placebo ABM). We explore this possibility next.

Neurobiology that supports negative attention bias in depression. Substantial work has examined the neural systems that support attention bias. The lateral prefrontal cortex (lPFC) appears to have a particularly important role in modulating attention biases for emotional information. In general, this region is implicated in cognitive control, especially when competing responses have to be inhibited or new information is selected[29-31]. Prior research indicates that the lPFC is critically involved during successful cognitive regulation of emotional information[32,33].

Several studies now indicate that altered lPFC function supports negatively biased attention in depression. For instance, our prior work documented that compared to women with few symptoms of depression, women with elevated depression symptoms showed weaker activation in two regions of lPFC: the inferior frontal gyrus and the middle frontal gyrus, along with the supramarginal gyrus of the parietal lobe, primarily in the right hemisphere, when required to shift attention away from negative stimuli. No depression group differences were observed in the lateral prefrontal cortex for shifting attention away from non-emotional cues, suggesting that effects were most robust for depression-relevant cues[34].

Further, adolescents at risk for depression by virtue of having a parental history of MDD, who have been shown to have a negative attention bias[35], showed lower levels of functional connectivity within a circumscribed network of brain regions underlying attentional control, including the right lPFC[36]. More relevant to the current study, in the R21 sample, we reported that lower right middle frontal gyrus (rMFG) and dorsal anterior cingulate cortex (dACC) connectivity was associated with greater negative attention bias (N = 52)[27] prior to the administration of ABM.

Does ABM alter neurobiology that supports negative attention bias in depression? Change in connectivity between the rMFG – dACC was significantly different across ABM training conditions, t(35) = -2.08, *p* = .04, effect size d = .70. Resting state connectivity between these two nodes increased for active ABM (*M* = .04, *SE* = .04) and decreased for placebo ABM (*M* = -.07, *SE* = .04). Further, change in rMFG – dACC connectivity was associated with change in negative attention bias in the active training condition (*r* = .40, *p* = .06). Taken together, this provides strong evidence that ABM alters negative attention bias in depression and functional connectivity within neural networks that support negative attention bias.

What might account for depression improvements in the placebo ABM condition? As reported above, significant symptom improvement was observed in the placebo ABM condition. To determine whether we could identify a possible mechanism for this improvement, exploratory analyses indicated that increases in pre- to post-ABM resting state connectivity between two different nodes of the attention control network predicted symptomatic improvement in the placebo condition: (a) the precuneus and right middle frontal gyrus (r_p = -.56, *p* = .02) and (b) left and right orbital frontal cortex (r_p = -.62, *p* = .01). When simultaneously entered

into a regression analysis with initial depression as a covariate, change in connectivity was associated with symptom change for both nodes (precuneus-rMFG: b = -1.78, *t* = -1.93, *p* = .07, effect size *d* = .65; lOFC-rOFC: b = -3.81, *t* = -2.39, *p* = .03, effect size *r* = .80), suggesting change in both nodes contributed to symptomatic change in the placebo condition. No other changes in resting state connectivity were significantly correlated with symptom change in the placebo condition.

Taken together, these findings suggest that active and placebo ABM may have led to symptomatic improvement via different mechanisms. Active ABM reduced negative attention bias, which in turn led to symptom improvements. Placebo ABM may have produced changes in resting state connectivity in nodes associated with sustained attention to visual information, which in turn contributed to symptom improvement. Consistent with cognitive theory[6], data from the ABM condition are consistent with the idea that negative attention bias plays an important role in the maintenance of depression. However, given the variability of findings across the ABM literature for depression and anxiety, we believe it is critical to conduct a well-powered replication of these findings to further examine whether altering negative attention bias can indeed significantly reduce symptoms of depression.

Next Steps for ABM Research in Depression: Motivation for the Proposed R33 Project

Our preliminary work provides strong evidence that our novel approach to ABM alters the primary intervention target (i.e., negative attention bias) that, in turn, is associated with symptomatic improvement. We have also identified a biological pathway (i.e., increased functional connectivity within a PFC circuit involved in attention control) that is altered by ABM to produce its clinical benefit.

Our team debated whether to move forward with a confirmatory efficacy trial (R01) or to invest more time in the development of this intervention (R33). There were several reasons why we selected the latter approach:

1. In our preliminary study we did not include an assessment-only comparison condition. In our prior work with dysphoric adults and other work[25], the placebo ABM condition did not report significant improvement in symptoms[26]. However, this was not the case in the R21 study, where placebo ABM was also associated with significant symptom reductions. Therefore, we believe it is important to now conduct a study that compares active and placebo ABM to a standard comparison condition where no ABM is delivered to properly account for the effects of time.
2. Changes in resting state connectivity from our preliminary study suggested that placebo ABM may improve depression symptoms by enhancing sustained visual attention in general. If replicated, it would point to an alternative cognitive training approach for depression that focuses on improving sustained attention. To better assess this possibility, we will now include a gold standard assessment of sustained attention, the PVT task[37], to determine if placebo ABM works via improvements in sustained attention.
3. Subsequent research since initiating our most recent ABM study indicates that higher dosages of cognitive training may be necessary to facilitate substantive transfer of learning[38]. We believe our prior trial provides a guideline for the minimal amount of training needed to observe target engagement. In the current study, we are proposing to increase the amount of training primarily by increasing the required amount of at-home ABM to be completed (from 1/week to 3/week) plus in-clinic ABM.
4. To better understand why ABM works, we now propose to assess attention bias and resting state connectivity more frequently throughout the course of the intervention. Doing so should increase our confidence about why ABM is effective and provide additional insight into the cognitive mechanisms that maintain depression.
5. Finally, we now propose to recruit a homogenous group of depressed individuals who are most likely to benefit from ABM. That is, we will identify individuals who have elevated symptoms of depression (regardless of whether they meet criteria for MDD) *and* exhibit an attentional bias for negative stimuli as measured by a reliable eye tracking method. Including participants with heightened depression severity regardless of diagnostic criteria that also possess the cognitive deficit ABM aims to alter is highly consistent with an experimental therapeutics approach to treatment development. *Indeed, the R33 RFA asks "Are subject inclusion/exclusion criteria well-justified and is the selection made on the basis of a measurable disruption in the mechanism under study? Will the inclusion/exclusion criteria maximize the probability that all subjects share the same perturbation?" We now provide empirical justification for our attention bias requirement and specifically designed our inclusion/exclusion criteria to be consistent with the approach recommended by the RFA.*

For these reasons, we felt it was appropriate to conduct further treatment development. Upon completion of this trial, we believe we will have definitive evidence regarding whether continued study of this intervention is worthwhile. If so, we will be well positioned to conduct a confirmatory efficacy trial of this intervention.

Innovation

Consistent with NIMH strategic priorities, we are utilizing an experimental therapeutics approach to develop an ABM intervention designed to target and alter a behavior (negative attention bias) and its associated neurobiology that empirical and theoretical work posits have a central role in maintaining depression.

Importantly, we have adapted our ABM approach to be consistent with findings from experimental psychopathology research in depression. We believe our approach will be successful for a number of reasons. First, we are using relatively long stimulus presentation times during ABM, which is consistent with the repeated finding that depression is maintained by sustained and prolonged attention to negative material[39]. We also use image rather than word stimuli, as negative images appear to have more potent training effects than words[24]. We are also combining in-clinic with at-home ABM in order to maximize ABM dosage. We utilized this hybrid approach in our past work[27]; however, in the proposed project we will increase the at-home dosage to maximize transfer of training effects[38,40]. We will also carefully measure putative mediators of ABM using eye-tracking to measure attention bias and resting state methods to measure functional connectivity between key brain regions that support negatively biased attention. These approaches provide the most sensitive assessments possible and should contribute important insight into the mechanisms of change for ABM. Although ABM approaches have been used successfully in other domains, few rigorous ABM trials have been completed with depressed samples. Taken together, we believe further development of ABM to treat depression and negative attention bias is very timely and highly innovative.

Given issues with reproducibility in psychology/psychiatry (and other scientific fields), it is important to emphasize that we are proposing a conceptual replication and extension of our initial R21 finding indicating that active and placebo ABM reduced depression. Notably, our first ABM trial with dysphoric college students[26] and other work[25] has found no symptomatic benefit for placebo training. However, if the R21 findings are replicated and placebo training produces significant symptomatic benefit, we are well positioned to determine whether similar or divergent mechanisms of change are operating in each training condition (see Aim 3). If placebo training does produce significant symptomatic improvement and we identify a mechanism of change for placebo training (e.g., enhanced sustained attention), we believe such a finding would be an important contribution to the literature in its own right. This could potentially spur the development of novel treatments specifically designed to target sustained attention. Should ABM improve negative attention bias but fail to improve symptoms, that too would shed important light on the etiological (non)significance of negative attention bias for depression. Thus, we believe this study will be highly informative for the field even if null findings are observed for active ABM.

Development of ABM would also meet an unmet need in depression treatment, as few treatments specifically target negative attention bias. A number of studies have examined the impact of antidepressant medication in depressed samples on emotion processing after short-term or acute dosages (in long-term studies it is difficult to determine whether information processing changes are due to medication or changes in mood)[41]. Although some studies find improvements in negative information processing, results are more robust for positive stimuli. For instance, one study found that 7 days of citalopram improved recognition of happy facial expressions compared to baseline[42]. Similarly, a second study found that reboxetine increased the ability to recognize happy facial expressions, decrease time to categorize words as positive, and increase memory for positive words. However, processing of negative information was not affected[43]. This is consistent with our prior work showing that depressed adults on an SSRI display greater attention bias for positive information than depressed adults not on an SSRI (no group differences were observed for negative stimuli)[44]. Further, even if antidepressant medications changed negative information processing, patient preference studies indicate that many depressed patients prefer non-pharmacologic treatment but experience difficulty accessing such treatment.[45,46] Thus, ABM targets a mechanism that is not robustly treated by existing treatment options and could provide an alternative non-pharmacologic treatment that is highly accessible.

Further, in line with the RFA, the proposed work is highly translational, as it is at the intersection of clinical and cognitive neuroscience. This cognitive training approach capitalizes on the capacity for brain plasticity and is an approach that has been advocated by numerous clinical scientists[47,48]. Indeed, as a reflection of this translational effort, key investigators have strong expertise in experimental psychopathology, including eye

tracking and cognitive bias expertise (Dr. Beevers), cognitive neuroscience, including fMRI expertise (Dr. Schnyer), intervention science (Dr. Smits), and biostatistics (Dr. Shumake). We believe this is a highly complementary set of expertise that has produced outstanding translational work in the past[10,27,34,49-52] and is ideally suited to translate these new discoveries into a novel intervention. Assessment across units of analysis distinguishes this work from most other ABM research and, more importantly, will potentially facilitate a comprehensive understanding of how ABM facilitates symptomatic change.

Approach

Design

We will randomly assign 123 adults with elevated depression symptom severity and negative attention bias to one of three conditions: (1) active ABM; (2) placebo ABM; or (3) assessment-only control. Participants assigned to active ABM and placebo ABM conditions will complete the interventions daily during a one-month period. Throughout the intervention period, we will obtain five in-clinic assessments of negative attention bias and general sustained attention separated by one week (pre-ABM, week 1, week 2, week 3, and post-ABM). Change in resting state connectivity will be assessed at pre-ABM, week 2, and post-ABM. The assessment only condition will complete all of the same assessments on the same schedule without receiving any ABM. *Participants randomly assigned to the assessment only condition will be offered a trial of ABM at the end of their participation. All participants who do not meet study criteria will receive treatment referrals to local mental health resources, including a clinic located within the study site at the IMHR. Anyone who continues to experience elevated symptoms at the end of the trial will also be given treatment referrals.*

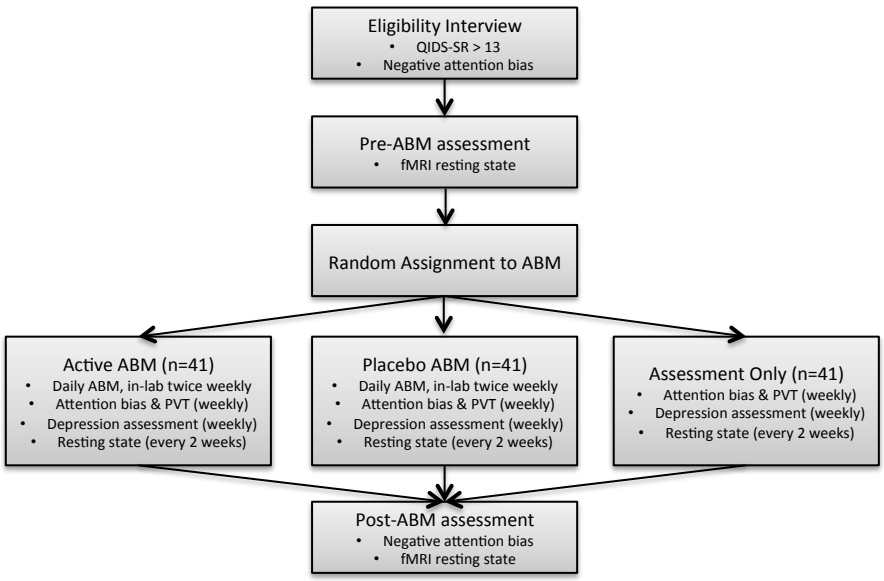


Figure 3. Overview of study design.

Design considerations. We debated whether or not to include placebo ABM in this study. We elected to include placebo ABM for several reasons. First, if our hypothesis is incorrect, and active ABM does not reduce depression symptoms as expected, inclusion of placebo ABM provides another possible intervention that may have therapeutic efficacy, as in our R21 study. Further, even if active ABM is successful, we have designed this trial to directly test the possibility that placebo ABM improves sustained attention, which would also provide important insight into the contribution of general sustained attention to depression.

We want to reiterate that we support a pragmatic approach to the development of these interventions. If "placebo ABM" is shown to be more effective than active training, then future efforts should be devoted to developing placebo ABM. Such a finding could also potentially move the field towards more non-affective forms of cognitive training. Indeed, a recent study with PTSD found that a "placebo" attention training condition, which they referred to as attention control training, was associated with improvements in PTSD[53]*. Thus, we believe that if either intervention shows promise for reducing depressive symptoms, such an outcome could be quite informative and have a significant impact on treatment development.*

Participants

We plan to recruit 123 adults ages 18-50 years old. Inclusion criteria are: 1) able and willing to provide informed consent; 2) fluent in English; 3) QIDS-SR[54] depression score of 13 or greater, which indicates depression severity in the moderate range or greater and is equivalent with an $HRSD_{17}$ of 17 or greater; and 4) have an attention bias for negative stimuli relative to neutral stimuli (i.e., total fixation time for negative stimuli > than total fixation time for neutral stimuli; see below for more detail). Exclusion criteria are: 1) meets criteria for current substance abuse or dependence, current or past psychotic disorder, *bipolar disorder,* or schizophrenia; 2) has any medical or physical conditions that would preclude participation in an fMRI study (e.g., orthodontic braces); *or 3) is currently receiving psychotherapy. As in our past R21 trial,* participants receiving pharmacological treatment for psychiatric disorders will be included if treatment is considered stable

(i.e., adequate dose of pharmacotherapy and had been on the same dose for at least 6 weeks). *We did not observe significant moderator effects for medication on ABM outcomes in our R21 trial.* Participants with significant suicidal ideation or who have enacted suicidal behaviors within 6 months prior to intake will be excluded from study participation and referred for appropriate clinical intervention.

Participant considerations. Consistent with the RDoC framework, we are proposing to recruit a sample of adults with elevated depression symptoms (not necessarily with DSM-5 MDD) *and*, most critically, a negative attention bias. We are therefore targeting a homogenous group of patients most likely to benefit from this intervention. In our past work, approximately 60% of depressed participants exhibited a negative attention bias[10,13,27]. Thus, we expect a sufficient number of participants should be available for recruitment, as the majority of people with elevated depression should exhibit this bias. We also restricted the age range to adults between 18 and 50 years old to limit the impact of cognitive aging on our behavioral and imaging data. Participant age is often restricted in imaging studies for this reason (i.e., to maximize signal to noise ratio), although we acknowledge that this decision does impact the generalizability of our findings to a small degree.

Empirical justification of the attention-bias criterion. *To validate the choice of total fixation time > 0 for sad stimuli relative to neutral stimuli (i.e., sad bias) for demonstrating sufficient negative bias, we applied k-means clustering to eye-tracking data from depressed participants in our R21 study to determine the optimal split point for dividing the sample into low and high bias groups. This analysis indicated that the point that maximally separated the two clusters was a bias score of 0.001. Therefore, this empirically determined cutoff supports our original theoretical choice of > 0 as an eligibility criterion. Figure 4 shows that this cutoff results in an approximate 60-40 (high bias-low bias) split, which demonstrates that a) screening and recruitment of the needed sample size is feasible, and b) there is still plenty of room for bias scores to be reduced, i.e., > 0 is far above the floor level of this measurement.*

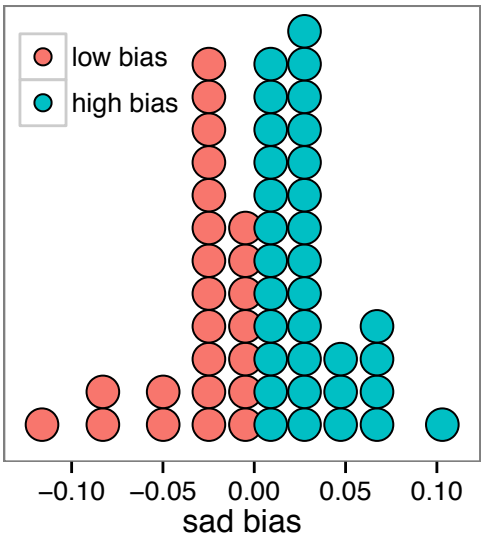


Figure 4. Distribution of bias scores and the k-means clustering groups from the R21 sample.

Recruitment. Our team has an extensive history of successfully recruiting and conducting NIH-funded trials. Consistent with previous and ongoing work, participants will be recruited from local clinics, advertisements placed online, in newspapers, on TV, and social media (see Other Attachments for more detail).

Determining eligibility. We will employ the same screening procedures that have proven effective and efficient in previous and ongoing studies. Participants that respond to various advertisements first complete an online screen that assesses inclusion and exclusion criteria. Potentially eligible participants will then take part in a phone screen with a staff member. The phone procedure is the first point of contact for participants, and it will allow us to ask critical information about the potential participant's willingness and ability to comply with the protocol, obtain informed consent, and verify initial assessment of inclusion and exclusion criteria. Consistent with past research projects, informed consent will be obtained verbally for the screening interview (conducted by phone) and in writing at the beginning of the baseline assessment. Rule out diagnoses will be determined by a trained research assistant using a brief screening interview (eMINI[55]) and the Columbia Suicide Severity Rating Scale (C-SSRS[56]) that we have experience with in numerous studies. Eligible participants will be scheduled for the pre-ABM behavioral assessment to confirm presence of negative attention bias. Imaging assessments will then be scheduled within one week. Following completion of the imaging assessment, participants will be randomly assigned to one of the three study conditions.

Randomization

The project biostatistician, Dr. Jason Shumake, will oversee randomization. He will use a stratified, random assignment approach, where participants will be stratified to intervention based on severity of depression symptoms and negative attention bias. Prior to data analyses, Dr. Shumake will check for the balance of randomization and control for any factors that are imbalanced. Importantly, our prior work using this approach resulted in very closely matched ABM intervention conditions.[27]

Interventions

In both ABM conditions, stimuli includes pairs of faces, each from a different actor and each expressing sad and neutral emotions, from the Pictures of Facial Affect (POFA) collection[57] and dysphoric and neutral images from the International Affective Picture System (IAPS)[58]. Faces and images were utilized in order to increase the variety of content participants viewed during the training sessions and because word stimuli has been shown less effective than image stimuli in prior ABM research[24].

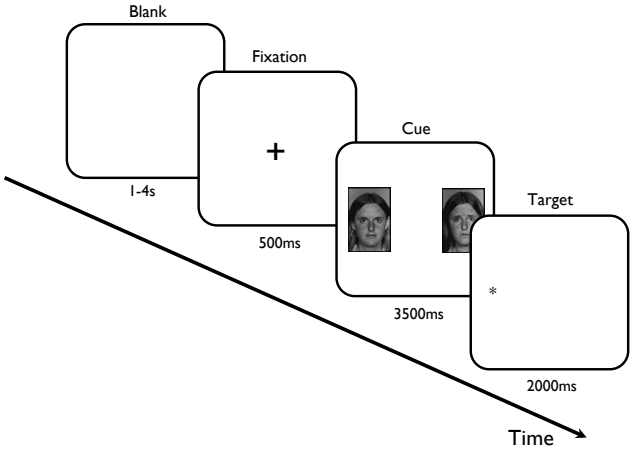


Figure 5. Schematic of the ABM intervention (not drawn to scale).

Each trial will consist of a fixation cross, followed by an image pair (Fig 5). POFA pairs will be presented for 3000ms and IAPS pairs will be presented for 4500ms. It has been hypothesized that longer stimulus duration times may allow for more elaborated processing and greater activation of relevant cognition[28]. 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. 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 placebo ABM, the target will appear in the location of the neutral and dysphoric stimuli with equal probability (50%). 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. The distribution of targets served as the critical manipulation whereby participants in active ABM were putatively trained to allocate their attention preferentially to the neutral stimuli and away from the dysphoric stimuli. Participants will complete 392 training trials per session, which will take approximately 25 minutes with breaks.

A full dosage of 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 in-clinic ABM dosage is identical to our prior work[27] but we have now slightly increased the at-home ABM to be consistent with research indicating that high training dosages are required to obtain substantial transfer effects[59-61]. The at-home ABM will be implemented on a website using JavaScript and HTML programming, with a MySQL database, so that participants can train on their home computers. We will match parameters to the in-clinic training task; hence the stimuli and presentation timing will be the same.

We combined in-clinic and at-home ABM for several reasons. We included in-clinic training to facilitate participant retention and to conduct attention bias assessments with laboratory eye tracking equipment at regular intervals. Frequent data collection facilitates mediation analyses and captures change with greater precision than less frequent assessments. At-home ABM is a convenient method to increase dosage of ABM while minimizing subject burden. We have successfully utilized a combination of in-clinic and at-home training in our prior work[62], thus we have experience with this approach and know that it is feasible and effective.

Rationale for training dosage. Evidence is accumulating in other cognitive training domains that repeated training is critical for obtaining sustained cognitive improvement[38,60]. To address this issue, we will require that participants come to the clinic for the same number of ABM sessions as in the our R21 design, but we are increasing the at-home training from one session per week to three sessions per week (i.e., a total of 5 sessions per week across a 1-month period). This does represent an increase in at-home training from our R21 study but we expect this to have a beneficial impact on the durability of training effects. We should note that compliance was good for once per week of at-home training in the R21. Participants on average completed 1.8 sessions of at-home training when asked to complete at least 1 session per week. Further, other work suggests that ABM every other day (4 days a week) produces lasting changes in depression (up to 3 months later).[25] We believe increasing the requirement to 3 at-home sessions per week does not

represent a substantial increase in burden and has the potential to produce more robust training effects. We now also address in our statistical approach how we will model training compliance and plan to examine whether training compliance is associated with variable effect sizes (see Data Analysis section for details).

Assessments

Table 1 lists the instruments we propose to employ for screening and measuring target engagement and symptom improvement, as well as the approach to documenting intervention integrity. As in our ongoing research, all self-report and interview assessment data will be captured with computers or iPads using REDCap (Research Electronic Data Capture; see equipment for more detail about REDcap).

Table 1. Schedule of assessments

Visit	Screen	Baseline	Week 1	Week 2	Week 3	Week 4 (End of Treatment)
Day	-7 - -1	1	7	14	21	28
Informed Consent	X	X				
Eligibility	X					
Attention bias (eye-tracking)		X	X	X	X	X
Resting state (fMRI)		X		X		X
QIDS, QIDS-SR, MASQ		X	X	X	X	X
C-SSRS		X				X
PVT		X	X	X	X	X
Treatment acceptability						X

Screening. We will use the same measures that we use in ongoing research to assess eligibility. Specifically, demographic information (e.g., age, sex, race, ethnicity) and MRI compatibility will be obtained using a standard self-report form, while depression symptom severity will be assessed using the Quick Inventory of Depressive Symptomatology (Self-Report; QIDS-SR) which has shown excellent psychometric properties[54,63,64]. UT staff will administer the electronic Mini International Neuropsychiatric Interview (eMINI), which is a structured screening interview for assessing psychiatric disorders[55], to assess for psychiatric exclusion criteria, and the Columbia Suicide Severity Rating Scale (C-SSRS), a clinician-administered measure designed to systematically assess suicidal behavior and ideation[56,65]. Concomitant treatment will be assessed using a standard self-report form. In order to determine adequacy of SSRI treatment (which will be used as a covariate in the analysis) we will administer the MGH Antidepressant Treatment Response Questionnaire (MGH ATRQ) which was shown to be superior in a head to head comparison with an alternate set of criteria and is concordant with clinician-rated assessments[66].

Primary ABM intervention target: Attention bias. To determine study eligibility and to measure change in bias during ABM, we will measure attention bias with a standard dot-probe task that utilizes eye tracking methods. We have significant experience with eye tracking methodology[8,12,67,68] and eye tracking has been shown to provide a more reliable estimate of attention bias than traditional reaction time assessments[69]. We will measure negative attention bias pre-ABM, week 1, week 2, week 3, and post-ABM, which is akin to obtaining weekly assessments of symptom change in traditional clinical trials. We will also use traditional and newly developed metrics for quantifying attention bias using reaction time data.[70]

For this task we will use a standard dot-probe task that utilizes affective image stimuli not used during ABM (near transfer). Two images depicting an emotional (sad, happy) or neutral facial expression from the KDEF stimuli collection[71] 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.

Throughout each trial, participants' gaze location and duration will be assessed using a remote optics eye tracking system (EyeLink 1000 Plus) from SR Research (Mississauga, Ontario, Canada). Gaze coordinates will be sampled at 1000 Hz (every 1 ms). Fixations will be defined as any period of 100ms or longer where

eye movements were stable within 1° of visual angle. The primary outcome will be total fixation duration for sad vs. neutral stimuli. Individuals with greater gaze bias towards sad relative to neutral stimuli will be recruited into the study and this outcome will be monitored over the course of the study. To determine fixation time for each stimulus category, we will identify an area of interest around the stimuli with a boundary of 1° of visual angle to account for error. All trials in which no pupil is detected or when participants do not fixate on stimuli will be dropped (typically less than 20% of trials). We have an automated data processing pipeline that can clean and process the eye tracking data and calculate the bias score immediately after it has been collected. Thus, we can determine study eligibility within minutes of task completion.

Secondary ABM treatment target: Resting state functional connectivity within the attention control network. Resting-state fMRI scans will be acquired on a whole body 3T Siemens Skyra MRI with a 32-channel head coil. The scanning protocol involves collection of a localizer followed by 2 high-resolution T1-weighted MPRAGE scans from each participant for anatomical coregistration with other datasets (TR = 2.3 s, TE = 3.08ms, flip angle = 9 degrees, slice thickness = .9mm, 192 slices, FOV = 22cm and matrix size = 256x256 mm), two resting state scans of 6 minutes each using a multi-band image sequence and a slice orientation to reduce artifact (TR/TE=1000/30ms, axial slices oriented approx. 20 degrees off the AC-PC plane, acquisition voxel size = 3x3x3 mm). 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 6-minute duration of the scan. Participant head motion will be minimized by instruction and the use of foam inserts. For more detail on the imaging parameters and analysis, please see our recent publication[27]. We will measure resting state functional connectivity pre-ABM, week 2, and post-ABM. A more frequent assessment schedule would be cost-prohibitive and not feasible.

Exploratory datasets will be acquired at no additional cost along with the resting state fRMI. For each study participant we will have an hour of scanning time, so we would like to maximize the amount of imaging data obtained from each subject given that resting state is a relatively short assessment. The first dataset will be an fMRI task previously used in an ABM neurofeedback application[49] and measures ability to control attention in the presence of negative distractors. Our previous work with this task has revealed that it engages the frontal-parietal attention control network and that this network is amenable to change as a result of ABM[49].

The second dataset collected at pre-training will be diffusion tensor (DTI) scan using single-shot echo planar imaging, and a twice-refocused spin echo pulse sequence, optimized to minimize eddy current-induced distortions (TR/TE=8300/84 ms, B=700, 2x2x2mm voxel size, T2 + 64 direction DWI). DTI data will be examined for white matter microstructural differences that are associated with negative attention bias as well as predict responsiveness to ABM. We have previously used DTI to show that depression vulnerability was associated with microstructure alterations in the frontal portion of the uncinate fasciculus[50].

Imaging data processing. We will use an automated approach to image quality check/preprocessing developed by the Laboratory of Neuroimaging (LONI; http://www.loni.usc.edu/). We have successfully used this approach for hundreds of TRACK TBI scans (see Dr. Schnyer's personal statement for more detail about the TRACK TBI study). All resting state analysis will be scripted and performed in batch on the Texas Advanced Computing Center (TACC) (see facilities for more detail regarding the TACC).

Placebo ABM intervention target: Psychomotor Vigilance Task (PVT). Our preliminary work suggested that placebo training may improve depression by improving general sustained attention. To directly assess this possibility, we will assess sustained attention with the PVT, a gold standard assessment. The PVT[37] 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. The PVT will be 10 minutes in length. The following PVT variables are typically analyzed: median RT, mean of the fastest 10% RT, mean of the slowest 10% reciprocal RTs, standard deviation of the RT, number of lapse trials (responses greater than 500 ms), and the number of trials during which commission and omission errors occur. We have used the PVT in our recent work[76]. We will measure sustained attention with the PVT pre-ABM, week 1, week 2, week 3, and post-ABM.

Depression symptom outcome measures. To determine symptom change during the intervention period, we will measure depression symptoms on a weekly basis with the QIDS-SR and the QIDS interview-based

assessment[54,63]. We find that using both self-report and interview-based assessments of depression severity results in the most comprehensive assessment of depression symptoms. These scales have excellent psychometric properties and have been used extensively[54,63,64]. For exploratory purposes, we will also measure other aspects of depression and anxiety (anhedonia, negative affect, anxious arousal) utilizing the MASQ[77,78]. We will measure depression symptoms pre-ABM, week 1, week 2, week 3, and post-ABM, which corresponds with the timing of the attention bias and sustained attention assessments.

Patient acceptability and feasibility. At the end of study participation (either study completion or drop-out), we will assess the acceptability and feasibility of the intervention. Specifically, via a questionnaire we will measure accessibility to the program, ease of use, ability to fit into participants' schedules, whether participants would recommend this program to other individuals, whether this program is preferred over in-person visits, and whether participants were satisfied with the program. We will also obtain reasons for drop-out among participants who do not fully complete the required number of training sessions or drop-out of the study. We have done this type of assessment as part of our past intervention research[79,80].

Data Analysis Plan

Prior to analysis, variables will be checked for internal consistency; frequency distributions and plots will be examined for unusual data distributions or data points. Missing data will be evaluated and appropriately imputed as needed.[81] Our biostatistician, Dr. Jason Shumake, has strong expertise with conducting data analyses for randomized studies and testing for mediation[85,86].

Our primary aim is to examine whether ABM has the following outcomes: (1) reduced negative attention bias measured behaviorally with reliable eye tracking methods; (2) improved resting state functional connectivity between the right middle frontal gyrus and anterior cingulate cortex; and (3) significant improvements in depression symptoms. The focus of the analysis will be on differences in the rate of change in these outcomes over the course of the study, which will be analyzed using mixed-effects regression models. We will perform a separate linear mixed effects analysis using the R package *lme4* for each outcome measure. Each set of analyses will test the main effects of time and training condition, as well as how individual time series vary by treatment group (treatment × time interaction), using random intercept and slope to account for each individual's distinct baseline profile and rate of change.

Training compliance. *After fitting these models, we will further test how much residual variance within each treatment group can be explained by variance in treatment adherence (the number of completed training sessions). If there is significant residual covariance between adherence and outcome, we will compute the expected treatment effect size conditioned on the number of sessions completed (e.g., the effect size given at least 80% adherence, the effect size given at least 90% adherence, etc.). This will provide informative information about whether the treatment effect size varies as a function of training compliance.*

Our secondary aim to is to identify mechanisms responsible for the putative efficacy of active and placebo ABM. For active ABM, we will test whether improvement in negative attention bias and/or improvement in resting state connectivity mediates the association between intervention condition (active ABM vs. assessment only) and depression symptom change. Further, we will examine whether improvements in general sustained attention mediates the efficacy of placebo ABM (vs. assessment only) for depression symptom change. *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 negative attention bias 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 negative attention bias 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 Fig 8, 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[87]. The parameters of this model will be estimated using a covariance structure analysis program (the *sem* 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.

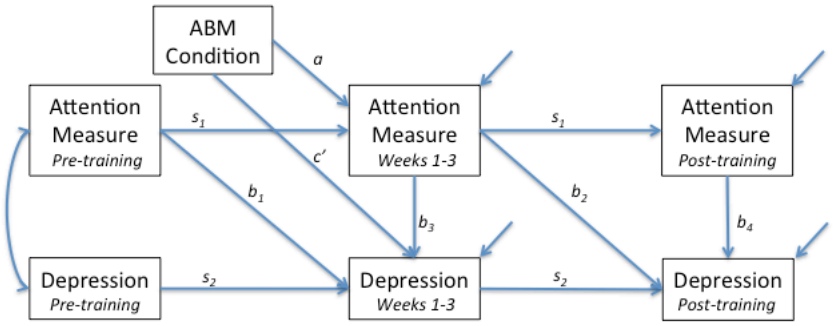


Figure 8. Mediation model that examines longitudinal and contemporaneous mediation of ABM on depression symptom change.

Completer analyses. *Our primary analyses will be intent-to-treat analyses, but we will also conduct secondary analyses that examine whether the pattern of results is consistent (or amplified) in the group that completes at least 50% of the assigned intervention.*

Go/No-Go Rule. *To move forward with a confirmatory R01 for ABM, the effect size of the treatment × time interaction must exceed d >= .5 for negative attention bias (measured with eye tracking) AND change in depression symptoms (measured with QIDS-SR). Thus we have a single Go/No-Go criterion. Importantly, the Go/No-Go analysis will only involve the active ABM and assessment only conditions (i.e., we will not include the placebo condition). We will not include the placebo condition in the treatment x time interaction as it could be possible to obtain an effect size d > .5 for the overall interaction if the placebo condition outperforms all other conditions. Further, we are utilizing the behavioral measure of attention bias in the Go/No-Go criterion (rather than functional connectivity) because prior research in anxiety indicates that change in attention bias is critical for observing symptomatic change. Further, if we only see symptomatic change in the absence of attention bias change, this would significantly question the mechanism of action for active ABM.*

Power analysis. As we expect effect sizes for ABM on proximal targets (attention bias, rMFG – dACC resting state 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 change.

To calculate the sample size requirements for linear models of these longitudinal data, we used methods outlined by Diggle et al.[88] 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. 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[89]: BDI = 1.13 + (.68)*CESD. Calculations 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 suggests that the effect may be much larger. We nevertheless used a medium effect for power analyses, given the difficulties associated with using pilot studies to accurately estimate effect sizes for power analyses[90]. Given these assumptions, 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.